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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Introduction

Declaration

This thesis is my own work with the collaboration and support of my supervisors, patients and colleagues. This work has not been submitted for any other degree or professional qualification in this, or any other university. Any included publications are my own. Permission has been obtained for all articles to be included in this thesis.

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Contribution to the PhD

The idea for the PhD was first proposed by Professor Charles Warlow and brought forward by Professor Stone. Having decided upon this topic for my PhD, my supervisors Prof Stone and Carson assisted with fellowship applications which I wrote. I led the design of the project. With support from my supervisors, I wrote the ethics application and created the interview and questionnaires. I organised and carried out patient recruitment and carried out the statistical analysis with the help of four medical students; Savva Pronin, Oli Shipston-Sharman, Matthew Wood and James Hazelwood. I wrote the papers with support and input from my supervisors and collaborators.

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Abstract

Uro-neurological disorders are those in which there is a disturbance of bladder function related to a neurological cause. However, many patients with a combination of urological and neurological symptoms, such as bladder voiding dysfunction and leg weakness or numbness, are not found to have explanatory abnormalities despite adequate clinical and radiological investigation, so-called 'scan negative' patients. In this PhD patients with 'scan negative' uro-neurological diagnoses were primarily investigated through studies of patients presenting with suspected Cauda Equina Syndrome and to a lesser extent Chronic Urinary Retention (including Fowler's syndrome).

The PhD goal was to deeply phenotype patients with 'scan negative' Uro- neurological disorders and in so doing, to improve our scientific understanding of these presentations and inform the development of clinical trials.

The PhD explores the historical literature linking patients with idiopathic urological dysfunction and functional disorders, reviews the incidence, research and definitions of cauda equina syndrome and phenotypes patients in a retrospective and prospective manner who present with acute scan negative urological dysfunction ('scan negative' cauda equina syndrome) as well as investigates for evidence of functional disorders in chronic scan negative urological dysfunction (Fowler's syndrome) and evidence of urological dysfunction in patients with functional disorders and neurological dysfunction.

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Lay Summary

The bladder and brain are in constant communication to ensure that voiding can occur in a safe and socially appropriate way. Many patients with bladder dysfunction and neurological symptoms are not found to have any clear cause of their symptoms despite investigation, including brain and spine imaging. My research focused on Cauda Equina Syndrome (CES) which, when due to a structural cause, describes damage to the nerves in the lower back which supply bladder, bowels, sexual function and the legs usually from slipped discs in the spine.

CES is as common as multiple sclerosis and is diagnosed using an MRI scan of the spine. However, about 50% of people presenting with the symptoms of CES have MRI scans which do not explain their symptoms, 'scan negative' patients. These patients are typically not given an explanation and are baffled by their disabling symptoms. This PhD includes the first large clinical studies focusing on neglected 'scan negative' CES patients to investigate why patients have weak legs and bladder problems when there is no abnormality on the tests. There is evidence that some patients have a functional neurological disorder which currently goes undetected but could be usefully diagnosed and treated with treatment like physiotherapy. Functional Neurological Disorder is a common problem in neurology where patients develop leg weakness and numbness related to a problem in the function rather than structure of the nervous system. Other important factors such as severe back pain, medications, panic and underlying bladder dysfunction affect all parts of the bladder brain network and we hypothesise ways these could lead to bladder dysfunction.

I also found evidence of an unusually high frequency functional neurological disorder in patients with chronic unexplained urinary retention including Fowler's syndrome where the person is unable to urinate and often requires catheters. I also found evidence of milder urological dysfunction in patients with functional disorders who attend neurology outpatient clinics.

The goal of these studies was to increase knowledge, awareness and treatment of these patients thus improving quality of life.

Acknowledgements

This thesis is dedicated to Adam, Rosa and bump (now Atticus).

Massive thanks to Jon and Alan for being incredible supervisors and mentors academically and in life.

I'd like to acknowledge the patients who took part in the study as cases and controls. Patients were often in pain and therefore unable to move from their beds. Despite this they undertook long interviews and questionnaires which often touched on difficult topics. Their honesty and willingness to participate has created this body of work.

To Jon Stone who has unfailingly helped me reach for the moon. I hope lots of other people have the chance to be mentored by you Jon. Your support and gentle push of improvement has been the thing that got this done.

To Alan Carson who was always there when I needed help or felt overwhelmed.

Thanks to my neurosurgical colleagues especially Patrick Statham, Andreas Demetriades and Julie Woodfield without whom this project would not have been possible.

My colleagues at Functional Disorders Research Group who provided lots of support, strong coffee (even when I didn't make it), buns and pertinent questions. Thank you for friendship, laughter and understanding the pain. My friends and particularly my parents whose help and belief in me has kept me going when I wanted to give up.

The excellent medical students I had the chance to work with, particularly Savva Pronin and Oli Shipston-Sharman. Thanks to the neurology consultants and neurosurgery and neurology nurses.

Finally, I'd like to thank the Association of British Neurologists who have funded this PhD and changed my life. I hope to repay your faith in me by improving the lives of patients.

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Appendix of relevant publications

Section 1: Cauda Equina Syndrome

- Evaluation of Nationwide Referral Pathways, Investigation and Treatment of Suspected Cauda Equina Syndrome in the United Kingdom. Daniel M. Fountain, Simon Davies, Mohammed Kamel, Paulina Majewska, Julie Woodfield, Ellie Edlmann, Aimun A.B. Jamjoom, **Ingrid Hoeritzauer**, Mueez Waqar, Dominic Mahoney, Dillon Vyas, Moritz Schramm, Georgios Solomou, Francesca Dawkes, Heidi Grant, Jonathan Attwood, Alexandros Boukas, Dominic Ballard, Emma Toman, Matthew Sanders, John E. Lawrence, Beverly Cheserem, Saurabh Sinha, Patrick Statham, Neurology and Neurosurgery Interest Group, British Neurosurgical Trainee Research Collaborative

- Understanding Cauda Equina Syndrome: protocol for a multi-centre prospective observational cohort study. Julie Woodfield1,2, **Ingrid Hoeritzauer1**,2, Aimun AB Jamjoom2,3, Savva Pronin2, Nisaharan Srikandarajah4, Michael Poon1, Holly Roy5, Andreas K Demetriades1, Phil Sell6, Niall Eames7, Patrick Statham1, British Neurosurgical Trainee Research Collaborative (BNTRC)

- Hazelwood JE[1,2,3,4], **Hoeritzauer I**[5,6,7], Pronin S[5,6,8,7], Demetriades AK[5,6,8,7].An assessment of patient-reported long-term outcomes following surgery for cauda equina syndrome. Acta Neurochir (Wien). 2019 Sep;161(9):1887-1894. doi: 10.1007/s00701-019-03973-7.

Section2: Defining new phenotypes

- **Hoeritzauer I**[1], Carson AJ[1,2,3], Stone J[1,3]. 'Cryptogenic Drop Attacks' revisited: evidence of overlap with functional neurological disorder. JNNP 2018 Jul;89(7):769-776.

- Stone J[1], **Hoeritzauer I**[1], Tesolin L[2], Carson A[1,3] Functional Movement Disorders of the Face: A Historical Review and Case Series. J Neurol Sci. 2018 Sep 26;395:35-40.

- Popkirov S, **Hoeritzauer I**, Colvin L, Carson A, Stone J. Complex Regional Pain Syndrome and Functional Neurological Disorders - time for reconciliation. J Neurol Neurosurg Psychiatry. 2018 Oct 24. pii: jnnp-2018-318298

Section 3: Bradford Hill Criteria

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Background

Uro-Neurology is the connection between urological symptoms and the neurological system, comprising a complex bladder-brain network involving the brain, spinal cord, sacral nerves and peripheral (pelvic) nerves. Bladder problems such as urinary incontinence or difficulty passing urine are very common[1,2] and are usually due to pathomechanical outflow dysfunction such as pelvic floor weakness or benign prostatic hypertrophy. Understanding and management of outflow dysfunction is undertaken by urologists or gynaecologists, and often results in good outcomes. Bladder problems seen in patients with neurological disease however, are due to coordination dysfunction between the brain, spinal cord and the lower urinary tract (bladder, urethra and sphincters) and are much less well understood[3].

Functional neurological disorders (FNDs), previously called psychogenic disorders, describe genuine neurological symptoms such as limb weakness in patients with a structurally normal nervous system. They exist at the interface between neurology and psychiatry and are often triggered by physiological events such as pain, panic, syncope or injury. Symptoms are usually driven by abnormal functioning due on an involuntary state of abnormal focused attention[4,5]. Positive evidence of the potential for the nervous system to functional normally (e.g. become briefly strong in Hoover's sign or tremor stopping briefly with the ballistic movements) is now part of the diagnostic criteria[6]. Specific and effective treatment for functional neurological disorders exists but, without this, the prognosis is poor[7]. FNDs often co-exist with the much more common functional disorders such irritable bowel syndrome, non-cardiac chest pain and chronic widespread pain[8].

The last twenty years has seen a resurgence in FND interest and research however, within the existing literature, the overlap between FNDs and urological disorders has not as yet been studied. In the last ten years there has only been one single centre Uro-Neurology case series of patients with functional movement disorder and bladder disorders[9] and two articles in the psychiatric literature[10,11].

Urological disorders, particularly urinary retention in women, were previously associated with functional disorders and formed part of the DSM III diagnosis for conversion disorder. Psychogenic urinary retention appeared frequently in the literature up until the 1980s when it was discovered that some women with chronic idiopathic urinary retention had abnormal urethral EMG readings[12,13]. These findings, of decelerating bursts and complex repetitive discharges, were felt to be in keeping with a channelopathy and the diagnosis of psychogenic urinary retention was

thereafter very infrequently made. Patients were instead diagnosed with dysfunctional voiding, Fowler's syndrome, chronic idiopathic urinary retention[14].

My PhD aims to take the first steps of re-investigating the relationship between Uro-Neurological disorders and functional neurological disorders. I chose to focus my main research around a group of patients who are often seen with acute onset bladder disorders but have normal or non-explanatory imaging and investigations. These patients present with suspected cauda equina syndrome.

Cauda equina syndrome (CES) is a devastating condition caused by compression of the cauda equina nerve roots resulting in bowel, bladder and sexual dysfunction and potential lower limb weakness[15]. CES requires urgent surgery and has serious potential morbidity and medico-legal consequences[16]. Suspected acute CES has a minimum incidence of 11 per 100,000 making it twice as common as multiple sclerosis. However, at least 43% of patients with clinical CES have normal or negative MRI scans, 'scan-negative', and receive no other diagnosis[17]. These patients have previously been acknowledged but never studied in depth to ascertain their phenotype or explore possible mechanisms of their bladder, bowel, sexual dysfunction and pain.

Smaller studies of patients with a form of chronic urinary retention, Fowler's syndrome, and bladder dysfunction in patients with functional disorders attending outpatient neurology were chosen to give an overall feel for whether a relationship existed between patients with FND and bladder disorders in a chronic context.

Aims

The main aims of my PhD were:

Aim1: To determine what proportion of patients with 'scan negative' CES have a functional disorder by clinical consensus

Aim 2: To describe associated clinical features relevant to diagnosis, mechanism and aetiology in patients with Scan negative and scan positive CES

Aim 3: To determine what proportion of patients with urinary retention from Fowler's syndrome or idiopathic causes (chronic idiopathic urinary retention/dysfunctional voiding/bladder outlet obstruction) have comorbid functional neurological disorder.

Aim 4: To determine what proportion of patients with functional neurological disorders have lower urinary tract dysfunction.

Methods

My PhD started with exploring the current understanding in literature of the relationship between Uro-Neurological disorders and functional neurological disorders. A systematic review of the incidence of cauda equina syndrome followed to investigate incidence as well as problems with cauda equina syndrome nomenclature and diagnosis. A pilot study allowed an examination of whether evidence existed for my hypotheses: that at least some of the symptoms in patients with CES symptoms but normal or non-explanatory scans, 'scan negative' CES, could be due to a functional disorder. The main part of the PhD was two studies of patients with cauda equina syndrome; a retrospective and a prospective case: control study of patients with CES and patients with 'scan negative' CES. Following these, a review of comorbidity in patients with Fowler's syndrome and a study of urological symptoms and levels of distress caused by lower urinary tract dysfunction in patients presenting with functional and pathophysical disorders to outpatient neurology clinics was also undertaken to address aim four. Finally, limitations of study methodology were explored, and conclusions drawn.

All major components have been published or submitted for publication. They are bookended by an introduction and conclusion which explains the rationale for each article, how the study addressed the PhD aims and the conclusions drawn. This is in keeping with the University of Edinburgh thesis guidelines point 1.12 "*it is in the interest of candidates to include any relevant published papers in their thesis. When published paper are to be included as a thesis chapter these must include an introduction and conclusion and be bound into the thesis at the appropatie point. These should either be by the bookbinder, as a chapter, an appendix or an electronic copy*".

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Papers included in the PhD

Paper One: Hoeritzauer I, Phe V, Panicker JN. Urological symptoms and functional neurologic disorders. *Hand Clin Neurol;* 2016; 139:469-481

Paper Two: Hoeritzauer I[2,3] MRCP, Wood M[1,2], Copley P MRCS [1,2,3], Demetriades AK[1,3] FRCSEd and Woodfield J[1,2,3.] What is the Incidence of Cauda Equina Syndrome? *In press Journal of Neurosurgery: Spine*.

Paper Three: Hoeritzauer I, CM Doherty, S Thompson, R Kee, A Carson, N Eames, J Stone. 'Scan Negative' Cauda Equina Syndrome: evidence of functional disorder from a prospective case series. *Brit J of Neurosurg.* 2015; 29 (2):178-180.

Paper Four: Ingrid Hoeritzauer[1,2,5], Savva Pronin[1,5], Alan Carson[1,2,3], Patrick Statham[2,4,5], Andreas K. Demetriades[1,2,4,5], Jon Stone[12]. The clinical features and outcome of scan negative and scan positive cases in suspected cauda equina syndrome - a retrospective study of 276 patients. *J Neurol.* 2018 Dec;265(12):2916-2926.

Paper Five: Ingrid Hoeritzauer[1,2], Alan Carson[1,2,3], Patrick Statham[4], Jalesh Panicker[5], Voula Granitsiotis[6], Maria Eugenicos[7], David Summers[7], Andreas K. Demetriades[4], Jon Stone[1,2.] A prospective case-control study of 198 patients presenting with symptoms of cauda equina syndrome. Submitted

Paper Six: Hoeritzauer I, Jon Stone, Clare Fowler, Suzy Elneil, Alan Carson, Jalesh Panicker. Fowler's syndrome of Urinary Retention: a Retrospective Study of Comorbidity. *Neurourology and Urodynamics*. 2016; 35(5): 601-603.

Paper Seven: I Hoeritzauer[1], O Shipman-Sharma[1], J Stone[1,2], A Carson[1,2,]3. Lower Urinary Tract Dysfunction in patients with Functional Disorders attending neurology outpatient clinics. Prepared for submission

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Exploration of the field

Paper One: Hoeritzauer I, Phe V, Panicker JN. Urological symptoms and functional neurologic disorders. Hand Clin Neurol; 2016; 139:469-481

Introduction: To explore the current understanding of the relationship between urological symptoms and functional disorders, including functional neurological disorders, a review of old and new literature was required, summarised in this book chapter.

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Chapter 38

Urologic symptoms and functional neurologic disorders

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Abstract

The term functional urologic disorders covers a wide range of conditions related broadly to altered function rather than structure of the lower urinary tract, mainly of impaired urine voiding or storage. Confusingly, for a neurologic readership, these disorders of function may often be due to a urologic, gynecologic, or neurologic cause. However, there is a subset of functional urologic disorders where the cause remains uncertain and, in this chapter, we describe the clinical features of these disorders in turn: psychogenic urinary retention; Fowler's syndrome; paruresis (shy-bladder syndrome); dysfunctional voiding; idiopathic overactive bladder, and interstitial cystitis/ bladder pain syndrome. Some of these overlap in terms of symptoms, but have become historically separated. Psychogenic urinary retention in particular has now largely been abandoned as a concept, in part because of the finding of specific urethral electromyogram findings in patients with this symptom now described as having Fowler's syndrome, and their successful treatment with sacral neurostimulation.

In this chapter we review the poorly researched interface between these "idiopathic" functional urologic disorders and other functional disorders (e.g., irritable-bowel syndrome, fibromyalgia) as well as specifically functional neurologic disorders. We conclude that there may be a relationship and overlap between them and that this requires further research, especially in those idiopathic functional urologic disorders which involve disorders of the urethral sphincter (i.e., voluntary muscle).

Keywords

lower urinary tract dysfunction, overactive bladder, functional urologic disorders, functional neurologic disorders, psychogenic urinary retention, dysfunctional voiding, interstitial cystitis/bladder pain syndrome, paruresis, Fowler's syndrome, opiate

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INTRODUCTION

Functional neurologic disorders, such as functional tremor or functional limb weakness, are diagnosed based on positive signs, such as entrainment of functional tremor or Hoover's sign of functional leg weakness, which demonstrate an underlying intact structure to the nervous system. Confusingly, for a neurologic readership, there is much less of a dichotomy in the urologic literature between functional and structural disorders. The term functional urologic disorders covers a wide range of disorders in which abnormal functioning of the lower urinary tract (LUT) causes urologic symptoms. Most functional urologic symptoms have a clear organic pathology (e.g., urologic, gynecologic, or neurologic) that is uncovered during clinical assessment or investigation. There are, however, some functional urologic disorders where the LUT dysfunction is evident through investigations, but the etiology is unclear.

Functional disorders of the LUT manifest as voiding dysfunction, storage dysfunction, or both. The symptoms of storage dysfunction include urinary urgency, daytime frequency, nighttime frequency, nocturia, and/or urge urinary incontinence (Abrams et al., 2002; Hayllen et al., 2010). Voiding dysfunction manifests with symptoms of urinary hesitancy, intermittent flow and slow stream, straining to void, a sensation of incomplete bladder emptying after voiding and double voiding, characterized by the need to urinate again soon after voiding (Abrams et al., 2002). In the most severe case, patients may even be in urinary retention.

We start this chapter with a description of LUT function in health and a summary of what is known about the brain–bladder axis. We then focus on the following presentations where there is no clear cause for dysfunction: psychogenic urinary retention; Fowler's syndrome; paruresis (shy-bladder syndrome); dysfunctional voiding; interstitial cystitis/bladder pain syndrome, and overactive bladder (OAB). Some of these overlap in terms of symptoms, but have become historically separated.

We then discuss what evidence there is for an overlap between these disorders and functional somatic disorders such as fibromyalgia (FM) and irritable bowel as well as functional neurologic disorders such as functional movement disorders or dissociative (nonepileptic) seizures. Functional somatic disorders have been recognized in patients with idiopathic functional urologic disorders, and LUT dysfunction has also been documented in patients with a range of functional somatic disorders. The nature of the association, however, is uncertain and whether these are the manifestations of a common underlying abnormal working of the nervous system, or merely represent the coincidental existence of two independent processes, is yet to be systematically explored.

LOWER URINARY TRACT FUNCTIONS IN HEALTH

In health, the LUT remains in the storage phase, acting as a low-capacity reservoir of urine, 99% of the time. Storage is dependent on sympathetic and somatic-mediated contraction of the internal and external urethral sphincters, respectively, and sympathetic-mediated inhibition of the detrusor. During the storage phase, the pontine micturition center (PMC) is tonically inhibited by activity from cortical and subcortical centers, such as the prefrontal cortex, anterior cingulate gyrus, and insula (de Groat et al., 2015). Increasingly stronger signals through the sacral afferents during the storage phase are primarily responsible for initiating a switch to the voiding phase (Valentino et al., 2011). When deemed socially appropriate and safe, tonic inhibition of the PMC from the periaqueductal gray (PAG) is released, resulting in relaxation of the urethral sphincters and relaxation of the pelvic floor,

and parasympathetic-mediated activation of the detrusor and voiding ensue (Panicker and Fowler, 2010).

CURRENT MODELS OF THE BRAIN–BLADDER AXIS

A more indepth review of the complex higher cortical pathways is useful to gain a better understanding of the bladder–brain axis and explore the association between functional disorders and LUT symptoms. Current understanding of LUT regulation suggests connection between the LUT and higher centers, including emotion, arousal, and motivation. Additionally, three circuits of micturition are postulated (Griffiths, 2015). The micturition system works largely unconsciously via PAG and parahippocampal regions of the temporal cortex to monitor the slowly filling bladder (Kavia et al., 2010; Tadic et al., 2013). Once it is socially appropriate and safe to void, activation of the medial prefrontal cortex triggers the PAG to activate the PMC. This circuit is hypothesized to be closely linked not only anatomically to the amygdala, but also emotionally linked to the crucial aspect of safety required for voiding.

In patients who experience the threat of involuntary leakage with or without the sense of urgency, two other circuits are activated. One involves the insula and prefrontal cortex. The insula is known to receive homeostatic information from the whole body, with increasing activation as the bladder progressively fills. The prefrontal cortex has connections to the limbic system, associated with emotional and social contextualized decision making and involved in working memory. In response to the threat of involuntary voiding, the medial prefrontal cortex is inhibited by activity from the insula and lateral prefrontal cortex. Reduced medial prefrontal cortex activation inhibits PAG activation and raises the threshold micturition level (Tadic et al., 2011).

The anterior cingulate gyrus is responsible for motivation and adjustments of bodily arousal states in response to mental stress. It is coactivated with the supplementary motor area, which controls striated muscles such as those in the pelvic floor and external urethral sphincter (Critchley, 2003). In response to the threat of involuntary voiding and the sensation of urge, activation of both the supplementary motor cortex and the dorsal anterior cingulate gyrus occurs. These two areas are thought to be responsible for simultaneous pelvic floor and urethral sphincter contraction and the anterior cingulate gyrus is thought to create the motivation to visit a toilet (Schrum et al., 2011).

The PAG is thought to play a significant role linking between higher centers and the LUT, with projections to the thalamus, hypothalamus, and amygdala, while also receiving information from the bladder (Griffiths and Fowler, 2013; Griffiths, 2015). The PAG modulates the voiding threshold using the information received from the higher centers. If it is unsafe or socially inappropriate to void, the micturition threshold will be increased and the need to void reduced until there are higher bladder volumes. Brainstem nuclei such as the locus coeruleus modulate behaviors related to LUT function. The locus coeruleus system initiates and maintains arousal and facilitates shifts between focused attention and scanning attentiveness (Berridge and Waterhouse, 2003). Activation of the PMC and hence the locus coeruleus results in a switch from nonvoiding to voiding-related behaviour. Experiments in rodent models have shown that the expected pattern of increased activity from the locus coeruleus with increasing bladder pressure is lost 2 weeks after partial bladder outlet obstruction, even when bladder pressure increased to the micturition threshold (Rickenbacher et al., 2008). This may be relevant in understanding why some individuals with chronic urinary retention may have high volume retention without a sensation of urge or bladder fullness. It also suggests that persistent outlet obstruction leads to a loss of central regulation of LUT function.

As well as the loss of sensitivity to increases in bladder pressure, the locus coeruleus neurons also showed increased basal activity of 40% compared with sham rats (Rickenbacher et al., 2008). This elevated basal activity is associated with hyperarousal, difficulty focusing on an ongoing task, and neurobehavioral impairments such as anxiety and sleep impairment. Theta oscillations were prominent on electroencephalogram, which ties in with loss of ability to differentiate between differing bladder pressures. Theta oscillations play a role in sensorimotor integration by coordinating activity in various brain regions on the basis of sensory input to update motor plans (Caplan et al., 2003). The presence of these may also cause difficulty with nonbladder sensorimotor processing.

ASSESSMENT OF FUNCTIONAL UROLOGIC DISORDERS

History and examination are essential to consider potential urologic and gynecologic pathologies such as prostate enlargement, pelvic organ prolapse, tumors, or neurologic disorders such as multiple sclerosis, spinal pathology, or Parkinson's disease. A bladder diary aids with assessment of the functional bladder capacity, urinary frequency, and the number of leakage or urgency episodes. Noninvasive investigations such as uroflowmetry and measurement of the postvoid residual by ultrasound or in–out catheterization help to uncover voiding dysfunction and incomplete bladder emptying. Urodynamics helps to identify the pattern of LUT dysfunction, such as detrusor instability or voiding dysfunction, but does not necessarily inform the etiology. Although the majority of patients presenting with "functional" problems with their bladder will have a cause identified during the course of investigations, many will not, and these are the disorders we consider in this chapter.

PSYCHOGENIC URINARY RETENTION

There are numerous causes for urinary retention and most commonly this arises in the setting of structural urologic lesions or an established neurologic disorder (Panicker et al., 2010; Smith et al., 2013). Reports of an association between psychologic factors and urinary retention began to appear in the 1800s, under the term "hysterical ischuria" (Charcot, 1877; Dejerine andand Gauckler, 1913). We have found reports of 109 patients with a diagnosis of "psychogenic urinary retention," with the majority (n = 84) reported prior to 1985. The diagnosis was made after medical investigations to exclude urologic, gynecologic, or neurologic causes (Margolis, 1965; Bridges et al., 1966; Blaivas et al., 1977; Barrett, 1978; Korzets et al., 1985; Nicolau et al., and 1991; Bilanakis, 2006). Triggering events and secondary gain were then sought and urologists were urged to look for recent life stressors and positive psychologic features to make the diagnosis (Wahl and Golden, 1963).

Psychogenic urinary retention was reported most commonly in young women, with an average age of onset of 29 years based on a review of 15 papers. Emotional deprivation during childhood seemed to be a predisposing factor (Wahl and Golden, 1963; Montague and Jones, 1979) in many cases, and there were several reports of patients having nocturnal enuresis and urinary tract infections (UTIs) (Wahl and Golden, 1963; Lamontagne and Marks, 1973; Christmas et al., 1991).

The literature is replete with predisposing and precipitating factors, including perceived stress, such as unhappy marriage or home life (Montague and Jones, 1979; Korzets et al., 1985), feelings of guilt or fear of punishment, often for promiscuous sexual activity (Wahl and Golden, 1963; Montague and Jones, 1979), and depression and anxiety (Blaivas et al., 1977; Montague and Jones, 1979). Patients' unhelpful thoughts about genitourinary sensations as being "dirty" (Williams and Johnson, 1956) and "tense and unassertive" (Lamontagne and Marks, 1973) or "emotionally overcontrolled" (Montague and Jones, 1979) personalities were also felt to predispose to abnormal bladder functions. In several

patients, urinary retention was precipitated by physical triggers such as UTI, road traffic accident, surgery, or childbirth (Cardenas et al., 1986).

Modeling from parents with genitourinary problems, sudden death of a friend or colleague from renal disease, iatrogenesis due to recurrent questions about urinary dysfunction, or minor symptoms which escalated with frequent medical reviews were also reported (Norden and Friedman, 1961; Wahl and Golden, 1963). Rape (Williams and Johnson, 1956; Montague and Jones, 1979) and murderous rage (Williams and Johnson, 1956) were reported in only 2 patients, but are often quoted in case series introductions or discussions as potential precipitating factors.

Many patients reported unexplained sensory symptoms or pain and headaches (Williams and Johnson, 1956; Lamontagne and Marks, 1973; Montague and Jones, 1979). These symptoms improved with improving urinary symptoms. Psychogenic urinary retention was only associated with renal dysfunction in 2 cases (Knox, 1960; Korzets et al., 1985). Perceived benefits included freedom from unhappy home or sexual situations, the ability to exert control in situations in which the patient was being exploited, and being unburdened from many household duties expected of a woman at that time (Wahl and Golden, 1963; Montague and Jones, 1979).

Treatment outcomes were generally only published in patients who significantly improved. However, many patients underwent unnecessary surgery, such as urethral dilatation, urethral elongation, and hysterectomy before a diagnosis of psychogenic urinary retention was made and specific treatment commenced (Montague and Jones, 1979; Cardenas et al., 1986). It is unclear, however, what proportion of patients diagnosed with psychogenic urinary retention were left with a permanent indwelling catheter or escalating surgical options for long-term treatment (Blaivas et al., 1977). Treatment was initially described with psychoanalysis, but in more recent literature, studies of systematic desensitization with relaxation training and biofeedback-monitored relaxation training were described (Lamontagne and Marks, 1973; Montague and Jones, 1979; Nicolau et al., 1991).

Reviewing the literature, there are also case reports of psychogenic urinary retention, which in hindsight clearly had a nonpsychogenic cause. For example, a case was reported in 1891 of a young woman developing urinary retention and was attributed to her being frightened by a man with a traveling bear. However, there was also mention of abnormal sensations of tight rings around her lower thighs, reduced sensation and power in her legs, and bowel disturbance, which gradually improved over 6 months (Little, 1891), and it seems possible that this was due to an inflammatory conus lesion which would not have been diagnosed with the investigations at the time. The danger of making a diagnosis of psychogenic or functional neurologic disorder in the absence of positive signs, such as Hoover's sign of functional weakness, is highlighted by this case and caution should therefore be exercised when exploring this area. Although urinary retention was included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) as one of the symptoms of somatization disorder, there are few studies which refer to this condition in the recent literature.

FOWLER'S SYNDROME

At a time when several of the cases of unexplained urinary retention were being labeled as "psychogenic," Clare Fowler and colleagues investigated the electromyogram (EMG) activity of the striated urethral sphincter and reported abnormal findings in 72% of the 48 women they examined (Fowler and Kirby, 1986). The findings they reported were complex repetitive discharges (CRDs) and

decelerating bursts (DB), and this abnormal EMG activity suggested a biologic basis for urinary retention in young women who hitherto were told they had psychogenic urinary retention. Further investigation of this patient subgroup found that they were young women with an average age of 27 years, who, despite retaining urine, typically more than 1 liter, did not report urgency. They often reported an unpleasant sensation of "something gripping" during catheter withdrawal (and insertion), which was so severe that 28% of the original cohort received suprapubic catheters (Swinn and Fowler, 2001). Two-thirds of patients reported a triggering event at the onset of retention, most commonly surgery but also childbirth, UTI, or an acute medical condition. Many women note a long history of voiding difficulty prior to their initial episode of urinary retention (Swinn and Fowler, 2001). Subsequent investigations showed that women with an abnormal EMG often had a high urethral pressure profile and sphincter volume (Wiseman et al., 2002). The abnormality is thought to be a nonrelaxing striated urethral sphincter, which causes abnormally high urethral pressures and impaired voiding. Activation of sphincter afferents is likely to be having a reflex inhibitory effect on detrusor afferent and efferent activity, resulting in complete urinary retention and poor sensations of bladder fullness (Ramm et al., 2012). Our current understanding of the etiology of Fowler's syndrome is that it likely occurs due to upregulation of spinal enkephalins (Panicker et al., 2012), naturally occurring opiates, which reduce bladder sensation and negatively feed back to the sacral nerve roots, so that urethral sphincter sympathetic tone remains elevated and the PAG and PMC are not activated, even with large-volume bladder filling. The effect of upregulated spinal enkephalins is likely to be exacerbated by exogenous opiates.

The diagnosis is often difficult to establish and women with Fowler's syndrome see on average three consultants before their diagnosis is reached (Kavia et al., 2006). Although the urethral sphincter EMG findings are characteristic for this condition, in recent years two papers and two abstracts, one of which was a 10-year follow-up of the first, reported that these findings may be seen in the external urethral sphincter of apparently healthy women (Kujawa et al., 2001; Ramm et al., 2012; Tawadros et al., 2015). The number of participants in these studies were small, but they do raise some interesting questions about the specificity of these EMG findings to Fowler's syndrome, and also the effects of the menstrual cycle on EMG changes. The finding of CRDs and DBs in apparently asymptomatic young women suggests that only when the inhibitory signal is sufficiently strong will urinary retention occur. The EMG changes should therefore be considered with the clinical features before making a diagnosis of Fowler's syndrome. The finding of an elevated urethral pressure profile (> 92 – age cm water) or urethral sphincter volume (>1.8 cm3) aids the diagnosis (Wiseman et al., 2002). The finding of CRDs and DBs, however, remains prognostically useful as patients with these changes have improved outcomes following sacral neuromodulation (De Ridder et al., 2007).

The only currently useful long-term treatment for Fowler's syndrome is sacral neuromodulation, which has successful outcomes, with up to 70% of patients regaining the ability to void normally with postvoid residuals of ≤100 mL, with a follow-up of up to 10 years (De Ridder et al., 2007; Elneil, 2010). Sacral neuromodulation appears to work by overriding the negative feedback from the sacral nerves. On imaging studies of 6 women with sacral neuromodulation, the previously reduced activity in the PAG and other higher brain centers shows restoration of normal or near normal activity after sacral neuromodulation insertion (Kavia et al., 2010). A recent open-label pilot study of 10 women demonstrated that urethral sphincter injection of botulinum toxin was associated with improvement in their urinary symptoms and objective improvements on urodynamic testing, and this potentially represents a less invasive option with few side-effects (Panicker et al., 2016).

Somatic comorbidities have been reported in women with Fowler's syndrome. A retrospective study of the hospital records of 62 women with Fowler's syndrome found that almost a quarter of patients (24%) with Fowler's syndrome had functional neurologic symptoms, including loss of consciousness, limb weakness, sensory disturbance, and memory impairment (Hoeritzauer et al., 2015). There are no comparison data in patients with other urologic or uro-neurologic disorders; however, based upon population prevalence of 2–33 per 100 000 (Reuber, 2008) for dissociative seizure or 1.7% of the population for patients with multiple idiopathic symptoms (Engel et al., 2002), this represents a high degree of comorbidity burden. Further studies are required to explore the reasons for this, whether due to a long diagnostic limbo prior to diagnosis or possibly because patients with Fowler's syndrome are more likely to have functional somatic comorbidities. Patients with Fowler's syndrome may be missing a useful opportunity to treat their disorder in the context of other relevant comorbidities. In a separate prospective series of 62 patients treated with sacral neuromodulation, 26.6% of patients with Fowler's syndrome and 44% of patients with chronic idiopathic urinary retention screened with the Patient Health Questionnaire were defined as being at risk for somatization based upon their scores (De Ridder et al., 2007).

Fifty percent of patients with Fowler's syndrome suffered from unexplained chronic abdominopelvic, back, leg, or widespread pain (Hoeritzauer et al., 2015). A recent study of gynecologic pathology in patients with Fowler's syndrome found rates similar to that expected in the general population, so it is unlikely that these chronic pain syndromes were caused by an underlying undiagnosed pelvic pathology (Karmarkar et al., 2015).

PARURESIS

Paruresis, also called "shy" or "bashful" bladder syndrome, is defined by DSM-5 (DSM-5 300.23: American Psychiatric Association, 2013) as a social anxiety disorder (social phobia) characterized by fear and avoidance of urinating in public toilets when other individuals are present. It is characterized by a situation-specific voiding dysfunction which usually occurs in adolescence following an unpleasant experience such as being rushed to urinate or being teased or harassed (Hammelstein et al., 2005; Soifer et al., 2010). Awareness of others waiting for the toilet often further exacerbates symptoms. Paruresis is not associated with the fear of contamination (Vythilingum et al., 2002), and 20% of patients report no anxiety, but merely the inability to void in public toilets. Despite the subgroup with no anxiety, rates of psychologic comorbidity are quite high in the general paruresis population. Social anxiety disorders (29%), a major depressive episode (22%), alcohol abuse (14%), preparuresis obsessive compulsive disorder or significant problematic embarrassment all occur and should be sought (Vythilingum et al., 2002; Kaufman, 2005).

Paruresis is seldom investigated, and there is poor knowledge about the disorder in medical circles. However, it is associated with significant morbidity and patients report high levels of shame, limitations to activities such as traveling or dating, and professional work (Vythilingum et al., 2002). The prevalence and gender ratios are uncertain; however, men are more likely to seek treatment and respond to questionnaires. Prevalence varies depending on how the question is phrased, as many as 6% of the population are fearful of using a public toilet (Ruscio and Brown, 2008), but situational inability to void seems to occur in only about 3% of the population (Hammelstein et al., 2005). Perhaps because of its low profile or the embarrassment associated with the condition, only about 30% of individuals seek treatment. Paruresis is often triggered by the triad of close physical or psychologic proximity with the individual, the presence of either familiar persons or the presence of

strangers in the toilet, and temporary psychologic states, especially anxiety. Cognitive behavioral therapy with graded exposure techniques and biofeedback is the treatment offered for this condition (Rogers, 2003; Boschen, 2008; Soifer et al., 2010).

DYSFUNCTIONAL VOIDING AND HINMAN–ALLEN SYNDROME

Dysfunctional voiding is characterized by an intermittent or fluctuating urinary flow which occurs due to involuntary intermittent contractions of the striated urethral sphincter and/or levator muscles during voiding in otherwise neurologically intact individuals (Jeong et al., 2014; King and Goldman, 2014).

Despite this being primarily a problem of voiding, individuals with dysfunctional voiding, who are most often females, commonly present with symptoms of urgency and frequency. Incomplete bladder emptying is common, resulting in recurrent UTIs. Most patients have symptom onset from childhood.

The etiology is unclear; however, it is currently thought that dysfunctional voiding is a learned behavior in response to infection, trauma, detrusor overactivity causing stress incontinence, or psychologic factors (Karmakar and Sharma, 2014). Rates of depression and anxiety are greater than in asymptomatic controls (Fan et al., 2008) and dysfunctional voiding is more common in individuals with a history of sexual abuse (Ellsworth et al., 1995; Davila et al., 2003). Dysfunctional voiding is found in 2% of adults referred for urodynamic assessment, and the most common finding is a specific staccato pattern and dilated proximal urethra seen on voiding cystourethrogram (Glassberg and Combs, 2014). Treatment is primarily with biofeedback, which is thought to be successful in 60–90% of patients (Chin-Peuckert and Salle, 2001). However, a recent meta-analysis of all randomized studies of biofeedback (n = 5) for dysfunctional voiding in children has shown no benefit over controls (Fazeli et al., 2015). This may be due to poor trial data and the heterogeneity within the dysfunctional voiding group. Biofeedback is thought to be much more successful in patients with involuntary intermittent contraction of the levator muscles.

The more severe form of dysfunctional voiding, known as Hinman–Allen syndrome or nonneurogenic neurogenic bladder, is characterized by external urethral sphincter dysfunction, recurrent UTIs, and damage to the upper urinary tracts (Phillips and Uehling, 1993; Hinman, 1994). Hinman–Allen syndrome has been attributed to primarily psychologic causes since its inception. Children were described as having "failed personalities," and parental divorce and "family disarray" were felt to be contributing factors (Hinman and Baumann, 2002). Up to 40% of patients have severe urinary tract morbidity, resulting in chronic renal failure (Yang and Mayo, 1997; Silay et al., 2011). The focus on psychologic etiology has been questioned with the publication of 9 cases of babies under 30 months having features of severe dysfunctional voiding (Jayanthi et al., 1997; Al Mosawi, 2007; Chaichanamongkol et al., 2008). There are moves towards allying this condition more closely to syndromes of elimination disorders such as urofacial syndrome (Ochoa syndrome or hydronephrosis with peculiar facial expression) (Ochoa, 2004; Roberts et al., 2014). Urofacial syndrome is a genetic disorder with similar findings on investigation to Hinman–Allen syndrome, but additionally patients have a characteristic facies on smiling, akin to crying (Ochoa, 2004; Roberts et al., 2014; Tu et al., 2014). It occurs due to an abnormality on chromosome 10 in the region of 10q23-q24 which codes for the genes HSPE2 or LRIG2 (Ochoa, 2004; Roberts et al., 2014). Only a small genetic study of 22 patients with Hinman–Allen syndrome has been performed and no abnormalities were detected; however, further studies are required (Bulum et al., 2015).

OVERACTIVE BLADDER

OAB is a syndrome defined by the International Continence Society as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence in the absence of UTI or other obvious pathology" (Abrams et al., 2002). The diagnosis is made based upon the patient's self-reported symptoms of urinary urgency, frequency, nocturia, and/or urgency urinary incontinence. Whilst urgency is difficult to measure clinically, urinary frequency is defined as voiding more than eight times per day, nocturia in OAB as passing small amounts of urine several times overnight, and urgency urinary incontinence can be recorded using a diary (Gormley et al., 2015). There are several conditions that may result in these symptoms; however, in a subset of individuals with "idiopathic" OAB, the cause remains obscure despite extensive investigations.

Patients with OAB report considerable morbidity. They have significantly worse health-related quality of life, are less likely than individuals without OAB to be employed, and may report sexual dysfunction (Ergenoglu et al., 2013; Tang et al., 2014). Patients with urinary incontinence (wet OAB) are more severely affected than those without incontinence (dry OAB). Disease-specific and global quality-of-life scores are lower and patients are comparatively less likely to be employed, less productive, and have greater health resource allocation (Tang et al., 2014). OAB is a long-term problem for the majority of patients and is underreported and undertreated (Getsios et al., 2005; Ergenoglu et al., 2013).

OAB is associated with high levels of anxiety and depression (Matsuzaki et al., 2012; Matsumoto et al., 2013; Vrijens et al., 2015). A recent systematic review reported a positive association between depression and OAB in 26/35 studies, and between anxiety and OAB in 6/9 studies. There was strong evidence of OAB developing in patients who had depression, with an odds ratio 1.15–5.78, although it was not possible to assess causality (Vrijens et al., 2015). The occurrence of OAB symptoms is associated with worse quality-of-life scores, embarrassment, and social isolation (Wagg et al., 2007; Tang et al., 2014).

Anxiety in healthy individuals can cause increased urinary frequency and urgency. Charcot and contemporaries used the term "pollakiuria" to describe "frequent and repeated micturition which one experiences under the stress of an emotion" (Dejerine and Gauckler, 1913). Animal studies suggested that chronic stress in anxiety-prone animals resulted in bladder hyperalgesia, which may contribute to the pathogenesis of LUT symptoms in affective disorders (Lee et al., 2015).

There is limited literature exploring LUT symptoms in patients with pathologic anxiety disorders. In one longitudinal community study, anxiety appeared to have a causative role in the occurrence of urge incontinence (Perry et al., 2006). Females aged over 40 years old were asked through a community postal survey about anxiety and depression using the Hospital Anxiety and Depression scale, and urinary symptoms, and followed up for a year. It was observed that the presence of urge incontinence and urinary frequency predicted the development of anxiety and depression. Moreover, anxiety predicted urge incontinence, whereas depression did not. In contrast, stress incontinence did not predict either anxiety or depression (Perry et al., 2006).

Four randomized controlled trials demonstrated that successful treatment of OAB resulted in a significant improvement in patients' affective symptoms (Vrijens et al., 2015). The relationship between depression, anxiety, and OAB is postulated to be due to altered serotonin and norepinephrine levels causing OAB. This is on the basis of animal models demonstrating that

serotonin and norepinephrine have a modulatory effect on Onuf's nucleus, which prevents accidental voiding when abdominal pressure increases, that serotonin inhibits the parasympathetic voiding activity and stimulates sympathetic activity, and that frequency is reduced after administration of selective serotonin reuptake inhibitors (Redaelli et al., 2015).

An alternative mechanism is through the central effect of increased corticotropin-releasing factor, released due to dysregulation of the hypothalamic–pituitary–adrenal axis, causing both bladder and mood symptoms, as seen in rodent models (Wood et al., 2013).

Recently three studies investigated functional somatic syndrome comorbidities in OAB and found irritable-bowel syndrome (IBS) occurring in up to one-third of patients with OAB with a background population rate of 20% (Matsumoto et al., 2013). Patients with FM were significantly more likely to have OAB and more severe OAB symptoms correlated to more severe FM symptoms. There was a significant overlap between OAB and functional dyspepsia in population-based studies (Persson et al., 2015). A history of sexual abuse was found to be associated with urinary frequency, urgency, and nocturia in at least three studies (Davila et al., 2003; Fitzgerald et al., 2007; Link et al., 2007). Among these studies, one fulfilled the Bradford Hill criteria for causality (Link et al., 2007).

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME AND FUNCTIONAL SOMATIC SYNDROMES

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined by the Society for Urodynamics and Female Urology as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable cause" (Hanno et al., 2011). Voiding helps to reduce pain (Hanno et al., 2011). Patients with IC/BPS have a worse quality of life compared to healthy individuals, as well as patients with OAB, due to effects on emotion, social limitations, and personal relationships (Kim and Oh, 2010).

Several studies have shown that patients with IC/BPS report comorbidities with functional somatic disorders such as IBS, FM, chronic fatigue syndrome (CFS), and vulvodynia (Aaron and Buchwald, 2001; Buffington, 2004; Rodríguez et al., 2009). Moreover, patients reporting an increasing number of functional somatic syndromes, particularly FM, CFS, and IBS, have a greater risk for IC/BPS (Warren et al., 2011). In a systematic review, 16 of 25 publications found overlap between painful urologic pelvic pain syndromes and nonurologic syndromes (Rodríguez et al., 2009). Four studies were of patients with IC, and these showed higher rates of IBS (22.5% vs. 7% of controls), higher rates of backache, dizziness, arthralgia, abdominal cramps, and headache than controls, generalized pain in 27% vs. 7% of controls, and the women with IC were 11 times more likely to be diagnosed with IBS compared with controls. In patients who had FM, 12% of patients met the criteria for IC, and in patients with chronic pelvic pain, IBS was found in 22.4% of patients, 40% of whom had IC. Twin studies found that twins with fatigue were 2–20 times more likely to have IC than twins without fatigue (Rodríguez et al., 2009). Most of the studies exploring the association of LUT symptoms and functional somatic syndromes have focused on pain disorders and therefore the association of IC/BPS and functional somatic symptoms may be overrepresented in the literature.

There is also evidence for sexual abuse, high levels of depression, and panic disorder in patients with IC/BPS (Peters et al., 2007; Clemens et al., 2008). Several studies have investigated the association between abuse and IC/BPS. Physical, mental, or sexual abuse was found in 37% of patients with IC vs. 24% of symptom-free controls, and sexual abuse occurred in 18 vs. 8% in a population responding to

a survey (n = 215 vs. n = 464 symptom-free controls) and 25/76 women (33%) seen in clinic (Peters et al., 2007).

There is no definitive treatment for IC/BPS. Treatment is tailored to the individual patient, with holistic multimodal multidisciplinary input to maximize efficacy. First-line treatments include stress reduction, patient education, use of nonprescription analgesics, pelvic floor relaxation, and dietary manipulation (De Bock et al., 2011).

Oral medications are generally the first-line treatment therapy, including antiallergics, amitriptyline, pentosan polysulfate sodium (Elmiron) and immunosuppressants. The choice of analgesic should be made in collaboration with a specialist pain management team. In case of failure of oral therapy, intravesical drugs (local anesthetics, hyaluronic acid, heparin) are administered; the intravesical route improves drug bioavailability, establishing high drug concentrations at the target, and is associated with fewer systemic side-effects. Disadvantages include the need for intermittent catheterization, which can be painful in BPS patients, cost, and risk of infection. Although bladder hydrodistension is a common treatment for BPS, the scientific justification is scanty. It can be a part of the diagnostic evaluation, but has a limited therapeutic role. Botulinum toxin A may have an antinociceptive effect through bladder afferent pathways, producing symptomatic and urodynamic improvement (Engeler et al., 2015). Sacral neuromodulation is associated with improvements in the symptoms of refractory BPS, with good long-term success seen in 72% (Engeler et al., 2015). Endourologic destruction of bladder tissue aims to eliminate urothelial lesions, mostly Hunner's ulcers, and can be helpful in the relief of pain and urgency. Ablative organ surgery should be a last resort and should be performed only by surgeons knowledgeable about BPS. Unfortunately, no single treatment seems to work for patients over a prolonged period of time (Hanno et al., 2011).

The etiology of IC/BPS is unclear and, whilst many studies have investigated association, causality remains elusive. Discussion of etiology involves physiologic and psychologic hypotheses (Aaron and Buchwald, 2001; Warren, 2014). The current favored s that central brain processing of pain is different in patients with IC than in healthy controls. A recent imaging study using voxel-based morphometry of 33 patients with IC and no other comorbidities showed increased gray matter in the supplementary motor area, the superior parietal lobule/precuneus bilaterally, and the right primary somatosensory cortex. In the right primary somatosensory cortex volume changes also correlated with clinical measurement of pain, anxiety, and urologic symptoms (Kairys et al., 2015). It was suggested by the authors that increased gray matter in the precuneus might be caused by alterations in the higher pain connections in a similar manner to those seen in FM. Alternatively, the increases could be due to bottom-up changes to the higher-center connections caused by prolonged severe pain.

FREQUENCY OF UROLOGIC SYMPTOMS IN FUNCTIONAL/PSYCHOGENIC DISORDERS

Although rarely reported in the literature, LUT symptoms have been observed in patients with functional neurologic disorders. The only study of LUT dysfunction in patients with functional neurologic disorders is a retrospective review of 150 patients diagnosed with definite or probable functional movement disorders between 2006 and 2014 from the National Hospital for Neurology and Neurosurgery in London (Batla et al., 2016). Patient notes were screened retrospectively and patients with LUT symptoms were administered questionnaires for urinary symptoms and LUT-related quality of life. Thirty of the 150 patients with functional movement disorders had LUT symptoms; 20 of the 49 (41%) patients with fixed dystonia, 8 of the 57 (14%) patients with tremor,

and 2 of the 14 (14%) patients with mixed movement disorders. LUT questionnaires were completed by 22 of the 30 patients, all of whom were female, the majority of whom had symptoms of OAB (n = 14). The remaining patients complained of stress urinary incontinence (n = 5) and low stream (n = 3). Opiate use was correlated with low stream (p = 0.02). The 5 most severely affected patients, 3 of whom had urinary retention and recurrent UTIs, and all of whom were using opiates, underwent urodynamic evaluation. No clear pattern of abnormality was evident and no neurologic or urologic cause was found. The 3 patients with urinary retention were initially managed with suprapubic catheterization and then had successful outcomes with sacral neuromodulation. Patients with fixed dystonia had the most severe symptoms, but the quality of life for all patients was negatively affected. LUT symptoms in other neurologic disorders are known to negatively affect quality of life; further studies in patients with functional neurologic disorders are required (Panicker and Fowler, 2015).

OPIATE USE AND LUT DYSFUNCTION

Pain is a well-known comorbidity in many functional conditions and high rates of prescription opiate use have been described (Pearson et al., 2014). The association between opiate use and LUT dysfunction is less well known amongst general physicians and patients, and could be contributing to LUT dysfunction in patients with neurologic and urologic disorders (Elneil, 2010; Panicker et al., 2012). In a study of 61 consecutive female patients reviewed at Queen's Square with unexplained urinary retention, 24 patients were taking regular opiates, 3 of whom were taking more than one opiate. Five of these patients were diagnosed with Fowler's syndrome, but 13 of the patients had no known cause for their voiding dysfunction. Patients had been prescribed opiates for unexplained predominantly abdominopelvic, musculoskeletal, or mechanical pain syndromes(Panicker et al., 2012). On discontinuing opiates, 2 of the 24 patients reported improvement in LUT symptoms. Intravenous (n = 72) (Malinovsky et al., 1998) and intrathecal (n = 45) (Kuipers et al., 2004) opiates have been shown to reduce bladder sensation, increase residual volume, and affect the urge to void and the ability to micturite in some patients, with dose-dependent effects (Kuipers et al., 2004). Opiates are thought to affect the bladder peripherally by increasing parasympathetic tone and centrally acting on spinal enkephalins and mu receptors in the PAG (Matsumoto et al., 2004).

Is there an association between LUT dysfunction and functional disorders?

The term "functional disorders" encompasses overlapping syndromes including CFS, FM, IBS, myofascial pain, and temporomandibular joint disease (Clauw, 2010). The overlap of symptoms is well documented (Wessely et al., 1999; Clauw and Crofford, 2003; Wessely and White, 2013). The way in which these conditions overlap with functional disorders seen in neurologic practice, such as functional movement disorder and dissociative (nonepileptic) attacks, is also now well documented.

Reflecting on the LUT dysfunction discussed in this chapter and its relationship with functional disorders, the initial problem is the dearth of studies that have attempted to specifically answer the question as to whether functional urologic disorders could share an etiology with functional neurologic and somatic disorders.

It is known that the LUT is regulated by a complex interconnected network of higher centers involved in arousal, focus, understanding of safety and social propriety, emotion and motor activity. This system is informed by afferent signals from the LUT via the spinal cord, and the PAG and PMC are important brainstem centers involved in the coordination of urethral, pelvic floor, and detrusor

contractions. There are many points at which this network can go wrong, yet present with a limited repertoire of LUT symptoms. Understanding of the bladder–brain axis is exponentially increasing through basic, clinical, and imaging science. Increasing knowledge of neural networks has changed the understanding of disease from simply biologic or psychologic processes to an awareness of disease as something spanning both, and affected by environment, beliefs, as well as genes, which all come together to create the patient's disease phenotype. In functional neurologic disorders, the field is moving away from the dualistic understanding of psychogenic versus organic etiology. This allows a functional model to emerge that comfortably incorporates psychologic and physiologic disturbances.

Considering whether these disorders have features which overlap with functional somatic syndromes, such as IBS, FM, or hyperventilation syndrome, the criteria from Wessely et al. (1999) will be used.

Patients with one functional syndrome frequently meet diagnostic criteria for other syndromes

The prevalence of other functional disorders in patients with OAB, IC, paruresis, and Fowler's syndrome has been discussed above.

Sex

IC, idiopathic OAB syndrome, Fowler's syndrome, and dysfunctional voiding affect predominantly women, whereas paruresis is likely to affect men more often. Some functional neurologic disorders such as functional propriospinal myoclonus have a male preponderance (van der Salm et al., 2014).

Emotional problems

Depression and anxiety are reported more in patients with idiopathic OAB, IC, paruresis, dysfunctional voiding, and Fowler's syndrome compared to healthy controls. However, the impact of a chronic LUT disorder on mood requires further study before attempting to make an association between psychologic comorbidities and urologic disorders.

Physiology

Much of the current research of IC, idiopathic OAB, and Fowler's syndrome hypothesizes that there is a central mechanism (brain ± spinal cord) causing the disorder rather than an abnormality which is solely bladder-based (Kavia et al., 2010; Tadic et al., 2011; Kairys et al., 2015). Paruresis is treated with cognitive-behavioral therapy, recognizing that a central mechanism of inhibition exists that must be unlearned.

History of childhood abuse or neglect

While this is frequently referenced in older psychogenic urinary retention literature, there are few studies which explore this, except in the IC and dysfunctional voiding literature (Ellsworth et al., 1995; Davila et al., 2003; Mayson and Teichman, 2009). In the Boston Area Community Health study (n = 5506), sexual and physical abuse and the prevalence of urinary frequency, urgency, and nocturia met the Bradford Hill criteria to suggest causality (Link et al., 2007). Given the frequency of these urinary symptoms in the population, background rates of childhood and adult adversity and potential pathophysiologic mechanisms should be investigated in a range of neurologic, gynecologic, and functional urologic conditions.

Many patients with idiopathic functional urologic disorders share similar characteristics with patients who have functional somatic disorders. The LUT is unique amongst visceral organs because of the highly organized central neural network that regulates its functions and affords higher-level voluntary input, and therefore it is likely that there exists an association between LUT dysfunction and functional syndromes. Though tests such as urodynamics help to uncover the pathophysiologic correlate of LUT symptoms, the test is unable to provide information about the etiology or behavioral underpinnings responsible for the LUT dysfunction. Studies are therefore required that are designed to specifically evaluate the nature of the association between LUT dysfunction and functional syndromes and explore causality. Recognizing the interface between emotion, motivation, memory, and LUT functions would allow for a more comprehensive approach to patients presenting with functional disorders.

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Conclusions: The book chapter developed my knowledge of the literature linking uro-neurological and functional disorders and my understanding of urological language. A major initial difficulty is the nomenclature. Although there are guidelines on what urology terminology should be used[18], papers intermix different terms which mean the same thing (detrusor overactivity, overactive bladder, irritable bladder). There are also terms which mean a direct correlation is found with a urodynamic test (detrusor sphincter dyssynergia) but equally terms which are not tied to a urodynamic diagnosis, such as overactive bladder. Overactive bladder can be diagnosed due to detrusor overactivity seen on urodynamics but can also be diagnosed when urodynamics do not show any abnormality based on symptoms of bladder overactivity. For the majority of patients diagnosed with conditions which may be functional such as overactive bladder syndrome, urodynamics are not undertaken.

There is additional complexity with nomenclature in relation to functional disorders. There is a category within urology called 'functional urology' which describes any disorder not caused by structural pathology. In this functional urology category are things like stress incontinence due to dysfunction of the pelvic floor but also unexplained syndromes, like dysfunctional voiding or Fowler's syndrome. Some 'functional' urological disorders such as dysfunctional voiding and Fowler's syndrome seem to have overlap with functional neurological disorders whilst others do not.

A major component of writing the chapter was understanding the bladder- brain network and how it may malfunction either due to bottom up or top down processes leading to a functional bladder disorder. During the writing process I investigated the uncertainty of a urological diagnosis being tied to a structural or functional cause. I also investigated ideas about mechanisms and risk factors for the urological disorders widely accepted to be functional, such as bladder pain syndrome and dysfunctional voiding. I found the point at which 'psychogenic' bladder disorders became seen as 'unscientific' and began to be avoided as a diagnosis.

Utilising this literature, I was able to start generating ideas about potential clinical features relevant to diagnosis, mechanism and aetiology linking uro-neurological and functional disorders.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Exploration of the field

Paper Two: What is the Incidence of Cauda Equina Syndrome? Hoeritzauer I[2,3] MRCP, Wood M[1,2], Copley P MRCS [1,2,3], Demetriades AK[1,3] FRCSEd and Woodfield J[1,2,3]

Introduction: Acute onset bladder disorders occurring in patients who presented as though they had cauda equina syndrome is the main focus of my PhD study, but I wanted to understand my control group with structural causes better. My **Aim 2** was: *To describe associated clinical features relevant to diagnosis, mechanism and aetiology in patients with Scan negative and scan positive CES*. I did this by carrying out a systematic review of the incidence of CES. Given the importance placed upon CES medico-legally and the large financial penalties when the diagnosis is delayed or missed it, I initially presumed the condition was well defined, had clear international diagnostic standards and clear incidence figures in various populations, such as community incidence and incidence in patients with back pain, which would be possible to elicit form the literature.

What is the Incidence of Cauda Equina Syndrome? A Systematic Review

Authors

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Exploration of the field

Abstract

Purpose

A systematic review of the incidence of cauda equina syndrome (CES). This research sought to establish the populations in which CES presents and whether incidence of CES varies across populations. Accurate incidence of CES could be used to inform investigation and management of individual patients as well as healthcare service design and delivery including out of hours imaging arrangements.

Methods

A systematic literature search was undertaken to identify original studies reporting the incidence of CES as described in the protocol registered with PROSPERO (CRD42017065865).

Results

1281 studies were identified and 26 studies were included in the review. The incidence of CES was 0.3-0.5 per 100,000 per year in two asymptomatic community populations, 0.6 per 100,000 per year in an asymptomatic adult population, and 7 per 100,000 per year in an asymptomatic working age population. CES occurred in 0.08% of those with lower back pain presenting to primary care in one study and a combined estimate of 0.27% was calculated for four studies of those with lower back pain presenting to secondary care. In 17 studies of adults with suspected CES, 19% had radiological and clinical CES.

Conclusions

CES occurs infrequently in asymptomatic community populations and in only a small proportion of those presenting with symptoms.

Key Words: Cauda equina Syndrome; Incidence; Systematic Review; Epidemiology; Population

Introduction

Cauda equina syndrome (CES) is an emergency with potentially significant consequences including bladder, bowel or sexual dysfunction, numbness, weakness, or pain.[1,2] Timely operative intervention can prevent symptom progression and potentially reverse existing symptoms.[3-5] Due to the high medical, personal, social, and legal costs, prompt investigation with MRI is recommended when CES is suspected.[6,7] In the United Kingdom (UK), patients are often transferred for investigation between

sites due to a lack of Magnetic Resonance Imaging (MRI) facilities operating outside normal working hours in district general hospitals and the potential need for specialist spinal or neurosurgical intervention.[8,9] However, many patients who present with clinical symptoms in keeping with CES will not have cauda equina compression on MRI[10] which complicates planning service design and delivery to encompass the needs of the whole population. Establishing the incidence of CES and populations at risk of CES would facilitate planning imaging and operative pathways for patients with suspected CES.

This systematic review aims to identify studies reporting the incidence of CES, describe the populations in which the incidence of CES has been studied, and any differences in incidence between these populations.

Materials and Methods

A systematic review was undertaken as described in the study protocol 'Incidence of Cauda Equina Syndrome: Systematic Review Protocol' registered with the International Prospective Register of Systematic Reviews (PROSPERO), reference number CRD42017065865, available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=65865.

Studies were included if they reported original data and assessed human subjects with CES. For inclusion, studies had to state the incidence of CES or the proportion of the studied population with CES, or provide sufficient figures for this to be calculated. We defined CES as a clinical diagnosis of CES with radiological cauda equina compression. Studies including only patients with a clinical CES type syndrome without radiological cauda equina compression were excluded. Studies of radiological lesions of the cauda equina or cauda equina compression without clinical features of CES were also excluded. Reference populations could be either asymptomatic populations or symptomatic populations investigated and found not have CES. Case series or studies without a reference population where the incidence of CES could not be established were excluded. Case series of operated lumbar discs, spinal stenosis, or iatrogenically caused CES were also excluded to ensure all included studies were applicable to an initial presentation with suspected CES. There were no

restrictions on the language or year of publication, the type, location, or age of the population studied, or whether the study was published or unpublished.

The final database search was carried out on the 30th July 2018 in Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily 1946 to July 27, 2018, Ovid,EMBASE 1980 to 2018 Week 31 and Scopus. The MEDLINE search strategy was:

1. Polyradiculopathy/
2. cauda equina.ti,ab.
3. Cauda Equina/
4. 1 OR 2 OR 3
5. Incidence/ or Prevalence/
6. Epidemiology/
7. (incidence* or prevalen* or epidemiolog* or frequenc* or rate* or ocurrence*).ti,ab
8. 5 OR 6 OR 7
9. 4 AND 8

No limits were applied. EMBASE and Scopus search strategies are in the supplementary material.

Duplicate studies were eliminated and then all abstracts and titles were screened by two reviewers independently (JW, IH, PC, or MW). Where reviewers disagreed, discussion with a third or fourth reviewer was undertaken to provide a consensus. The full text of all included abstracts was retrieved and independently reviewed by two reviewers (JW, IH, PC, or MW). Any disagreements were resolved through discussion with a third or fourth reviewer. The reference lists of all included studies were screened independently by two reviewers to identify any additional relevant papers. Studies citing the included studies were identified using Scopus and also screened by two reviewers independently. Multiple papers or abstracts reporting the same study were treated as a single study.

Data were extracted from each included paper by two reviewers independently and all instances where data did not match were checked by a third reviewer (JW, IH, PC, or MW). The data items extracted were: incidence of CES in the population (including confidence intervals and standardised estimates where given); number of cases of CES; size of the reference population; description of the

population (location, demographics, time period studied, inclusion criteria); and definition of CES used in the study including any sub-categorisation.

Study quality and risk of bias was assessed using the following questions adapted from those used in prior systematic reviews of incidence of neurological conditions[11,12] based on published quality assessment guidelines.[13,14] As there are no validated diagnostic criteria for CES, studies were assessed on whether they described the definition of CES used.

1. Was the target population clearly described?
2. Were cases ascertained by survey of the entire population or by probability sampling?
3. Was the sample size >300 subjects?
4. Was the response rate >70%?
5. Were non-responders clearly described?
6. Was the sample representative of the population?
7. Were data collection methods standardised?
8. Were the diagnostic criteria used to assess the presence of disease described?
9. Were estimates of incidence given with confidence intervals?
10. Were standardised estimates reported?

The incidence of CES was reported per 100,000 population per year in asymptomatic populations. The percentage with CES was reported in symptomatic populations. Statistical heterogeneity was assessed using the Q statistic and the I^2 test.[15] Proportions were combined using the inverse variance method and a DerSimonian-Laird estimator for τ^2.[16] Confidence intervals for individual studies were calculated using Clopper-Pearson confidence intervals.[17] All statistics were calculated using the meta package in R version 3.4.0.[18]

Results

The studies identified and excluded at each stage and reasons for exclusion are shown in the PRISMA flow diagram[19] in Figure One. Of the 1281 studies identified after removal of duplicates, 26 were included. Four studies reported the incidence of CES occurring in asymptomatic community

populations.[20-23] Twenty-three studies investigated the incidence of CES in patients presenting with symptoms.[8,9,22,24-43] One study was included in both of these categories.[22]

Figure 1. PRISMA Flow Diagram. Studies identified, included, and excluded.

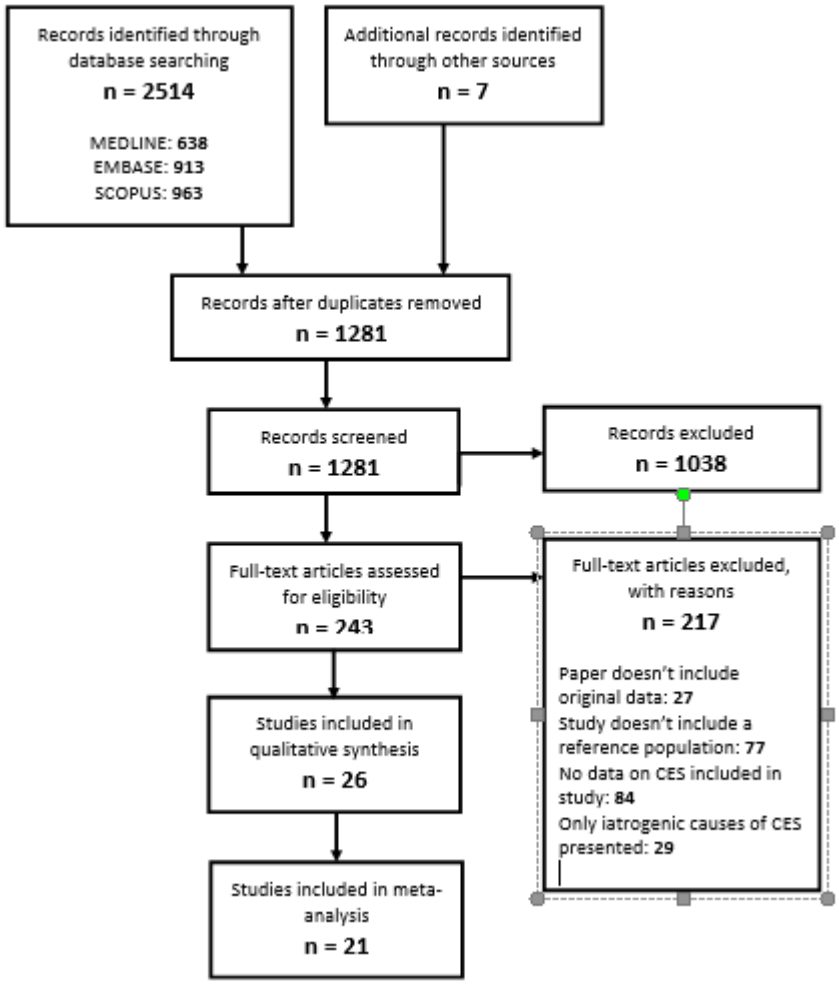

Table 1.
Incidence of Cauda Equina Syndrome (CES) in Asymptomatic Community Populations

Study	Dates & Time Period	Reference Population	Definition of CES	Total Population	Total Cases	Cases per 100,000 per year (95%CI)
Hurme 1983	1975-1979 5 years	Hospital catchment population, Finland	Undergoing operation for CES	455,000	11	0.48+
Podnar 2007	1996-2004 8 years	Population of Slovenia	History, examination, neurophysiology & radiology	1,989,198	67	0.34
Schoenfeld 2012	2001-2010 9 years	American Military Database, USA	ICD code	13,871,384 person years$	976	7
Reito 2018	2012-2014 3 years	Hospital catchment population, Finland	ICD code SBNS guideline subcategories - based on clinical records	661,902 adult person years$	4	0.6 (0.16-1.5)

(ICD: International Classification of Diseases; +: calculated from values given in paper; $: reported as total number of people in the population in the total number of years during the study time period)

Population Incidence of CES

Study details and incidence figures for the four studies reporting the incidence of CES in community dwelling asymptomatic populations are shown in Table 1. Hurme *et al*[20] and Podnar *et al*[21] investigated European community dwelling populations and identified similar incidence figures of 0.48 and 0.34 cases per 100,000 population per year respectively despite different methods of case ascertainment. Hurme *et al*[20] identified cases of CES using surgical records, whilst Podnar *et al*[21] used a comprehensive clinical and neurophysiological assessment at a rehabilitation centre. Reito *et al*[22] reported the incidence in an only adult population and found a slightly higher incidence of 0.6 per 100,000 adult population per year. Schoenfeld *et al*[23,44] studied an American military personnel healthcare database and found a higher incidence of 7 per 100,000 population per year in this working age population. Reito *et al*[22] was the only study to divide CES into sub-categories. Two patients had CES with retention and two patients had incomplete CES making the incidence of each subtype 0.30 per 100,000 per adult population per year. Both Reito *et al*[22] and Schoenfeld *et al*[23] used coding to identify cases of CES. Reito *et a*[22]*l* also reviewed clinical notes of the identified cases.

Meta-analysis of the incidence estimates was not undertaken due to the heterogeneity in the reference populations studied and the methods of CES case ascertainment.

Table 2:
Incidence of Cauda Equina Syndrome (CES) in Patients Presenting with Back Pain

Study	Dates & Time Period	Reference Population	Definition of CES	Total Population	Total Cases	Proportion with CES (95% CI)
Henschke 2009	2003-2005 20 months	Primary Care, Australia	Rheumatologist assessment (history, exam, tests)	1172	1	0.08% (0.0-0.5%)
Thiruganasam-bandamoorthy 2014	2009-2010 3 months	Adults, ED, Canada	Clinician determined	329	1	0.30%
Kiberd 2018	* 7 years	ED, Canada	*	38714	57	0.15%
Premkumar 2018	2005-2016 11 years	Spinal surgeon, US	ICD code	9940	36	0.36%
Reito 2018	2012-2014 3 years	Adults, ED, Finland	ICD code SBNS guideline subcategories – based on clinical records	900 visits 737 patients	4	0.44% per visit 0.54% per patient

(SBNS: Society of British Neurological Surgeons; ED: Emergency Department; ICD: International Classification of Diseases; *: not stated in paper)

Incidence of CES in Patients with Back Pain

Five studies reported the proportion of patients presenting with non-traumatic lower back pain who were found to have CES.[22,34,37,39,43] Study findings are shown in Table 2. Henschke et al[34] found 0.08% of adults presenting to primary care in Australia with lower back pain were diagnosed with CES by the study rheumatologist using clinical assessment and investigation. The other four studies investigated patients presenting to secondary care and reported proportions between 0.15-0.54%.[22,37,39,43] The diagnosis of CES was determined by ICD code in two studies,[22,39] the clinician in one study.[43] and the method was not reported in one study.[37] Study estimates for the proportion with CES in those presenting to secondary care with non traumatic lower back pain were combined using a random effects model to give an estimated proportion of 0.27% (95% CI: 0.14-0.54%). Study

estimates and confidence intervals are shown in the forest plot in Figure 2. There was a high level of statistical heterogeneity with I^2=85.2% (95% CI: 63.3%-94.0%) and Q=20.2 (p<0.001).

Figure 2. Forest plot. Proportion and number (events) of patients with cauda equina syndrome amongst those presenting with non traumatic lower back pain to secondary care. Summary proportion calculated using a random effects model

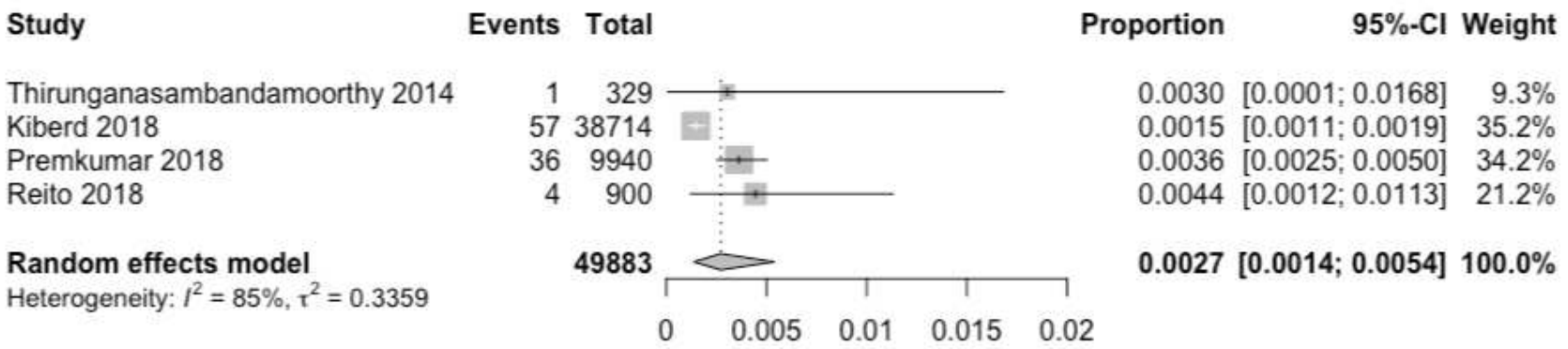

Table 3:
Incidence of Cauda Equina Syndrome (CES) in Patients Presenting with Suspected Cauda Equina Syndrome

Study	Dates & Time Period	Reference Population - Potential CES	Definition of CES	Total Population	Total Cases	Proportion with CES (95% CI)
Bell 2007	* 4 months	MRI for ?CES, Neurosurgery, UK	MRI CE compression	23	5	21.7%
Crocker 2008	2 years	OOH MRI for ?CES, Neurosurgery, UK	Surgery for CES	82	27	32.9%
Demetriades 2009	2008 1 year	OOH MRI for ?CES, Neurosurgery, UK	Disc on MRI & surgery for CES	33	10	30.3%
Domen 2009	2003-2007 5 years	Urgent MRI for ?CES Neurology/ED, The Netherlands	Radiology report MRI CE compression	58	8	13.8%
Rooney 2009	2004 10 months	MRI for ?CES, Neurosurgery, UK	Surgery for CES	66	16	24.2%
Balasubramanian 2010	2008 1 year	MRI for ?CES, Spinal Surgery, UK	Radiology report >75% canal compromise	80	15	18.8%
Thangarajah 2011	2006-2007 1 year	Urgent spinal MRI, Teaching Hospital, UK	*	81	0	0%
Gooding 2013	2008 1 year	MRI for ?CES, Hospital with Spinal Unit, UK	Radiology report CE compression	57	13	22.8%
Haworth 2013	2009-2011 3 years	OOH MRI for ?CES, Neurosurgery, UK	MRI CE compression	162	39	24.1%
Sideris 2014	2010-2013 4 years	?CES, Neurosurgery, UK	Clinical and radiological CES	663	80[+]	12.0%
Ahad 2015	2012-2013 8 months	Urgent spinal MRI, Hospital, UK	MRI CE compression	79	5	6.3%
Blades 2015	2008-2014 7 years	?CES, Spinal Unit, UK	MRI CE compression	344	137	40%
Hoeritzauer 2015	2013-2014 6 months	Urgent MRI for ?CES Spinal Unit, UK	MRI CE compression	18	7	38.9%
Hoeritzauer 2017	2013-2014 16 months	?CES, Neurosurgery, UK	MRI CE compression	290	91	31.4%
Kostusiak 2018	2014-2017 4 years	OOH MRI for ?CES, Neurosurgery, UK	Radiology report CE compression	323	15	4.6%
Hussain 2018	2013-2014 14 months	?CES, Neurosurgery, UK	>50% canal compromise on MRI	250	32	12.8%

Banerjee 2018a	2014- 2016 3 years	?CES, District Hospital, UK	MRI CE compression	43	7	16.3%
Banerjee 2018b	2012 – 2017 5 years	Children (0-15yrs), ?CES, District Hospital, UK	MRI CE compression	15	0	0%
(CE: cauda equina; MRI: magnetic resonance imaging; OOH: out of hours; ED: Emergency Department; *: not stated in paper; +: calculated from paper)						

Incidence of Confirmed CES in Patients Suspected of CES

Eighteen studies reported the proportion of patients presenting with signs and symptoms suspicious for CES who had clinical and radiological confirmation of CES. The study details are shown in Table 3. Eleven studies included only patients undergoing MRI for suspected CES.[8,24,25,28,30-33,35,38,40,42] The other six studies stated they included all patients referred with suspected CES.[9,26,27,29,36,41,45] All studies assessed populations referred to either secondary or tertiary care. Banerjee et al[27] studied only children. All other studies included adult populations but did not state whether they specifically excluded paediatric patients. A diagnosis of CES was established by cauda equina compression on MRI or operative intervention for CES. Only two studies described findings on MRI defining a diagnosis of CES and this was more than 50% canal compromise in one study[9] and more than 75% in another. Three studies stated that cauda equina compression was determined by the reporting radiologist but did not state the criteria used.[31,32,38] The cause of cauda equina compression was described in six studies. Demetriades et al[30] only included disc prolapses. Five studies included all or some of disc prolapses, tumours, trauma, and haematoma.[8,24,29,31,32] One study discussed subtypes of CES (with urinary symptoms, or incomplete) but did not report the numbers in each group.[29] None of the other studies used subcategories or descriptors. The proportion with confirmed CES in those presenting with suspected CES ranged from 0% to 40% in the eighteen studies. We excluded the study that included only children,[27] and combined the other estimates using a random effects model to give an overall estimate of confirmed CES in 18.9% (95% CI:13.6-25.6%). The forest plot is shown in Figure Three. There was a high level of heterogeneity in the study designs and the statistical heterogeneity was high with I^2 = 91.9% (95% CI 88.6-94.3%) and Q = 197 ($p<0.001$).

Figure Three. Forest plot. Proportion and number (events) of patients with confirmed cauda equina syndrome amongst those referred to secondary or tertiary care facilities for assessment for possible cauda equina syndrome. Summary proportion calculated using a random effects model.

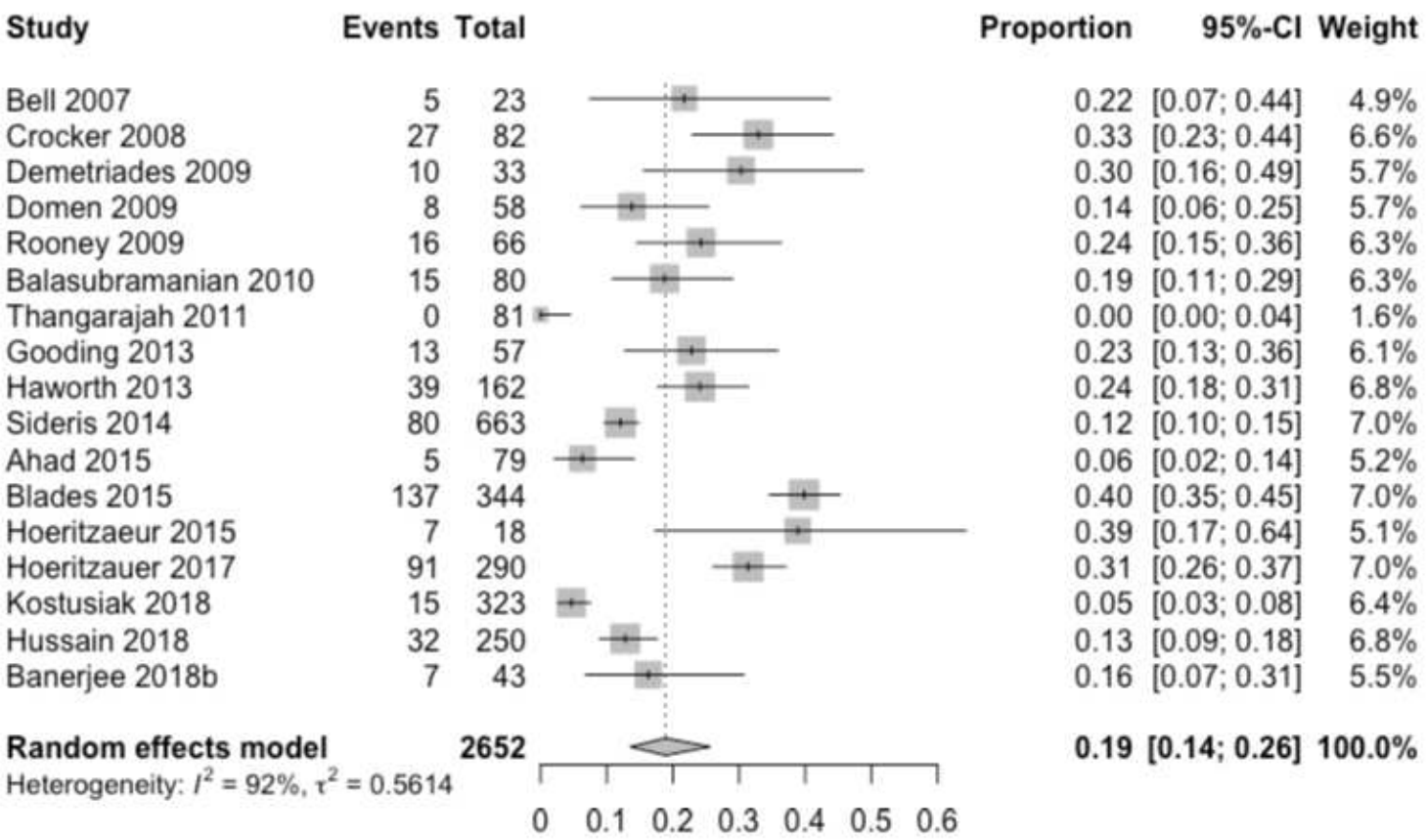

Table 4: Study Quality and Risk of Bias in Included Studies										
Study	**Target population clearly described**	**Cases from entire population probability sampling**	**Sample size >300**	**Response rate >70%**	**Non-responders clearly described**	**Sample representative**	**Standardised data collection**	**Diagnostic criteria described**	**Estimates given with confidence intervals**	**Standardised estimates reported**
Hurme 1983	Y	Y	Y	?	N	Y	Y	N	N	N
Podnar 2007	Y	N	Y	?	N	Y	Y	Y	N	N
Schoenfeld 2012	Y	Y	Y	?	N	Y	Y	Y	N	N
Reito 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Henschke 2009	Y	N	Y	?	N	Y	Y	Y	Y	N
Thiruganasamb-andamoorthy 2014[1]	Y	Y	Y	?	N	Y	Y	N	N	N
Kiberd 2018	Y	Y	Y	?	N	Y	?	N	N	N
Premkumar 2018	Y	N	Y	?	N	Y	Y	Y	N	N
Bell 2007	Y	Y	N	?	N	Y	Y	Y	N	N
Crocker 2008	Y	Y	N	?	N	Y	Y	N	N	N
Demetriades 2009	Y	Y	N	?	N	Y	?	Y	N	N
Domen 2009	Y	Y	N	?	N	Y	Y	Y	N	N
Rooney 2009	Y	Y	N	N	N	Y	Y	Y	N	N
Balasubramanian 2010	Y	Y	N	?	N	Y	Y	Y	N	N
Thangarajah 2011	Y	Y	N	?	N	Y	N	N	N	N
Gooding 2013	Y	Y	N	?	N	Y	?	Y	N	N
Haworth 2013	Y	Y	N	?	N	Y	?	N	N	N
Sideris 2014	Y	Y	Y	?	N	Y	Y	N	N	N
Ahad 2015	Y	Y	N	?	N	Y	Y	N	N	N

Blades 2015	**Y**	**Y**	**Y**	**?**	**N**	**Y**	**Y**	**N**	**N**	**N**
Hoeritzauer 2015	**Y**	**Y**	**N**	**?**	**N**	**Y**	**Y**	**Y**	**N**	**N**
Hoeritzauer 2017	**Y**	**Y**	**N**	**?**	**N**	**Y**	**Y**	**N**	**N**	**N**
Banerjee 2018a	**Y**	**Y**	**N**	**?**	**N**	**Y**	**?**	**N**	**N**	**N**
Banerjee 2018b	**Y**	**Y**	**N**	**?**	**N**	**Y**	**?**	**N**	**N**	**N**
Hussain 2018	**Y**	**Y**	**N**	**?**	**N**	**Y**	**Y**	**Y**	**N**	**N**
Kostusiak 2018	**Y**	**Y**	**Y**	**?**	**N**	**Y**	**Y**	**N**	**N**	**N**
Studies were assessed against the 11 pre-specified criteria. Y represents "Yes" and N represents "No". Where no information is given in the study report there is a question mark.										

Study Quality

Study quality assessment is shown in Table 4. All studies described the population being studied and had representative samples. However, only two studies reported excluded patients,[22,40] and only one study described the excluded patients.[22] Studies assessing asymptomatic populations were larger than those assessing asymptomatic populations. Only three studies assessing those presenting with suspected CES included more than 300 participants.[29,38,41] Methods used to ascertain the diagnosis of CES varied between studies and many studies did not adequately describe their methods in a way that could be easily reproduced. Only two studies calculated confidence intervals for the incidence estimates[22,34] and none reported population standardised estimates. Of the 26 studies included in this review, nine were published only in abstract form.[26,27,29,30,33,36-38,41]

Discussion

This systematic review of the incidence of CES identified 26 relevant studies. The incidence of CES was 0.34-0.48 per year per 100,000 population in two studies of asymptomatic complete populations.[20,21] One study of an adult population reported an incidence of 0.6 per 100,000 per year,[22] and one study of an adult working age population reported an incidence of 7 per 100,000 per year.[23] In patients with back pain, the proportion diagnosed with CES presenting to primary care was 0.08% in the single study identified.[34] A combined estimate of 0.27% was calculated from four studies of patients presenting to secondary care with back pain. In 17 studies of patients referred to secondary or tertiary care with suspected CES the combined estimate with CES was 18.9%.

This is the first systematic review of studies estimating the incidence of CES. One study was carried out in Australia,[34] four studies were carried out in North America,[23,37,39,43] and the remainder studied European populations. It is not known whether these estimates are relevant outwith the populations and healthcare settings studied. Patients with known pathology of the cauda equina region such as prolapsed intervertebral discs or tumours were not included, so these estimates cannot be applied to patients with known pathology.

This review identified a paucity of literature on the incidence of CES. We included all studies from which incidence of CES could be calculated, but few of the studies had a primary aim to calculate

incidence. Many did not meet expected epidemiological standards as can be seen from Table 4. Sample sizes were small in symptomatic populations and estimates did not have confidence intervals and were not standardised for the populations. Few studies described exclusions or missing data. Nine studies were only published in abstract form and provided fewer methodological details and had not been through the peer review process. All abstracts and full text articles were screened by at least two reviewers and we only identified seven further studies[8,24,31,32,35,42,43] through searching reference lists and citations. We are confident that these methods should not have missed any further important studies on this topic.

The criteria used to establish a diagnosis of CES were described in only 13 of the 26 studies, and only two studies subdivided CES into clinical categories.[22] Diagnosis was determined through clinical coding, record review, urgent operative intervention, radiology reports, clinical assessment, or any combination of these. The variation in definitions and reporting of diagnostic criteria likely reflects the lack of agreed definitions and multiple classifications of CES in use clinically and in the literatures.[1] The lack of specific clinical phenotyping covered by a broad CES definition hampers accurate assessment of incidence and contributes to the statistical heterogeneity as the incidence will likely differ depending on the definition and case ascertainment methods used. In addition, differing medico-legal concerns or clinical guidelines in different healthcare settings may affect the threshold for diagnosing CES, which will ultimately affect estimates of incidence. Adopting agreed definitions or defining subtypes such as those listed by Todd and Dickson[46] might enable more consistent reporting in future studies and allow more accurate incidence figures to be established.

This systematic review confirms that CES occurs infrequently in the general population, and also that the majority of patients presenting with symptoms do not have a clinical and radiological CES. Healthcare service planning for the investigation and management of CES needs to balance the needs of the majority population with the few CES cases in whom a missed diagnosis or delayed treatment could have significant consequences. All but one[31] study reporting the proportion of patients with CES from those with suspected CES were carried out in the UK where guidance from the British Association of Spine Surgeons recommends an emergency MRI for suspected CES[47] and yet only 14% of hospitals in England and Wales surveyed in 2012 reported 24 hour access to MRI.[48] As clinical symptoms and signs in those with radiological cauda equina compression are very difficult to

distinguish from those without cauda equina compression,[49] this leads to a situation in which many patients are transferred to specialist centres for an MRI and then either transferred back or discharged from locations that can be far from home. Although final diagnoses in patients without cauda equina compression include demyelination, myelitis, and infection, the majority of patients do not have a structural cause found.[10] Either further characterisation of these patients to identify potentially distinguishing features such as Hoover's sign of functional weakness,[10] or an expansion of local out of hours MRI facilities could improve care for those investigated for CES with and without structural radiological cauda equina compression.

In conclusion, the incidence of CES is low at fewer than 1 per 100,000 asymptomatic population per year. Only 0.27% of those with lower back pain and only 18.9% of those with signs and symptoms consistent with CES will have a final diagnosis of radiological and clinical CES.

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Conclusions: The systematic review, particularly the assessment of the quality of literature, was useful for highlighting the problems with diagnosis, lack of use of diagnostic categories in clinical work and the dearth of good large studies of cauda equina syndrome.

Although there are clinical and radiological requirements to make a diagnosis of CES, no internationally agreed definition of CES either clinically or radiologically exists. In fact the classifications of CES are so manifold that a systematic review solely on the definition of CES exists[15]. The lack of consensus on what CES is creates difficulty in comparing patients diagnosed with CES across studies. Despite the multitude of CES definitions, in the systematic review I found that only one of the 18 studies of patients presenting with CES (6%) split patients up based upon the literature definitions.

Despite acknowledgement of CES as having major clinical and medicolegal importance most of the research is retrospective and based on small numbers[19]. 58% of all studies contained less than 300 participants in total and 50% of studies investigating patients who presented with clinical CES were only presented as an abstract and never published as a full article. In all studies of patients presenting with clinical CES 0-40% had cauda equina nerve root compression on MRI.

The systematic review was helpful for allowing me to understand the current level of knowledge about CES and the lack of agreement of clinical or radiological criteria. This meant I would have to decide where patients with 'impending CES' fitted into my study, and also helped me appreciate the difficulty in finding any current positive predictive factors to diagnose 'scan positive' CES or 'scan negative' CES and the highly UK-centric CES data.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Pilot study

Paper Three: Hoeritzauer I, CM Doherty, S Thompson, R Kee, A Carson, N Eames, J Stone. 'Scan Negative' Cauda Equina Syndrome: evidence of functional disorder from a prospective case series. *British Journal of Neurosurgery.* 2015; 29 (2):178-180.

Introduction: Before engaging in larger retrospective and prospective studies of CES I carried out a pilot study to test my hypothesis that patients with 'scan negative' CES were more likely to have evidence of a functional neurological disorder. I wanted to explore some potential mechanisms and to investigate whether a clinical sign of functional leg weakness, Hoover's sign, with good specificity and sensitivity in general neurology populations[20] would also provide useful information in patients with 'scan negative' CES.

'Scan Negative' Cauda Equina Syndrome: evidence of functional disorder from a prospective case series

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Abstract:

In the first prospective comparison of 'scan negative' (n=11) and 'scan positive' (n=7) patients with Cauda Equina Syndrome (CES) we found that Hoover's sign of functional leg weakness but not routine clinical features differentiated the two groups ($p<0.02$). This offers a new direction of study in this area although MRI is still required for all patients with possible CES.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Introduction

Cauda Equina Syndrome (CES) is a devastating condition which requires urgent surgery and has serious potential morbidity and medico-legal consequences(1). Despite the high profile of CES correlation between clinical assessment and MRI findings is often poor, even amongst experienced clinicians. In previous neurosurgical series, nearly 50% of patients presenting with possible CES had MRI scans which did not explain their symptoms , so called 'scan negative' patients(1),(2).This interesting 'scan negative' group is not well studied and given their heavy resource utilisation certainly warrants scrutiny. We investigated these patients prospectively for the first time in a pilot study and compared them to 'scan positive' patients with MRI confirmed CES.

Methods

At the Royal Victoria Hospital, Belfast patients with a possible diagnosis of CES are typically admitted under the orthopaedic team. We recruited prospective consecutive cases from weekday orthopaedic meetings over a six month period in 2013/4 whose history and examination were suggestive enough of CES for the orthopaedic team to request urgent MRI lumbosacral spine imaging. We divided them into those with scan positive CES (changes seen on MRI causing CES), scan negative CES (normal MRI or changes seen on MRI but not causing CES e.g. L5 nerve root entrapment) and 'other' (with an alternative explanation for symptoms). We aimed to see all patients blind to the diagnosis.

We collected data on: Age ; Sex; Symptoms (back pain, leg weakness and numbness, urinary and bladder dysfunction and saddle anaesthesia); Presence of dissociation (using Peritraumatic Dissociative Experiences Questionnaire (PDEQ)); whether there were symptomatic criteria for a Panic attack (using DSM-IV); physical examination (tone, power, sensation, reflexes, plantars); a specific sign of functional (also called psychogenic/non-organic) limb weakness was performed (Hoover's sign: weakness of hip extension that returns to normal with contralateral hip flexion against resistance) (3); residual bladder volume on bladder scan or volume on initial catheterisation if recorded; lumbosacral MRI scan reported by a consultant radiologist; length of in-patient stay; follow up length and clinical outcome through information on their Electronic Care Record which documents all A&E, out-patient hospital attendances, admissions and mortalities in Northern Ireland. Statistical significance was determined using Fisher's exact test and unpaired t-test.

Results

Twenty patients were seen as part of the prospective study, of whom 18 were suitable for inclusion.. Two patients were excluded as other diagnoses were made to explain the presentation (n=1 thoracic malignant lesion, n=1 neurosarcoid). Of the 18 included patients, eleven (61%) were 'scan negative' (7 females, mean age 38 yrs.) for CES and seven (39%) were 'scan positive' for CES (4 females, mean age 57yrs). They are described in table 1.

The most striking differences between the' scan negative' and 'scan positive' groups were found in the frequency of Hoover's sign of functional leg weakness (9/10 scan negative and 0/3 scan positive, 100% seen blind to the diagnosis: no assessment possible in 7 cases (table 1)). There were also notable differences in the frequency of symptoms compatible with a panic attack (8/11 scan negative (72%) vs 2/7 scan positive (29%), p 0.14) and in Peritraumatic Dissociative Experiences scores (5/11 scan negative (45%) >20 PDEQ vs 1/7 scan positive (14%) >20 PDEQ, p 0.32).

By contrast classical CES symptoms showed poor ability to discriminate between 'scan negative' and 'scan positive' patients: the frequency and nature of leg pain, weakness and numbness, urinary retention and/or saddle anaesthesia; use of opioids (scan negative (63%), scan positive (71%)).

Only four patients had bladder scans done, of whom three were in the 'scan negative' group (600mls and 900mls and 1000mls) and one in the scan positive CES group (1200mls).

Four of the eleven patients in the 'scan negative' group had definite nerve root impingement on MRI (L4 (n=1), L5 (n=1), S1 (n=2)) but no changes explaining their CES symptoms. In the 'scan negative' group the average length of inpatient stay was one day with only two patient's admission lasting more than two days.

Follow up data was available on all patients ('scan negative' mean= 5.7 months, 'scan positive' mean=6.8 months). None of the eleven' scan negative' patients represented with CES. One scan negative patient had a discectomy 3 weeks after initial presentation for back pain, urinary incontinence and possible S1 root compression on MRI but no CES. All scan positive patients had improvement on follow up.

Discussion

Our prospective study demonstrates that a high proportion of patients with CES symptoms are 'scan negative'. CES represents an important disabling disorder and patients consume significant emergency resources.

Two previous retrospective studies found 43%(2) and 48%(1) of patients with CES were scan negative but were unable to determine any discriminating clinical features to help differentiate them from scan positive patients. Likewise in this study our 'scan negative' patients had similar CES symptoms and progression to the patients with imaging confirmed CES.

However, on the basis of our clinical experience and the published literature, we propose the hypothesis that some of the 'scan negative' patients may be experiencing acute functional (non-organic) weakness, numbness and possibly even urinary retention triggered by acute back pain[1]. We know that functional weakness can present with CES symptoms and that urinary symptoms are often present in patients with functional symptoms. Functional limb weakness is commonly triggered by injury or pain and is commonly acute and "stroke like" with symptoms of panic or dissociation like these scan negative CES patients[3]. We were able to test this systematically in our prospective study and found some preliminary evidence to support this hypothesis with the presence of a blinded assessment of Hoover's sign of functional leg weakness (90% vs 0%) a panic attack (72% vs 29%) symptoms of dissociation (45% vs 14%) all performing as possible useful discriminators in the clinical assessment of patients with CES symptoms.

It could be that some of our 'scan negative' patients may have had a dynamic problem in the disc, with scanning in the supine position not demonstrating disc changes present when standing or flexed. Alternatively, other issues such as incomplete radiology or the presence of a non-structural causes for CES such as acute inflammatory or infectious lumbosacral polyradiculopathy or vasculitis which would not necessarily appear on imaging(1). Our MRI scans were reported by a consultant radiologist with an interest in spinal imaging or a consultant neuro-radiologist. Rapid improvement and quick discharge in the majority of 'scan negative' patients and lack of any new explanation at follow up suggests that a missed structural or other organic cause of CES symptoms is unlikely.

In some cases there could be acute on chronic sacral nerve degeneration. This may only be found using bulbocavernous reflex or anal sphincter EMG testing which is not commonly performed although could be in patients with ongoing sacral nerve symptoms.

Limitations of this data include: the small sample size and ability to detect differences between group; the risk of non-blinding influencing the data; possible missed alternative organic causes of CES symptoms in the 'scan negative' group; incomplete data in some cases (for example 4 of the 'scan positive' CES patients could not be examined for a Hoover's sign) and lack of detailed systematic follow up.

Our preliminary findings were in keeping with two previous studies, showing that 'scan negative' cauda equina syndrome accounts for up to half of cauda equina emergency admissions and is associated with similar disabling symptoms. What our prospective study adds is a new description of some positive clinical findings which may differentiate' scan negative' and 'scan positive' patients. MRI will continue to be an essential part of the investigation of all patients with possible CES, whether or not they have positive features of a functional disorder. However, if these findings are confirmed by larger prospective studies they may significantly alter the subsequent clinical management of those CES patients who are 'scan negative'. Patients with functional limb weakness benefit from specific explanation and physiotherapy approach which emphasises the positive nature of the diagnosis.(4)

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Conclusions: This was the first study investigating whether a difference existed in a positive sign of a functional neurological disorder (Hoover' sign of functional leg weakness) between patients with 'scan negative' and 'scan positive' CES. I found that patients with 'scan negative' CES were much more likely to have a positive Hoover's sign (90% vs. 0%), although the numbers in the study were small. I also found that there were some potentially important differences in reports of dissociation (45% vs 14%) and panic symptoms (72% vs 29%) between the groups which were not statistically significant but did provide further evidence to support a possible hypothesis in how uro-neurological and functional conditions overlap. The study was limited by the small numbers of patients involved but provided useful pilot evidence supporting my PhD hypothesis.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Paper Four: **Hoeritzauer I**, Pronin S, Carson A, Statham P, Demetriades AK, Stone J. The clinical features and outcome of scan-negative and scan-positive cases in suspected cauda equina syndrome: a retrospective study of 276 patients. J Neurol. 2018 Dec;265(12):2916-2926. doi: 10.1007/s00415-018-9078-2

Introduction: This study was designed to address **Aims 1 and 2**. **Aim 1**: *To determine what proportion of patients with 'scan negative' CES have a functional disorder by clinical consensus* and **Aim 2***: To describe associated clinical features relevant to diagnosis, mechanism and aetiology in patients with Scan negative and scan positive CES*. I undertook a retrospective notes review of all patients who were referred with possible CES to the neurosurgeons between August 2013 and November 2014 investigating their clinical features, whether there was evidence of comorbid functional or psychiatric disorders and outcomes such as pain, re-presentation rate and long term bladder function.

The clinical features and outcome of scan negative and scan positive cases in suspected cauda equina syndrome - a retrospective study of 276 patients

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

ABSTRACT

Background: The majority of patients presenting with suspected clinical cauda equina syndrome (CES) have no identifiable structural cause for their symptoms ('scan negative' CES) Understanding these patients aids clinical differentiation and management in CES.

Methods: A retrospective electronic notes review was undertaken of patients presenting with suspected CES, defined as ≥1 of acute bladder, bowel, sexual dysfunction or saddle numbness, to a regional neurosciences centre. We investigated radiology, clinical features, psychiatric and functional disorder comorbidities and outcome of patients with 'scan negative' CES and patients with MRI confirmed compression of the cauda equina ('scan positive' CES).

Results: 276 patients were seen over 16 months. There were three main radiologically defined patient groups:1. 'scan positive' CES(n=78, mean age 48yrs, 56% female), 2.'scan negative' CES without central canal stenosis but with lumbosacral nerve root compression not explaining the clinical presentation(n=87, mean age 43yrs, 68% female) and 3. 'scan negative' CES without neural compromise(n=104, mean age 42yrs, 70% female).

In the two 'scan negative' groups (no neural compromise and nerve root compression) there were higher rates of functional disorders (37% and 29% vs. 9%), functional neurological disorders(12% and 11% vs 0%) and psychiatric comorbidity(53% and 40% vs 20%).

On follow up (mean 13-16months) only one of the 191 patients with 'scan negative' CES was diagnosed with an explanatory neurological disorder (transverse myelitis).

Conclusions: The data supports a model in which scan negative cauda equina syndrome arises as an end pathway of acute pain, sometimes with partly structural findings and vulnerability to functional disorders.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Key Points

The majority of patients presenting with clinically suspected cauda equina syndrome will have a normal or non-explanatory scan ('scan negative' CES).

Roughly half the patients with 'scan negative' CES have some nerve root compression (L3-S2) not explaining the clinical presentation.

Patients with 'scan negative' cauda equina syndrome are significantly more likely to have a functional disorder or psychiatric comorbidity.

Patients with 'scan negative' cauda equina syndrome are significantly more likely to have chronic pain on follow up.

Patients with 'scan negative' cauda equina syndrome are unlikely to have a new diagnosis explaining their symptoms on follow up.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

INTRODUCTION

Cauda equina syndrome (CES) is a devastating medical emergency caused by compression of the cauda equina nerve roots which without timely surgery results in bladder, bowel and sexual dysfunction with potential lower limb weakness and numbness[1]. Diagnosis is based on the clinical picture and MRI findings of cauda equina nerve root compression ('scan positive' CES). However, at least half of all patients presenting with the acute clinical CES phenotype (acute bladder, bowel and sexual dysfunction, saddle anaesthesia and pain) have no radiological correlate, so called 'scan negative' CES. A systematic review of the correlation between history, physical examination and MRI scan result found that the mean prevalence of patients having both clinical and radiological evidence of CES was 14-48% with no single individual sign or symptom being helpful in diagnosing CES[2]; senior neurosurgical trainees asked to predict who would have a positive scan based on history and clinical findings had an accuracy of only 56%[3].

There has been little descriptive study of the 'scan negative' CES group but a better understanding of their presentation may aid clinical differentiation and management. Based on our clinical experience and an initial pilot study of 18 patients from a different centre which demonstrated Hoover's sign of functional leg weakness in 82% of patients with 'scan negative' CES and 0% of patients with 'scan positive' CES, we hypothesised that some patients with 'scan negative' CES would have evidence of a functional disorder and this may explain at least some of their clinical presentation[4]. By a functional disorder we mean a disorder which is genuine but which is due to an abnormality of nervous system functioning rather than of structure[5]. Functional neurological disorders describe symptoms of abnormal motor and sensory function such as limb weakness or numbness, but does not include chronic pain, even when that is unrelated to a structural cause. Common examples of functional disorders are irritable bowel syndrome and functional neurological disorders. We investigated the radiological findings, demographics, clinical features, comorbidity and outcomes of a retrospective consecutive series of patients referred to a tertiary neurosurgery centre with suspected clinical cauda equina syndrome. Our aims were to better phenotype patients with 'scan negative' CES, to test our hypothesis that at least some patients had evidence of a functional disorder and to generate hypotheses about how functional disorders, medication, pain with or without nerve root compression may interact to explain the bladder symptoms that cause patients to present actuely with 'scan negative' CES.

MATERIALS AND METHODS

Definitions

Clinical CES was defined using the Fraser et al criteria for CES : one or more of bladder, bowel, sexual dysfunction or saddle numbness +/- lower limb neurological deficit[1].

Radiological cauda equina compression was defined as >75% canal stenosis or lack of CSF around the cauda equina nerve roots[5]. 'Impending' CES was defined as a) Fraser et al clinical criteria b) an MRI scan showing a compressive lesion which was large enough to compress the cauda equina nerve roots but which did not meet our radiological criteria and c) the opinion of the consultant neurosurgeon that the compressive lesion was causing the clinical symptoms and would progress to irreversible CES unless urgently treated.

Patients were defined as with 'scan positive' CES if they had both clinical *and* radiological evidence of CES or 'impending' CES based on the definitions above. Patients were defined as 'scan negative' CES if they satisfied the Fraser et al criteria, had an urgent MRI scan for possible CES and had no evidence of radiological cauda equina compression on their MRI.

M*ethod*

Recruitment

In July 2016 we carried out a retrospective electronic record review of consecutive referrals with possible cauda equina syndrome to our regional neurosurgery service in Edinburgh between August 2013-November 2014 with electronic notes follow up until July 2016. Consecutive neurosurgical referrals documented as possible cauda equina syndrome were reviewed manually by two of the authors (IH, SP). Patients were only included in the study if they met clinical criteria for CES. All patients with 'scan positive' CES were included as they were all assessed in the local health board, NHS Lothian, and had clinical symptoms, comorbidities and follow up outpatient appointments recorded in NHS Lothian. Many patients referred to the neurosurgery service were from other NHS Scotland regions with a different electronic notes record which it was not possible to access centrally and were not seen in NHS Lothian; these patients were not included. To ensure that clinical data and follow up were as complete as possible, patients with 'scan negative' CES were only included if referred from an address within the local health board with NHS Lothian documentation of their

signs and symptoms or referred via the local health board accident and emergency department. The study received local ethical approval from NHS Lothian (Caldiott Guardian ref 1594).

Measures

With respect to the initial admission, all patients had urgent MRI lumbosacral scans which included the cauda equina down to the S5 foramina of the sacrum. A local protocol dictates that a T2 sagittal of cervical and thoracic spine should be done if the MRI lumbosacral spine is normal. All scans were reported by a consultant neuroradiologist.

Using a standardised proforma we assessed the radiological features, demographics, clinical symptoms and signs, completeness of clinical documentation, timing of operation (urgent: classified as during the initial admission; elective: classified as after discharge but scheduled due to symptoms and radiology from admission).

We carried out follow-up using electronic records until July 2016 by interrogating scan requests, accident and emergency attendances, all secondary care inpatient and outpatient visits. Information was obtained on: functional disorder comorbidity (fibromyalgia; irritable bowel syndrome; chronic fatigue syndrome; non-cardiac chest pain); functional neurological disorders (as defined in DSM 5 including functional motor disorders and non-epileptic seizures); psychiatric comorbidity (such as anxiety/depression/Post traumatic stress disorder (PTSD)/personality disorder/ obsessive compulsive disorder(OCD)/suicidal ideation or deliberate overdose/ anorexia nervosa); the presence of chronic pain documented in letters; urological symptoms; re-presentations with clinically suspected CES and new diagnoses which explained suspected CES presentation in patients with 'scan negative' CES. When patients had urological symptoms documented during their follow up, electronic notes were retrospectively reviewed back to 2009 to accurately document the onset of urological symptoms.

Statistics

Statistics used were Chi squared or Fisher's exact two-sided testing for all symptoms, signs, comorbidities and outcomes. ANOVA was used for comparing mean ages. Statistics were carried out using Statsdirect (http://www.statsdirect.com). All p values are comparisons between one of the 'scan negative' groups and the 'scan positive' group.

RESULTS

276 patients were referred with clinically suspected cauda equina syndrome between August 2013-November 2014 (Table 1 and Supplementary Figure One).

Radiological and Demographic findings

During initial admission seven patients were found to have alternate neurological causes mimicking or causing sacral nerve dysfunction: two patients had evidence of demyelination on MRI of their thoracic cord and both were subsequently diagnosed with multiple sclerosis; two patients had infections causing bladder or sacral symptoms (urinary retention due to urosepsis (n=1) and systemic infection with abscess at L2/3 (n=1)); three patients had CES mimics, (thoracic subdural haematoma (n=1), L1 lumbar fracture (n=1) and metastatic epidural deposit causing thoracic cord compression (n=1)). We excluded these seven patients from further analysis.

Patients divided into three main radiological groups:

- 78 had 'scan positive' clinico-radiological CES, including 'impending' CES (mean age 48yrs (range 21-91), 56% female),
- 87 had 'scan negative' CES but with nerve root compression of at least one nerve root L3-S2 (mean age 43yrs (range 20-79), 68% female). We separated this group on the grounds that some L3-S2 nerve root compression would not have caused sphincter dysfunction but may have impacted on bladder function or promoted functional motor/sensory symptoms in the legs.
- 104 had 'scan negative' CES without neural compromise (mean age 42yrs (range 16-81), 70% female)

We will continue with these subdivisions: 'scan positive' CES, 'scan negative' CES with root compression and 'scan negative' CES without neural compression, throughout the rest of the paper.

'Scan positive' diagnoses and surgical timing

Of the 78 patients with 'scan positive' CES, 67 (86%) were caused by disc protrusion, the other eleven had various lesions compressing the cauda equina nerve roots: n=4 fractures, n=4 had metastatic deposits, n=1 fracture and a metastasis, n=1 a primary tumour and n=1 large cyst.

68 patients (87%) with 'scan positive' CES had an emergency operation, seven were treated conservatively (n=2 too unwell, n=2 symptoms >1 week and resolving, n=2 metastatic deposits, n=1 vertebral fracture). In three of these patients sphincter symptoms of CES either turned out to have another cause or resolved but the patients were operated on electively anyway for leg pain.

Sixteen patients with 'scan negative' CES had an operation, two urgently, both of whom had nerve root compression and severe pain which did not settle after admission, and fourteen electively for leg pain.

Table One: Clinical Features of Scan positive and negative cauda equina syndrome

	Scan +ve (n=78) n (%)	**Scan -ve with root compression (n=87) n (%)**	**P value**	**Scan -ve no root compression (n=104) n (%)**	**P value**
Age (mean, SD)	48yrs +/- 16.8	43yrs +/-12.1		42yrs+/-12.6	
Gender	56% female	68% female		70% female	
<u>Operation</u>					
Emergency	68 (87%)	2 (2%)	**<0.001**	0	**<0.001**
Elective	3 (4%)	12 (14%)		2 (2%)	
<u>Bladder symptoms</u>					
<u>Storage problems</u>					
Incontinence	17 (22%)	20 (23%)		42 (40%)	
Urgency/frequency	0	3 (3%)		1 (1%)	
<u>Voiding problems</u>					
Retention	16 (20%)	21 (24%)		26 (25%)	
Reduced awareness	4 (5%)	6 (7%)		3 (3%)	
Hesitancy/difficulty passing	15 (19%)	18 (21%)		11 (11%)	
Mixed problems	0	3 (3%)		11 (11%)	**0.01**
Normal	22 (28%)	15 (17%)		9 (9%)	**0.0005**
<u>Bowel symptoms</u>					
Incontinence	6 (8%)	14 (16%)		13 (12%) 1 chronic	
Constipation	11 (14%)	8 (9%)		11 (11%)	
Reduced awareness	1	2 (2%)		2 (2%)	
Normal	27 (35%)	39 (45%)		42 (40%)	

Sexual function **Abnormal** **Normal** **No info**	 6 (8%) 0 (0%) 72 (92%)	 4 (5%) 2 (2%) 81 (93%)		 2 (2%) 0 102 (98%)	
Sciatica **Yes**	 69 (88%)	 75 (86%)		 80 (77%)	
Bilateral Sciatica	32 (41%)	17 (20%)	<0.001	22 (21%)	0.001
No	5 (6%)	7 (8%)		12 (11%)	
Other leg pain	0	1 (1%)		3 (3%)	
Weakness **Yes** **No weakness**	 35 (45%) (bilateral 13)(17%) 26 (33%)	 43 (49%) (bilateral=12) (14%) 37 (42%)		 52 (50%) (bilateral 19) (18%) 36 (35%)	
Leg numbness **Nerve root distribution**	48 (61%)	24 (28%)	**<0.001**	38 (36%)	**<0.001**
Bilateral root numbness	18 (23%)	4 (5%)		13 (12%)	
Whole leg	1 (1%)	8 (9%)		9 (9%)	
No numbness	6 (8%)	20 (23%)	**0.01**	17 (16%)	
Non-dermatomal numbness	2 (2%)	16 (18%)	**0.001**	16 (15%)	**0.004**
Saddle numbness*	50(64%)	47 (54%)	**0.04**	54 (52%)	**0.02**
Normal	18 (23%)	35 (40%)		42 (40%)	
Digital rectal exam* **Reduced anal tone** **Normal**	 14 (18%) 17 (22%)	 18 (21%) 39 (45%)		 19 (18%) 44 (42%) 1 refused (1%)	
Post void residual **<100mls** **>100-500mls** **>500mls** **No info**	 5 (6%) 7 (9%) 3 (4%) 63 (81%)	 14 (16%) 11 (13%) 2 (2%) 60 (69%)		 12 (9%) 5 (5%) 6 (6%) 81 (78%)	

P values refer to comparison against scan positive group and are only shown if significant
SD*=standard deviation
Saddle numbness*: as assessed by pin prick sensation

Clinical features

Urinary function (n=263, 98%), lower limb pain (n=250, 93%) saddle sensation (n=247, 92%), lower limb power (n=229, 85%) and sensation (n=225, 84%) were often documented. Bowel function (n=177, 66%), anal tone from digital rectal examination (n=151, 56%) and sexual function (n=14, 5%) were poorly or very poorly documented.

Symptoms

Patients with scan positive CES were more likely to have symptoms of bilateral sciatica and, surprisingly, were *less* likely to have documented bladder dysfunction than patients in either of the 'scan negative' CES groups (see table one). These are two controversial findings so we reviewed them in detail. Even when both 'scan negative' groups were combined bilateral sciatica was still significantly more likely in patients with 'scan positive' CES' (38% vs. 20%, n=30/78 vs. n=39/191, p=0.002). The patients with normal bladder function met our criteria as 'impending' cauda equina syndrome. These patients all had radiological evidence of cauda equina compression and one or more other signs of clinical cauda equina syndrome, most commonly saddle numbness, documented in twenty patients or bowel or sexual dysfunction in four patients each.

Signs

Patients with 'scan positive' CES were more likely to have saddle numbness (64% vs 54% and 52%, p=0.04, 0.02), although rates were relatively high (>50%) in all groups.

Comorbidity functional and psychiatric disorders

Both patient groups with 'scan negative' CES were more likely to have a comorbid functional disorder, functional neurological disorder and psychiatric diagnoses than patients with 'scan positive' CES when assessed at follow up in July 2016 (see **Table Two**). The specificity of finding a

comorbid functional neurological disorder in 'scan negative' CES at presentation was 1 (0.95-1) although sensitivity was low, 0.09 (6-14).

Table Two: Functional and Psychiatric Comorbidity in Scan positive and negative cauda equina syndrome

	Scan +ve (n=78) (n) %	**Scan -ve with root compression (n=87) n (%) P value**	**Scan -ve no root compression (n=104) (n) % P value**
Functional Disorder comorbidity	7 (9%)	26 (30%) **0.0007**	39 (37%) **<0.0001**
Functional Disorders**			
Irritable Bowel Syndrome	2 (3%)	9 (10%)	12 (11%)
Non-cardiac chest pain	0	7 (8%)	17 (16%)
Chronic widespread pain	5 (6%)	5 (6%)	8 (8%)
Other		1 Atypical Facial Pain	2 Functional Cognitive Disorder
Functional neurological disorders**	0	10 (11%) **0.0014**	13 (12%) **0.0005**
Limb Weakness		3 (3%)	6 (6%)
Sensory/ Hemisensory		4 (5%)	5 (5%)
Dissociative Seizures		2 (3%)	1 (1%)
Other:		2 (2%) Dysphonia	2 (2%) Visual
Psychiatric Diagnoses**	17 (22%)	34 (39%) **0.02**	55 (53%) **<0.0001**
Depression	14 (18%)	26 (30%)	43 (41%)
Anxiety	8 (10%)	21 (24%)	17 (16%)
Personality disorder	0	2 (2%)	1 (1%)
Other		1 anorexia 1 OCD 1 suicidal ideation	3 (3%) PTSD 2 deliberate overdose
Timing of FND in relation to CES presentation			
Prior		6 (7%)	6 (6%)
At the same time		2 (2%)	4 (4%)
After		2 (2%)	3 (3%)

FND= Functional Neurological Disorder. OCD= obsessive compulsive disorder. PTSD= post-traumatic stress disorder. **Several patients had more than one disorder.

Outcomes: Pain, Re-presentation rate, and Bladder function

There were no significant differences between the three groups in follow up frequency (93% vs. 89% and 87%) or mean duration of follow up (average 13 months, 16 months, 16months) (Table Three)

Only one patient in the scan negative groups presented at follow up with an alternative neurological explanation for CES. This patient had transverse myelitis. They had no comorbid functional disorders.

Four patients with 'scan positive' CES (4%) re-presented during the study time with a new episode of clinical cauda equina syndrome, two of whom required re-operation. Representations with possible cauda equina syndrome necessitating an urgent scan during follow up occurred in 22 of the 191 patients (11%) with 'scan negative' CES, all of whom continued to have negative scans. Fifteen patients re-attended once, five re-attended twice and two patients re-attended three times (see breakdown in Table Three). Only five patients (23%) re-presented within one month suggesting their recurrent presentations related to one episode of ongoing symptoms, the other seventeen presented over a longer period suggesting multiple different episodes of symptom occurrence.

Patients with 'scan negative' CES in both groups were more likely to have chronic pain recorded in the electronic patient record on follow up (26% vs 58% and 59%).

Rates of bladder dysfunction in the electronic patient record were not significantly different in all groups. Pre-existing bladder symptoms were found in two patients with 'scan positive' CES, one patient within the 'scan negative' CES with root compression group and in four patients in the 'scan negative' without neural compression group. One patient from each group had prior episodes of urinary retention. After CES presentation, idiopathic urinary retention affected one person in the 'scan negative' with root compression group and three patients without neural compression.

Table Three: Follow up and Outcomes

	Scan +ve (n=78) n (%)	**Scan -ve with root compression (n=87) n (%) P value**	**Scan -ve no root compression (n=104) n (%) P value**
Average follow up/ months	13	16	16
No Follow up	10 (13%)	6 (7%)	12 (11%)
Deceased or palliative	4		1

Cause of clinical CES found	100%	0	1 (1%)
Re-presentation with clinical CES **Once** **Twice** **Three times**	3 (4%) 3 (4%) N/A	10 (11%) 8 (9%) 2 (2%) 2 (2%)	12 (11%) 7 (7%) 3 (3%) 2 (2%) 3 (3%)
Prior 'scan positive' CES **Prior 'scan negative' CES**	2 (3%)	3 (3%) 6 (7%)	2 (2%) 9 (9%)
Chronic pain	20 (27%)	52 (60%) **<0.0001**	60 (58%) **<0.0001**
Bladder disorders **Total Affected:** **Storage Problems** Neurogenic bladder Overactive bladder Stress incontinence Urge incontinence **Voiding Problems** Idiopathic urinary retention Urethral stenosis BPH **Other**	 8 (10%) 7 (9%) 1 (1%)	 8 (9%) 0 1 (1%) 1 (due to prolapse) 0 1 (1%) 1(1%) 1 (1%) 1 (1%)UTI 2 idiopathic haematuria	 11 (11%) 0 1 (1%) 0 2 (2%) 3 (3%) 2 (2%) 1(1%) 1 bladder outlet obstruction 1 enuresis
Timing of Urological diagnoses **Before CES presentation** Stress urinary incontinence Urge incontinence Idiopathic urinary retention Bladder outlet obstruction	 2 (3%) 1 (1%) 1 (1%)	 1 (1%) 1 (1%)	 4 (4%) 2 (2%) 1 (1%) 1 (1%)
At time of diagnosis	0	1 (1%) UTI	0
After CES presentation	6 (8%)	6 (7%)	7 (7%)

Discussion

We found that patients with 'scan positive' and 'scan negative' CES presented with similar core symptoms. Saddle anaesthesia and bilateral sciatica with radicular sensory abnormalities were common in patients with 'scan positive' CES; whilst non-dermatomal sensory loss and mixed urinary problems were more commonly seen in patients with 'scan negative' CES. However, as in previous studies, no individual clinical symptom or sign could accurately differentiate between scan positive and 'scan negative' CES[7]. The explanation for scan negative CES does not appear to be latent neurological disease, of which there are many causes (Table Four)[8–19], at least in the majority of patients, since we only found one patient where this was the case at follow up.

The neurological differential diagnoses for 'scan negative' CES were considered by the authors and encompasses inflammatory, infectious, vascular, neoplastic and neurodegenerative disorders (Table four). In some cases, these conditions can be difficult to diagnose and may present initially as peripheral disorders but are caused by central mechanisms. This is particularly the case in patients with arteriovenous malformations including dural AV fistula[15]. Patients may present several times prior to diagnosis but symptoms are progressive and ultimately upper motor neurone signs appear. Transient infectious causes of lumbosacral polyradiculitis, such as Elsberg syndrome, caused by HSV, may also be difficult to pick up as lumbar puncture results normalise quickly and can have poor positive predictive value[12]. In a recent study at the Mayo clinic five patients over a 16year period were felt to have Elsberg sydnrome causing cauda equina radiculitis[12]. Bladder symptoms affect approximately 75% of patients with multiple sclerosis and are often cited as one of the most unpleasant symptoms by patients[8]. However, it is unusual for patients to present with bladder symptoms only and the diagnosis of multiple sclerosis is based upon clinical events and lesions separated in time and space.

In keeping with our hypothesis, patients with 'scan negative' CES did have notably more functional somatic disorders, psychiatric comorbidity and especially functional neurological disorders than patients with scan positive CES who had similar sphincter and leg symptoms. The specificity for functional neurological disorders in this scenario for 'scan negative' CES was 1 (0.95-1) although sensitivity was 0.12 (7-17) with around half of patients developing their functional neurological disorders during their 'scan negative' CES presentations (Table Two).

The data supports our earlier pilot study and strongly suggests that at least some patients with 'scan negative' CES have symptoms due to acute functional limb weakness, numbness and functional, pain or medication related urinary symptoms. Our findings are in keeping with other studies showing

functional neurological disorders are commonly triggered by pain. For example a systematic review of 869 patients with functional motor and sensory symptoms found that physical injury preceded onset in 37% cases[20, 21]. In the last ten years the understanding and awareness of functional neurological disorders has increased significantly. Diagnosis is made on the basis of positive clinical signs, such as Hoover's sign of functional leg weakness – weakness of hip extension which normalises with contralateral hip flexion, which have good diagnostic sensitivity and specificity[22]. A positive diagnosis and tailored physiotherapy seems to be more effective for functional motor disorder than standard treatment with 72% of patients improving in a recent randomised trial compared to only 18% of the control group[23]. Understanding of the mechanism of functional neurological disorders has expanded from Freudian ideas of conversion to Bayesian ideas of 'top down' expectation and abnormal self-directed attention overriding the normal sensory and motor pathways[24, 25].

Psychiatric disorders are not uncommon in the population however levels of 40 or 50% are higher than would be expected even in patients with chronic neurological disease[26] and in higher than psychiatric comorbidity in some studies of patients with chronic back pain[27]. Patients with avoidance and panic are more likely to develop chronic pain so knowledge and appropriate treatment of these comorbidities are important[28]. Urological symptoms requiring urology input were similar in both groups. This is noteworthy given that urological symptoms are one of the most common reasons why patients with 'scan positive' CES must be urgently operated on. High numbers of patients in the 'scan negative' groups represented with clinical CES requiring an urgent scan which was always negative. This suggests that not only are patients having recurrent symptoms which correlate with clinical CES, as per the Fraser et al criteria, but that they are high resource users and we should make more effort to understand and treat them.

Hypothetical Mechanisms for 'scan negative' CES

The excess of abnormal bladder symptoms in the patients with 'scan negative' CES were of particular interest and potentially counter to many clinicians expectations. There are several possible hypotheses about the origin of bladder symptoms in patients with 'scan negative' CES. Firstly, pain causing sympathetic hyperactivity and increased inhibitory signals via the hypogastric and pelvic nerves could be resulting in increased contraction of the internal urethral sphincter and override normal voiding parasympathetic processes causing difficulty voiding. Secondly, pain or panic may have exacerbated underlying bladder dysfunction including incontinence which occurs in up to one

fifth of middle aged women[29] and is more common in patients with anxiety and depression[30] or chronic back pain[31]. Thirdly, analgesic medications have significant effects on the bladder. Medications such as pregabalin, gabapentin and benzodiazepines can cause or exacerbate urinary incontinence[32, 33]. Opiates are well known to affect the bowels but the effect on the bladder, which if severe can lead to chronic urinary retention, is less well recognised[34]. Opiates can also cause severe constipation and there is a case report of constipation causing pelvic nerve entrapment and mimicking cauda equina syndrome[35]. From the authors experience, it is much more common that patients are constipated from medications and this results in more pain and difficulty passing a bowel motion. Fourthly, a cause of chronic urinary retention triggered by pain or medications is Fowler's syndrome, which describes primary failure of the external urethral sphincter to relax. Patients with Fowler's syndrome have high rates of chronic pain and functional neurological disorder comorbidity[36]. Fowlers syndrome has detectable neurophysiological changes and its aetiology remains uncertain but one possibility is that it represents a primary functional disorder of the urethral sphincter and a chronic model of the type of retention or voiding dysfunction seen in some patients with scan negative cauda equina. Lastly, previous studies of patients presenting for routine lumbar decompression found bladder symptoms in 55%[37] and an additional urodynamics study of a similar patient group found 26% had urodynamic evidence of detrusor areflexia all of whom reported abdominal straining to void[38]. This may be due to downstream effects of compression or inflammation from higher nerve roots, however, there was only one patient with idiopathic urinary retention in the 'scan negative' with root compression group on follow up so this explanation seems unlikely to be a major cause of symptoms in the 'scan negative' groups.

Considering these ideas, we propose that at least some patients with scan negative CES patients can be best understood to have a functional disorder explaining some, or all, of their presentation. We hypothesise that many patients have a vulnerability either to functional disorder and/or a prior underlying bladder dysmotility disorder. In some cases, patients may respond to severe back muscle spasm or pain from disc herniation and nerve root entrapment with panic and dissociation> resulting in either inability to contract the pelvic floor causing incontinence or inability to relax the pelvic floor and urethral sphincter causing urinary retention. Acute or long-term analgesia such as opiates may cause further retention, or gabapentinoids may cause incontinence, worsening the bladder dysfunction. Patients then present to hospital with clinical CES where they typically receive reassurance (although no explanation for why they had sphincter symptoms), pain relief and physiotherapy. However, for the 50% who develop chronic pain and the 11% who have recurrent

episodes of suspected CES, fear of movement and an attentional focus of symptoms may lead to deconditioning and a centrally generated pain syndrome with consequent inability to return to normal activity.

Limitations

The retrospective nature of the study and its dependence on electronic notes resulted in missing data. The design means that data about clinical features were not collected through routine practice and not systematically. This may explain our potentially controversial findings of bilateral sciatica being more common in patients with 'scan positive' CES, although we think this is unlikely, especially given the high rate of symptom documentation (95%). Patients with 'scan positive' CES, including those with 'impending' CES, were more likely to have normal bladder function than patients with 'scan negative' CES which also was an unexpected finding of our study. The high frequency of missing data about sexual function was surprising and may be important in differentiating 'scan positive' from 'scan negative' CES. Not all patients with normal radiology saw a neurologist, for example if they were discharged quickly. This means that functional comorbidity may have been underestimated. All patients with 'scan positive' CES from South East Scotland were included whereas only 'scan negative' CES patients from a smaller area (NHS Lothian) with complete medical records were included so this study cannot be used to estimate CES incidence or compare incidence of 'scan positive' vs. 'scan negative' CES. However, this limitation means that scan negative CES is likely to be pil*even more* common than we have demonstrated in this study. Medication records were not accurate enough for inclusion in the study and this is a gap in the data. Primary care data about outcome on follow up was not available and this may lead to an underestimation of urological or pain symptoms during follow up in all groups. Some additional neurological diagnoses may have been missed however our departmental policy of a T2 sagittal MRI of the thoracic and cervical spine for lumbosacral scan negative CES identified seven patients who immediately obtained a non-CES diagnosis. Only one additional diagnosis was found on follow up at 16 months with 88% follow up. and among the 22 patients who re-attended and were investigated again for 'scan negative' CES, no new diagnoses were made. This suggests that alternative neurological diagnoses are unlikely to explain a high proportion of scan negative CES. We believe immediate investigation and diagnosis is one of the reasons there was only one new diagnosis at follow up.

Conclusion

We found that of 276 consecutive CES patients 28% (n=78/276) were 'scan positive', 69% (n=191/276) were 'scan negative' and 3% (n=7/276) had an alternative cause mimicking or causing sacral nerve dysfunction. There was no single clinical feature which differentiated between the groups. Of the scan negative patients, just under half of patients had a nerve root compression that may have contributed but did not explain their clinical presentation. These patients with 'scan negative' CES were more likely to have comorbid psychiatric and functional disorders and have chronic pain on follow up. The data support a model in which 'scan negative' cauda equina arises as an end pathway of acute pain, sometimes with partly structural causes, medication side effects and vulnerability to functional disorder. A prospective study with systematically collected clinical data, additional imaging and neurological assessment would reduce these limitations.

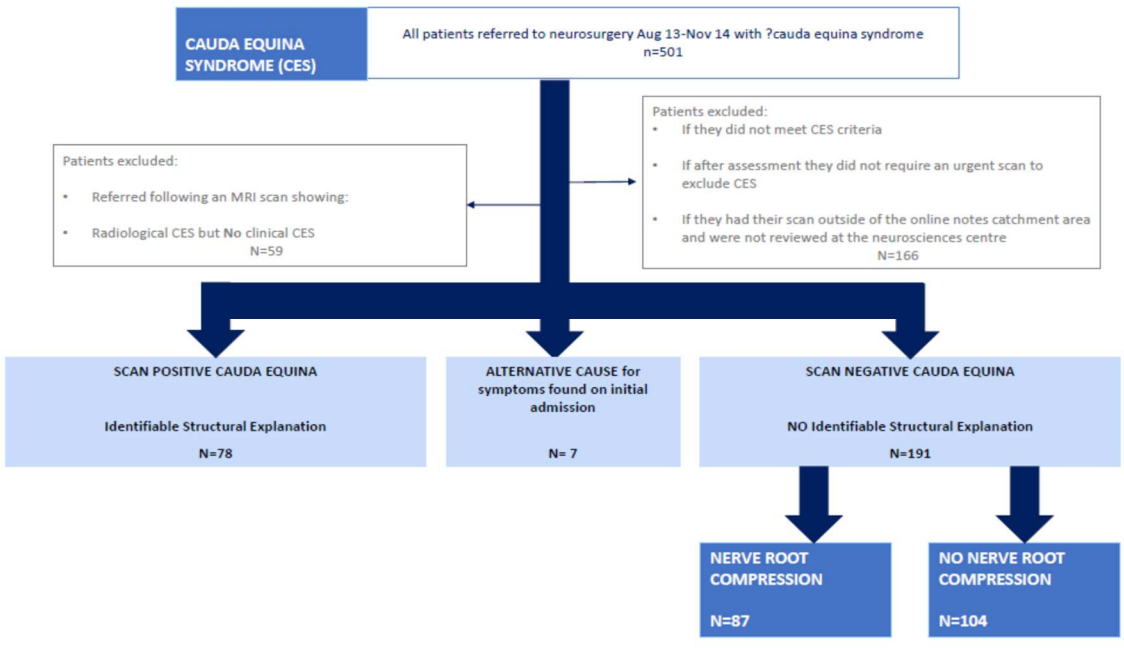
Table Four: Uro-Neurological Differential Diagnoses of clinical Cauda Equina Syndrome with Normal MR Imaging		
	Urinary Retention	**Urinary Incontinence**
Neurological Differential Diagnoses*		
Inflammation:	Myelitis	Multiple Sclerosis[8] Myelitis especially Neuro Myelitis Optica spectrum Disorder[9]
***Infectious*:**	Elsberg's syndrome[12], Varicella zoster, cytomegalovirus, herpes simplex, HIV[13, 14]	
Vascular:	Arteriovenous malformation[15], spinal infarction[16]	Cerebral stroke[17]
Neoplastic:	Neoplastic or radiation induced[18]	
Neurodegenerative:	Multiple System Atrophy[19]	Parkinson's Disease[19]
Urological Differential Diagnoses		
	Fowler's Syndrome[10] Idiopathic Urinary Retention	Exacerbation of prior urinary incontinence (affects 20% women over 40)[29] Bladder Pain Syndrome[11]
Medications (Side effects recorded from the British National Formulary)		
	Opiates Anticholinergics (e.g. tricyclics) Benzodiazepines NSAIDs (risk increases in elderly and with higher doses)	Benzodiazepines Pregabalin SSRIs ACE inhibitors/ Diuretics
Other Possibilities	Pain: radiculopathy is a common comorbidity Many cervico/thoracic pathologies can lead to cauda equina symptoms.	

Supplementary Table One: Total 'scan positive' CES group vs. combined 'Scan negative' CES groups			
	Scan positive CES (n=78)	Scan negative CES (n=191)	Significance; two sided Fisher's exact test ($p<0.05$)
Weakness	(37/60 recorded) 61%	(99/171 recorded) 58%	0.7
Numbness	(49/ 52 recorded) 94%	(111/148 recorded) 75%	0.002
Urinary symptoms	(57/74 recorded) 77%	(165/189 recorded) 87%	0.05
Bowel symptoms	(25/45 recorded) 77%	(51/131) 39%	0.06
Bilateral sciatica	(31/73) 40%	(39/190) 20%	0.005
Saddle numbness	(50/66) 76%	(102/179) 60%	0.007
Functional comorbidity	5 (6%)	62 (32%)	0.0001
- Of which Functional neurological Disorder	1% (1%)	21(11%)	
Psychiatric co morbidities	(17/78) 22%	(88/191) 46%	0.0002
Outcome: chronic pain	(20/78) 26%	(97/191) 51%	0.0001

Supplementary Table Two: Investigation of Urological Symptoms

Investigations	**Scan +ve (n=78)** **Total n=8**	**Scan -ve with root compression (n=87)** **Total n=8**	**Scan -ve no root compression (n=104)** **Total n=11**
Post void residual			1
Gynaecology Review*		1	4
Urology Review*		1	2
Trail removal of catheter	1		
Urethrogram	1		
Uroflowmetry	2	2	
Cystoscopy		3	2
Urodynamics	1		2
Video-urodynamics	2		
Other	1 no information but referred to urology	1 UTI diagnosed by neurosurgical team	
*= no additional investigations			

Supplementary Figure One



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Conclusions: The data led me to split the patients into three groups, those with purely negative scans, patients with some nerve root entrapment and patients with 'scan positive' CES to assess for step wise progression of functional symptoms and signs. Only one of the 191 patients with 'scan negative' CES, had a diagnosis which explained their clinical CES presentation despite a notes follow up of an average of 15months.

Clinical features which were statistically different between the groups included saddle anaesthesia and bilateral sciatica, which were more common in the 'scan positive' CES group and non-dermatomal sensory loss in the 'scan negative' CES groups. Functional somatic disorder, psychiatric disorders and functional neurological disorders were more common in patients with 'scan negative' CES. The study of 276 patients demonstrated that 12% (n=23) of patients with normal or non-explanatory MRI imaging, 'scan negative' CES had evidence of a functional neurological disorder.

I explored possible mechanisms and aetiology of 'scan negative' CES focusing on bladder dysfunction. Mechanisms and aetiology discussed including pain overriding normal bladder function, exacerbation of commonly occurring bladder dysfunction by pain, panic or medications, functional or idiopathic urological problems such as Fowler's syndrome. I also explored evidence of downstream urological effects caused by higher nerve root compression, although I felt this was more unlikely. A model of how 'scan negative' CES may occur as a functional neurological disorder was put forward.

The study was limited by its retrospective nature, by the limitations of a notes review and by the definitions of CES. As a retrospective review it was able to investigate the functional comorbidity only in so far as it was recorded, which often depended on the patient being seen by a different speciality. The low numbers seen by neurology may suggest that patients with 'scan negative' CES have symptoms which spontaneously improve but a prospective study was required to investigate this and mechanistic hypotheses further.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Paper Five: Ingrid Hoeritzauer[1,2], Alan Carson[1,2,3], Patrick Statham[4], Jalesh Panicker[5], Voula Granitsiotis[6], Maria Eugenicos[7], David Summers[7], Andreas K. Demetriades[4], Jon Stone[1,2] "Scan Negative" Cauda Equina Syndrome: a prospective case control study

Introduction: This study was designed to address **Aims 1 and 2**, building upon the learning from the retrospective study. **Aim 1**: *To determine what proportion of patients with 'scan negative' CES have a functional disorder by clinical consensus* and **Aim 2***: To describe associated clinical features relevant to diagnosis, mechanism and aetiology in patients with Scan negative and scan positive CES*.

I identified and recruited consecutive patients who presented to Edinburgh neurosurgery with clinical CES. 198 patients agreed to take part and undergo a semi-structured interview, neurological examination and questionnaires with follow up questionnaires at three months.

"Scan negative" cauda equina syndrome: a prospective case-control study

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Abstract

Cauda equina syndrome (CES) is a surgical emergency with major clinical and medicolegal consequences. Yet, between 60 and 100% of patients presenting with clinical CES have no identifiable structural lesion causing their symptoms ('scan negative' CES). We planned the first large prospective case-control study phenotyping patients with 'scan negative' CES in order to improve clinical differentiation and management of CES. We carried out a prospective study of consecutive patients presenting with the clinical features of CES to a regional neurosurgery centre over 28 months comprising semi-structured interview, examination and questionnaire. 198 patients presented consecutively over 28 months. 47 were diagnosed with 'scan positive' CES (mean age 48yrs, 43% female). 76 patients had some evidence of nerve root compression or displacement and were placed into a 'mixed' category (mean age 46yrs, 71% female) and 61 patients had 'scan negative' CES (mean age 40yrs, 77% female). Fourteen patients were given an alternative neurological diagnosis explaining their clinical CES symptoms during admission. Patients with 'scan positive' CES were more likely to have chronic leg pain (20% 'scan positive' CES vs. 6% and 2% mixed and 'scan negative' CES groups, p=0.04, p=0.004) and reduced or lost bilateral ankle jerks (78% vs. 30% and 12%, p=<0.0001). Patients with 'scan negative' CES had more positive signs of a functional neurological disorder on examination (11% v. 34% and 68%, p=<0.0001) despite similar rates prior to admission (2% vs. 7% and 16%, p=0.5). They were more likely to have their worst ever back pain (41% vs. 46% and 70%, p=0.005) and symptoms of a panic attack (37% vs. 57% and 70%, p=0.001) at symptom onset.

Signs typically used to differentiate between 'scan positive' and 'scan negative' CES such as reduced anal tone, saddle numbness and urinary retention showed no significant differences.

Four patients out of 151 (4%, mixed group n=3, 'scan negative' group n=1) had a neurological diagnosis after discharge which potentially explained their clinical CES presentation (CNS inflammatory disorders (n=2), sacral chordoma (n=1), cervical epidural haematoma(n=1). The first well phenotyped, prospective study of patients with 'scan negative' CES, supports the hypothesis that many such presentations arise from acute pain and have features consistent with a functional disorders.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Introduction

Cauda Equina Syndrome is a surgical emergency caused by compression of the cauda equina nerve roots. It is suspected when patients present with new back or leg pain accompanied by bladder, bowel, sexual dysfunction or saddle numbness. An MRI scan is required to demonstrate cauda equina compression and it is recommended that this occurs within 1-4 hours of presentation to hospital, creating significant pressure on emergency care, neurosurgical, orthopaedic and radiology staff to provide a responsive 24 hour service (Haworth *et al.*, 2013; Todd and Dickson, 2016). However, a mean of 81% of patients referred to neurosurgery with cauda equina syndrome (CES) have normal or non-explanatory imaging, 'scan negative' CES (Hoeritzauer *et al.*, 2019) despite having similar rates of pain, bladder and neurological dysfunction. These patients have never been prospectively studied and the mechanism underpinning symptom presentation in 'scan negative' CES is unknown. Two previous studies suggest that at least some of the patients presenting with 'scan negative' CES have symptoms partially or fully explained by functional neurological disorders (Hoeritzauer *et al.*, 2015, 2018). This hypothesis has not been tested in a large prospective study

We aimed to use a case control design to prospectively phenotype patients with 'scan negative' CES, comparing their radiological findings, clinical features, level of functional disorders and psychological comorbidities, and clinical outcome with patient with 'scan positive' CES.

Materials and methods

Definitions and Classification of CES patients in this study

Clinical CES was determined by the Fraser et al definition of: one or more of acute bladder, bowel, sexual dysfunction or saddle numbness +/- leg or back pain(Fraser *et al.*, 2009));

Radiological findings were divided into: 1) 'scan positive' cauda equina syndrome - defined as compression of the cauda equina nerve roots with >75% central canal occlusion or no CSF around the cauda equina nerve roots on axial view(Delamarter *et al.*, 1991); 2) a 'mixed' category not meeting radiological criteria for cauda equina compression but with some radiological evidence of

nerve root compression or displacement 3) 'scan negative' cauda equina syndrome with no nerve root compression or other radiological reason for any of their clinical CES symptoms; 4) neurological or other diagnoses explaining clinical CES presentation identified during admission.

Setting and Recruitment

A prospective study of consecutive patients with clinical cauda equina syndrome presenting to a secondary care regional neurosurgery centre at the Western General Hospital, Edinburgh serving a population of over 1.3 million (Carter *et al.*, 2001). Patients were included if they had: 1) Clinically defined CES presentation 2) the presentation necessitated a scan to exclude 'scan positive' cauda equina compression. Recruitment was undertaken between November 2015 and December 2017. Patients were identified through the daily neurosurgery handover. Patients were given an information leaflet by a member of their clinical care team in person or by post and if interested in the study were consented by one of the authors for interview, examination and questionnaire (IH). They were seen either during their inpatient stay, or if they had been discharged quickly, were contacted by post and were offered the opportunity to take part in the questionnaire components of the study (September 2016 - February 2017).

Neuroimaging and other investigations

All patients with CES symptoms and a normal lumbosacral MRI scan received a T2 sagittal MRI scan of the cervical and thoracic spine as per the local neuroradiology protocol. MRI brain scan and other investigations such as lumbar puncture were carried out at the discretion of the clinical team. All scans were reported by a consultant neuroradiologist.

Structured Interview and Examination

A semi-structured interview encompassed demographics, work status, clinical symptoms including; back pain and leg pain (including assessment of S1 radicular pain: "did your leg pain radiate down the back of your leg to your ankle?"), leg numbness and arm weakness. Back and leg pain were rated by patients on a four-point Likert scale; 'worst ever', 'severe', 'somewhat painful', 'not very painful'. Additional clinical symptoms enquired about included; panic attack at onset as defined by DSM-5 (≥

four specific panic symptoms reaching a peak within 10 minutes) ; dissociative symptoms ("did you feel disconnected from part of all of your body or disconnected from your surroundings?"(Stone, 2006)) and; current and prior bladder symptoms based on definitions from the Urogenital Distress Index: urge incontinence, stress incontinence, other incontinence, difficulty voiding(Shumaker *et al.*, 1994). Medications patients were taking when admitted were recorded which were likely to be associated with bladder dysfunction either retention; opiates (classed as tramadol or stronger), benzodiazepines, codeine and tricyclics or incontinence; gabapentinoids, or benzodiazepines (Tsakiris *et al.*, 2008; Verhamme *et al.*, 2008; Kibar *et al.*, 2015). Several of these medications also have negative effects on sexual function (opiates, gabapentinoids, codeine, tricyclics).

The structured interview also included past or current history of functional disorders (functional neurological disorder, irritable bowel syndrome, chronic pain, chronic fatigue syndrome, non-cardiac chest pain) and the structured clinical interview for DSM-IV for current depression, past depression, panic disorder, agoraphobia, health anxiety, generalised anxiety disorder, obsessive compulsive disorder and post-traumatic stress disorder. IH was trained and supervised in the structured clinical interview for DSM-IV, and all case histories were reviewed blind to the diagnosis for the first twelve months and thereafter when the diagnosis was unclear by author AC.

A full neurological examination was carried out by IH or recorded from the notes if the patient declined. Routine clinical testing for CES including saddle sensation, anal tone and post void bladder scanning was done by the neurosurgical registrars or other members of the clinical team and recorded from the clinical notes. Functional neurological disorders were diagnosed according to DSM-5 criteria on the basis of positive evidence from the clinical presentation and examination by IH(Daum *et al.*, 2015) (Hoover's sign and thigh abductor sign of functional leg weakness, collapsing weakness, whole leg non-dermatomal sensory loss, hemisensory loss, dragging gait with hip externally or internally rotated, clinical symptoms of persistent postural perceptual dizziness((Popkirov *et al.*, 2018). Features were also sought for other neurological disorders which may present as 'scan negative' CES, such as inflammatory, infectious, vascular, neurodegenerative and neoplastic causes (Hoeritzauer *et al.*, 2018). Abnormal findings were discussed with one of the authors (JS).

Questionnaires

We administered patient-reported questionnaires about bladder (Urinary Symptom Profile; measuring stress incontinence, overactive bladder symptoms and low stream) (Haab *et al.*, 2008),

bowel (Neurogenic Bowel Dysfunction Score(Krogh *et al.*, 2006)), sexual function (Arizona Sexual Experiences Questionnaire (McGahuey *et al.*, 2000)), quality of life (Work and Social Adjustment Scale), physical function (SF-12 physical function scale), somatic symptoms (Patient Health Questionnaire Somatic Symptom Severity Score PHQ-15), anxiety and depression (Hospital Anxiety and Depression Scale), dissociation (Peritraumatic Dissociation Questionnaire) and adverse childhood experience (Adverse Childhood Experiences questionnaire (Kandel and Davies, 1982)) . In an effort to understand premorbid health status patients were additionally asked to fill out all of the scales above, apart from illness perception and adverse childhood experience, based upon the month prior to symptom onset.

Follow Up -Clinical Outcome and Diagnosis

Repeat questionnaires were sent out three months after discharge regarding bladder, bowel, sexual function, quality of life, physical function, somatic symptoms, anxiety and depression and outpatient follow up appointments.

Diagnostic follow up was carried out using electronic notes review in the 'scan negative' and mixed groups in October 2018 to determine whether patients had developed a neurological, urological or other condition which, with the benefit of hindsight, explained their initial clinical CES symptoms.

Statistical Analysis

Questionnaires were only analysed if fully complete. Data was tested for normality with the Shapiro-Wilk test. Chi squared 2xk, Fisher's exact two-sided testing and Mann Whitney U tests were performed with scan positive CES as the control group using Statsdirect (http://www.statsdirect.com).

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

The study received formal ethical approval by the NHS Grampian Research Ethics Committee (Study ID 15/NS/0112 - IRAS Project ID: 192413www.clinicaltrials.gov NCT03325374).

Results

Recruitment, Radiology and Demographics

198 patients were consecutively recruited over 24 months and an additional 28 patients declined to participate (mean 48yrs old, 71% female). 177 patients were seen as an inpatient. Twenty-one patients were recruited after discharge for questionnaires only ('scan positive' CES (n=6), mixed (n=9), 'scan negative' CES (n=5), alternative neurological cause of CES (n=1).

47 patients (24%) had 'scan positive' CES (43% female, average age 48yrs old). 76 patients (38%) were in the mixed category (71% female, average age 46yrs old). Radiologically the 'mixed' group comprised cauda equina crowding (n=25), bilateral nerve root compression (n=5), unilateral nerve root compression (n=27) and unilateral nerve root displacement (n=19). 62 patients (31%) were in the 'scan negative' CES group (77% female, average age 40yrs old). Finally, 13 additional patients (7%) were identified as having alternate aetiologies which explained their clinical CES presentation during or in the immediate aftermath of the initial inpatient admission (54% female, average age 48yrs old); inflammatory cord lesions (n=4) and one each of acute inflammatory demyelinating polyneuropathy, probable paraneoplastic lumbosacral polyradiculitis, high lumbar fracture, abscess, discitis, cervical myelopathy, cord infarct, lumbosacral plexus injury following vaginal delivery and extraspinal renal tumour. Data from these thirteen patients was excluded from further analysis.

81% of patients with 'scan positive' CES returned their questionnaires (n=38), 80% of patients in the mixed group (n=61) and 66% of patients with 'scan negative' CES (n=41).

Clinical Features

Symptoms

Patients with 'scan positive' CES were significantly more likely than patients in the mixed or 'scan negative' CES groups to describe saddle numbness (73% v. 52% and 53%, p=<0.003 p=0.04) and have had leg pain for >3 months (20% v. 6% and 2%, p=0.04, p=0.004). (Table One)

At onset of symptoms patients in both the mixed and 'scan negative' CES groups were significantly more likely to meet DSM-5 criteria for a panic attack (37% v. 57% and 70% p=0.046 and p=0.001).

Patients with 'scan negative' CES were significantly more likely to describe having their 'worst ever' back pain (41% v. 46% and 70%, p=0.005) and report dissociation (32% v. 39% and 65%, p=0.03) at onset. On admission patients with 'scan negative' CES described more leg weakness, including bilateral leg weakness (17% v. 18% and 39%, p=0.02), leg pain which was not in keeping with an S1 radiculopathy (5% v. 18% and 33%, p=0.0005) and arm weakness (7% v. 10% and 23% p=0.04).

At admission, the prevalence of all forms of incontinence urge and stress and voiding difficulties was similar between groups in the semi-structed interview. However, in the month prior to admission patients with 'scan negative' CES described higher rates of urge, stress and other incontinence (Supplementary Table One).

Signs

Four patients in the 'scan positive' group, six patients in the mixed group and four patients in 'scan negative' group refused examination. Routine examination findings were taken from the notes.

Patients with 'scan positive' CES were significantly more likely to have reduced or absent bilateral ankle jerks than patients in the mixed or 'scan negative' CES groups (78% vs 30% vs 12%) (Table One). Patients with 'scan positive' CES were also more likely to have abnormal saddle pinprick sensation that patients in the mixed group (75% v. 55%, p=0.04) but not than patients with 'scan negative' CES (75% vs. 70%, p=0.6).

Despite patients in both the mixed and 'scan negative' CES groups being more likely to complain of leg weakness, on examination all three groups had similar proportions of patients with leg weakness (46% v. 47% and 49%, p=0.9. p=0.8). Positive signs of a functional neurological disorder causing weakness, sensory or gait disturbance were more common in the mixed and 'scan negative' CES group; overall positive signs (11% v. 34% and 68%, p=0.009, p=<0.0001), in those with leg weakness (16% v. 42% and 71%, p=0.002, p=<0.0001), positive functional sensory signs (3% v. 25% and 49%, p=0.002, p=<0.0001).

Abnormal anal tone on digital rectal examination and post void residual of >200mls or >500mls were unhelpful in differentiating between the three groups (Table Two).

Medications on admission

When admitted the majority of patients in all three groups were on at least one analgesic associated with bladder +/- sexual dysfunction (88% v. 81% and 82%). Patients with 'scan negative' CES were more likely to be taking benzodiazepines (12% v. 18% and 32%, p=0.01), opiate use was similar across all three groups (32% v. 42% and 45%). See Table Two.

Table One: Symptoms and Signs at Onset and on admission

DEMOGRAPHICS	**'Scan positive' CES n=41**		**Mixed n=67**		P value	**'Scan negative' CES n=57**		P value
Mean age	48yrs		46yrs			40yrs		
Female %	43%		71%			77%		
SYMPTOMS – at onset	n	**%**	n	**%**		n	**%**	
"Worst ever" back pain	17	**41%**	31 (46%)		0.6	40 (70%)		**0.005**
Meet DSM 5 criteria for Panic Attack	15	**37%**	38	**57%**	**0.046**	40	**70%**	**0.001**
SYMPTOMS – on admission	n	**%**	n	**%**		n	**%**	
Leg weakness	25	**61%**	52	**78%**	0.07	49	**86%**	**0.006**
Both legs weak	7	**17%**	12	**18%**	0.9	22	**39%**	**0.02**
Both legs numb	13	**32%**	14	**21%**	0.2	20	**35%**	0.7
Unilateral sciatica	19	**46%**	36	**54%**	0.5	18	**19%**	0.1
Bilateral sciatica	15	**37%**	14	**21%**	0.08	14	**25%**	0.2
Non dermatomal leg pain	2	**5%**	12	**18%**	0.051	19	**33%**	**0.0005**
Arm weakness	3	**7%**	14	**22%**	0.06	15	**27%**	**0.04**
Neurogenic Claudication	13	**27%**	15	**22%**	0.3	11	**19%**	0.2
SIGNS Exam and from notes	**'Scan positive' CES n=41[1]**		**Mixed n=65[1]**			**'Scan negative' CES n=57[1]**		
	n	**%**	n	**%**		n	**%**	
Bilateral reduced/absent ankle jerks	32	78%	20	30%	**<0.0001**	7	12%	**<0.0001**
Abnormal saddle pinprick	30	75%	35	55%	**0.04**	40	70%	0.6
Refused		1		1				
Reduced anal tone on digital rectum exam	20	61%	19	33%	**0.04**	28	51%	0.9
Refused/not done pre scan		8		7			2	
Unilateral reduced/absent ankle jerks	4	10%	17	25%	**0.04**	14	25%	0.07
Any leg weakness	19	46%	31	47%	0.9	28	49%	0.8
Positive signs of Functional Neurological Disorder from Examination								
Refused FND testing	4		6			4		

Total number of patients with positive FND signs	4	11%	21	34%	**0.009**	36	68%	**<0.0001**
In patients with weakness								
*Hoover's **	3 of 19	16%	13 of 31	42%	0.06	23 of 28	82%	**<0.0001**
*Thigh abductor sign **	2 of 19	11%	6 of 31	19%	0.5	15 of 28	54%	**0.003**
Functional Sensory Symptoms	1	3%	15	25%	**0.003**	27 of 55	49%	**<0.0001**
Functional Gait Disorder	0		2	3%	0.1	3	5%	0.1
Statistically significant findings in bold. Examination findings for these patients were taken from the notes. *test results in patients with leg weakness.								

Bladder, Bowel and Sexual Dysfunction from Questionnaire

The severity of stress incontinence, overactive bladder and low stream from the Urinary Symptom Profile in the month prior to admission was significantly greater in patients with 'scan negative' CES (all $p<0.0001$) (see Table Two). On admission severity of voiding dysfunction was similar in all groups. Stress incontinence on admission was significantly more severe in patients with mixed and 'scan negative' CES and overactive bladder symptoms were more severe in patients with 'scan negative' CES. There was no difference in rates of bowel or sexual dysfunction between all three groups on admission or in bowel function the month before (see Supplementary Table One).

Additional Investigations in Mixed and Scan Negative Group

In the mixed group (n=76) fifteen patients had an MRI brain scan, all of which were normal. In the 'scan negative' CES group (n=62) 31 patients had an MRI brain and one had a CT brain. MRI brain scans were abnormal in three patients in the 'scan negative' CES group including an incidental enlarged pituitary and an incidental temporal cavernoma. The final patient had possible inflammatory brain white matter changes not meeting McDonald criteria for MS, a normal MRI whole spine and no unmatched oligoclonal bands in his CSF. This individual did not attend for follow up and had not presented with new neurological symptoms 26 months after initial presentation.

Eight lumbar punctures were undertaken, three in the mixed group and five in the group of patients with 'scan negative' CES. In the 'scan negative' group one individual had unmatched oligoclonal bands, considered to be a false positive finding after normal MRI of brain and whole spine and specialist clinical review.

Table Two: Bladder Dysfunction and Medications

Bladder symptoms in the month prior to symptom onset								
Questionnaire Data	**'Scan positive' CES n= 38**		**Mixed n=61**			**'Scan negative' CES n=41**		
Questionnaire Data	Mean Score		Mean Score		**P value**	Mean Score		**P value**
Stress Incontinence	0.54		1		0.3	3		**< 0.0001**
Overactive Bladder	1.83		3.62		0.06	5.7		**< 0.0001**
Voiding Dysfunction	0.89		0.91		0.5	1.8		**< 0.0001**
Bladder symptoms on admission								
Questionnaire Data	**'Scan positive' CES n= 38**		**Mixed n=61**			**'Scan negative' CES n=41**		
	Mean Score		Mean Score		**P value**	Mean Score		**P value**
Stress Incontinence	0.92		3.57		**0.02**	3.8		**0.0009**
Overactive Bladder	4.43		6.43		0.07	7.6		**0.04**
Voiding Dysfunction	3.73		3.81		0.8	3.8		0.8
Bed side Investigations of Bladder Dysfunction								
	N	**%**	**n**	**%**		**N**	**%**	
Post void residual Total	n=28	68%	n=58	86%		n=49	86%	
>500mls	10	36%	19	33%	0.8	16	33%	0.8
>200mls	17	61%	24	50%	0.4	23	47%	0.3
Medications taken PRIOR to admission which could impair bladder dysfunction								
Total taking ≥ 1	36	88%	54	81%	0.4	47	82%	0.5
Opiates	13	32%	32	42%	0.1	28	45%	0.09
Gabapentinoids	12	29%	33	43%	**0.04**	21	34%	0.4
Benzodiazepines	5	12%	14	18%	0.3	20	32%	0.01
Codeine	24	59%	30	45%	0.2	23	37%	0.08
Tricyclics	8	20%	19	25%	0.3	13	21%	0.7
NSAID	23	56%	25	33%	0.06	24	42%	0.18

P values compare patients in the 'scan positive' CES group with the mixed and 'scan negative' CES groups.
Urinary symptom Profile measuring stress incontinence (0-9), overactive bladder symptoms (0-21) and low stream (0-9);

Distress and Disability

On admission patients in both the mixed and 'scan negative' CES groups were significantly more likely to have impaired social functioning as measured by the Work and Social Adjustment Scale (WSAS score >20, (12% v. 80% and 77%, both p<0.0001). Using the same scale, patients with 'scan negative' CES reported higher rates of social functional impairment in the month prior to symptom onset (9% vs. 11% and 43%, p=0.0007). Patients in all three groups had similar levels of physical function and emotional distress on admission as measured by SF-12 physical function and HADS scores (Table Three). Patients in both mixed and 'scan negative' CES groups had higher numbers of symptoms on the PHQ (p=0.001, p<0.0001) and higher mean scores on the peritraumatic dissociation questionnaire (p=0.005 and p=0.01).

Table Three: Distress and Disability on admission

Questionnaire Data	**'Scan positive' CES**	**Mixed**		**'Scan negative' CES**	
Work and Social Adjustment Scale					
	N (%)	N (%)	P value	N (%)	P value
Abnormal (>20)	4/34 (12%)	44/55 (80%)	**<0.0001**	29/38 (77%)	**<0.0001**
Median scores	21	28	**0.08**	31	**0.1**
SF-12 Physical Function					
Mean scores (SD)	5(+-2.46)	4(+-1.65)	0.1	5(+-1.910)	0.5
HADS					
Mean scores (SD)	14(+-0.62)	19(+-10.10)	**0.02**	17(+-10.11)	0.1
PHQ					
Mean scores (SD)	9 (5)	13 (6)	**0.001**	15 (7)	<0.0001
Peritraumatic Dissociation Questionnaire					
Mean scores (SD)	15 (7)	21 (10)	**0.005**	22 (13)	0.01
P values compare patients in the 'scan positive' CES group with the mixed and 'scan negative' CES groups.					

Predisposing Factors: Functional Disorder, Psychiatric Comorbidity, Adverse Childhood events and Employment

Prior to admission patients in the mixed or 'scan negative' CES group were more likely to have a functional disorder such as pain, irritable bowel syndrome etc. Pain was the most common

functional disorder subtype particularly chronic widespread or back pain (20% v. 51% and 81%, p=0.003, p=<0.0001) (Table Four). However, this study was specifically investigating prevalence of functional neurological disorders in patients with 'scan negative' CES and there was no difference in rates of pre-admission functional neurological disorders between groups (7% vs. 6% and 12%, p=0.8, p=0.5).

There were relatively high frequencies of psychiatric comorbidity in all groups and significantly higher total frequencies of psychiatric comorbidity in patients in the 'mixed and 'scan negative' CES groups (lifetime rates 51% vs. 84% and 90%, p= 0004 and p<0.0001; current rates 44% vs. 75% and 90%, p=0.002 and p=<0.0001)(Table Four). Patients with 'scan negative' CES had higher frequencies of all assessed psychiatric disorders particularly post-traumatic stress disorder (PTSD) (10% v. 27% and 43%, p=0.0003) and panic disorder (20% v. 56% and 61%, p= 0.00002). Interestingly, there was no difference between means, numbers of patients in all three groups with ≥1 or ≥4 adverse childhood events or reporting sexual abuse on the adverse childhood events questionnaire.

Similar rates of all three patient groups were working or on maternity leave on admission (54% v. 47% and 48%, p=0.4, p=0,6) and expected to return to work (63% vs. 57% and 55%, both p=0.5). Patients with 'scan positive' CES were more likely to be retired (22% v. 6% and 2%, p=0.02, p=0.002). A higher proportion of patients in the both the mixed and the 'scan negative' CES group were off sick prior to admission (7% v. 28% and 36%, p=0.02, p=0.001) and patients with 'scan negative' CES were more likely to be on benefits at the time of admission (7% v. 22% and 27%, p=0.01).

Table Four: Predisposing factors

	'Scan positive' CES n=47	**Mixed N=76**		**'Scan negative' CES N=61**	
Total Functional Disorder comorbidity *	10 (24%)	43 (64%)	**<0.0001**	46 (81%)	**<0.0001**
Subtypes of functional disorder:					
Chronic back pain *Chronic pain***	8 1 widespread	34 5	**0.002**	25 10	**0.008**
Irritable Bowel Syndrome *Non-cardiac chest pain* *Other*	1 0	1 3		6 0 5 ***	

Functional neurological disorders* *Limb Weakness* *Dissociative Seizures*	3 (7%) 1 1	4 (6%) 2 2	0.8	7 (12%) 1 7	0.5
Other:	1 (n=1 memory)	1 (n=1 memory)		1 (n=1 visual,/movement disorder)	
Psychiatric Diagnoses (SCID DSM-5) on admission**					
Lifetime Total	21 (51%)	54 (84%)	**0.0004**	50 (90%)	**<0.0001**
Current Total	18 (44%)	48 (75%)	**P=0.002**	50 (90%)	**<0.0001**
Current Depression	4 (10%)	26 (41%)	0.0008	21 (38%)	**0.002**
Past Depression	14 (34%)	33 (52%)	0.1	37 (66%)	**0.002**
Panic	8 (20%)	34 (56%)	**0.003**	34 (61%)	**0.00002**
Agoraphobia	5 (12%)	22 (36%)	**0.04**	24 (43%)	**0.003**
Health Anxiety	1 (2%)	7 (11%)	0.1	9 (16%)	**0.03**
Generalised anxiety disorder	9 (22%)	18 (28%)	0.6	24 (43%)	**0.03**
Obsessive compulsive disorder	5 (12%)	19 (30%)	0.051	23 (41%)	**0.002**
Post-Traumatic Stress Disorder	4 (10%)	17 (27%)	0.92	24 (43%)	**0.0003**
Adverse Childhood events Score (ACE) from questionnaires					
	'Scan positive' CES n=38 (81% total)	**Mixed N=61** (80% total)		**'Scan negative' CES N=41** (66% total)	
Refused	2	1		1	
Mean (SD)	1.5 (2)	1.7 (2)	0.3	2.2 (3)	0.2
ACE scores ≥1	17 (45%)	37(62%)	0.1	23 (59%)	0.3
ACEs core ≥4	6 (16%)	12 (20%)	0.6	12 (31%)	0.1
Sexual abuse	2 (5%)	8 (13%)	0.2	8 (20%)	0.07
Employment					
Working/on maternity leave	22 (54%)	30 (47%)	0.4	27 (48%)	0.6
Off sick on admission	3 (7%)	18 (28%)	**0.009**	20 (36%)	**0.001**
Receiving state related disability benefit	3 (7%)	14 (22%)	0.06	15 (27%)	**0.01**
* some patients had more than one disorder. **Chronic pain in mixed group: n=2 abdomen, n=2 shoulder, n=1 hip; chronic pain in 'scan negative' group: n=6 widespread, n=3 abdominal, n=1 groin, ***other in 'scan negative' group: n=2 hyperventilation syndrome, n=2 CFS, n=1 globus					

Outcome at 3 months in Mixed and Scan Negative groups

New Diagnoses

During follow up (mean duration 24 months, 92% and 89% follow up) four patients acquired neurological diagnoses which fully or partially explained their clinical CES symptoms. Table Five and supplementary table two detail the diagnoses found.

Two patients died during follow up (n=1 unexpected death with no cause found at post-mortem in the mixed group, n=1 unrelated cardiac failure in the 'scan negative') group.

Fourteen patients represented urgently with possible CES, but none had radiological evidence of CES or other explanations for their symptoms (mixed n=6, 'scan negative' group n=8).

Three patients (4%) in the mixed group and ten patients (16%) in the 'scan negative' CES group received a new diagnosis of a functional neurological disorder after an outpatient neurology appointment(16%) during the follow up period. The most common symptoms in both groups were functional limb weakness (n=2 and n=6), followed by dissociative seizures (n=3) which only occurred in the 'scan negative' CES group, sensory symptoms (n=1 and n=2) and persistent postural perceptual dizziness (n=1 in both).

Twenty patients(26%) in the mixed group and twelve patients (19%) in the 'scan negative' CES group had persistent urological symptoms on discharge and were referred to urology or gynaecology although 5% of both groups did not attend (see Supplementary Table three). Only one patient was diagnosed with neuropathic voiding dysfunction after investigation; the patient with the cervical transverse myelitis. Approximately one third of patients (32%) had symptom resolution, normal investigations or they were unable to tolerate investigations, 28% had idiopathic voiding problems and 12% had storage symptoms, stress incontinence was only diagnosed in patients with 'scan negative' CES (n=2).

Table Five: Follow up and Outcomes from Notes +/- GP Review		
	Mixed Notes Review **n= 76**	**'Scan negative' CES** Notes and GP Review **n= 62**
Follow up achieved	70 (92%)	55 (89%)
Average follow up/ months	24	23
Deceased or palliative	1 no cause found on post-mortem	1 unrelated to CES presentation, Left ventricular failure
Cause of clinical CES presentation partially or fully explained with hindsight	3 Transverse myelitis (n=1) Small cervical epidural haematoma (n=1)^ Presumed CNS inflammatory disorder (n=1)*	1 Sacral chordoma (n=1)
Re-presentation with clinical CES without explanation	6 (8%)	8 (13%)
New diagnosis of Functional Neurological Disorder	3 (4%)	10 (16%)
^cervical epidural haematoma picked up on outpatient MRI of cervical spine, patient had fall from horse at symptom onset; *spasticity left leg, normal MRI Brain and spine, OCBs unique to CSF		

Three Month Follow Up Questionnaires

66% of patients with 'scan positive' CES returned the three months follow up questionnaire (n=31), 62% (n=47) in the mixed group and 47% (n=29) patients in the 'scan negative' CES group (Supplementary Table Three). Patients in all groups who returned their questionnaires had high rates of overactive bladder symptoms (74-86%) and similar levels of bowel and sexual dysfunction. Patients in the mixed or 'scan negative' CES groups had higher distress (HADs average 8.3 v. 16.9 and 16.2, p=<0.0001, p=0.0005), this appeared to be due to a *reduction* in HADs score in the patients with 'scan positive' CES. Employment outcome was similar amongst the groups with approximately half of patients in all groups working at follow up and one fifth on disability related benefits.

Discussion

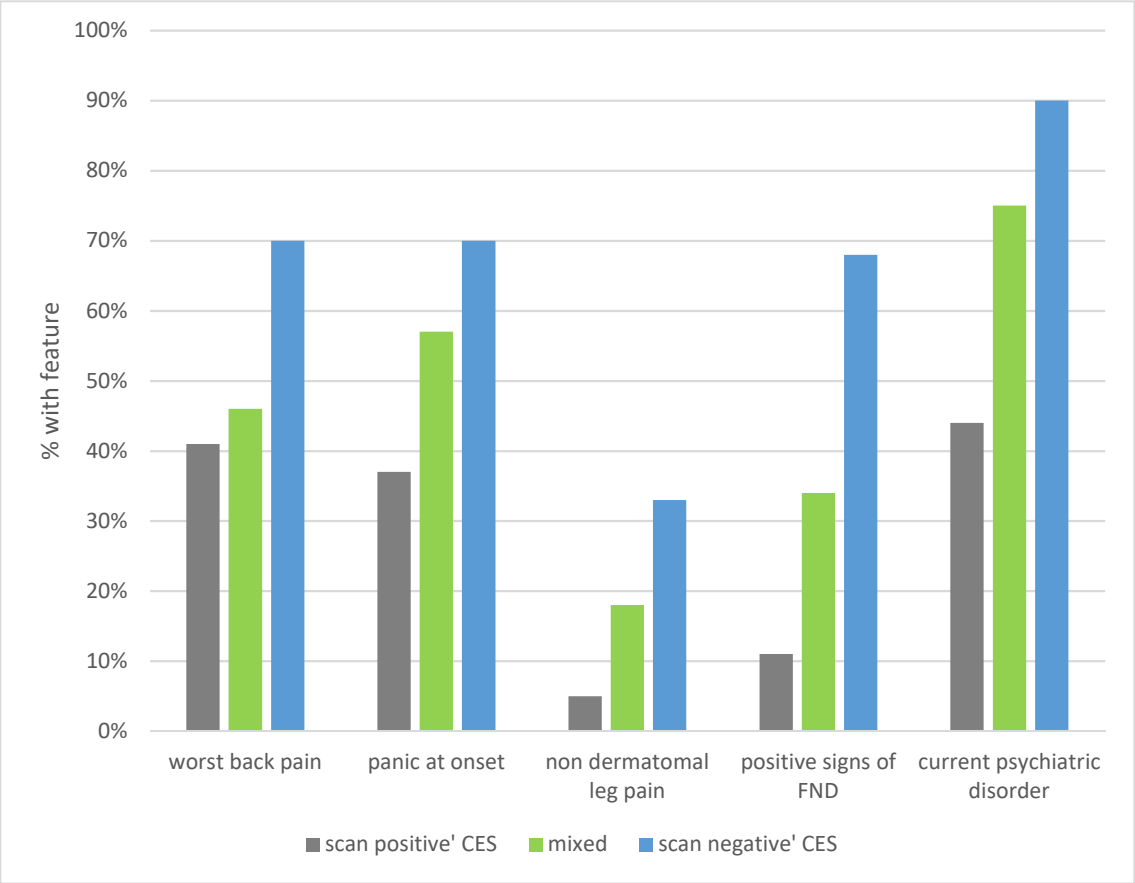
This is the first large prospective study of patients with 'scan negative' CES, phenotyping patients at presentation through a mixture of semi-structured interview, examination and questionnaire. We have also supplemented this 'real-world' data with follow up mindful of the possibility of other neurological explanations for patient's clinical CES symptoms.

Symptoms and Signs

As with other studies there was no one clinical symptom or sign of sufficient discriminatory value to render an MRI scan unnecessary. Some symptoms and signs, in our study chronic leg pain and absent ankle jerks, may be helpful in increasing pre-test probability of 'scan positive' CES.

There were also potential positive predictors for patients with 'scan negative' CES including "worst ever back pain", symptoms of a panic attack or dissociation at onset, non-dermatomal leg pain and more bladder symptoms in the month prior to admission. Most strikingly, inpatient assessment patients with 'scan negative' CES were much more likely to have positive evidence of a functional neurological disorder (FND) on examination despite having similar rates of FND prior to their admission. For many of the studied variables there was a dose-response effect with higher values in mixed, and higher values again in scan negative patients (Figure 1).

Figure One: Dose Response of factors in support of 'scan negative' CES often being explained by a Functional Neurological Disorder (FND)



Potential explanations of 'scan negative' CES

Alternative neurological disease explanation

From this prospective study and from previous retrospective work we carried out in 276 individuals from the same centre(Hoeritzauer *et al.*, 2018) it does not appear that alternative neurological disease explanations are a major cause of 'scan negative' CES. In this prospective study only 4% were given a new diagnosis partially or fully explaining their symptoms during follow up of mean 23 months. This small number supports retrospective work which found only one similar patient out of 191 scan-negative CES with a follow up of 15 months(Hoeritzauer *et al.*, 2018).

The authors considered the differential diagnoses for clinical CES throughout the study (see Table 4 in (Hoeritzauer *et al.*, 2018)). Some diagnoses such as infectious lumbosacral polyradiculitis from

HSV, Elsberg syndrome, can be difficult to diagnose due to lack of diagnostic suspicion and be associated with clinical investigations and symptoms which may normalise quickly. Elsberg syndrome causing cauda equina radiculitis occurred in 5 of 1,035 patients investigated at the Mayo clinic with both myelitis and radiculitis between 2000-2016(Savoldi *et al.*, 2017). Patients were predominantly male (80%) and one fifth had prodromal symptoms such as headache, myalgia, fever or sacral or oral herpes infection. Spinal arteriovenous malformations (AVM) often present initially as a peripheral disorder and also more commonly affect men, particularly between 55-60 years old. Patients may face a significant delay in diagnosis but progressive symptoms with stepwise deterioration, distal to proximal sensory loss and emerging upper motor neurone symptoms lead to targeted imaging which is abnormal in 67-100% of patients with spinal AVMs(Jellema *et al.*, 2006). Both the mixed and 'scan negative' CES groups were predominantly made up of middle-aged women. The most common inflammatory disorder affecting women in the UK is multiple sclerosis, and bladder symptoms are common, affecting approximately 75% of patients. However, pain and bladder dysfunction are unusual as a first presentation in multiple sclerosis. Similarly, Myelin Oligodendrocyte Glycoprotein Autoantibody mediated inflammatory disease is associated with conus medullaris inflammation and bladder, bowel and sexual dysfunction. However, it occurs more commonly in men in their mid-twenties with viral like prodrome or vaccination and is associated with longitudinally extensive spinal cord lesions, multiple cord lesions and bilateral optic neuritis(Narayan *et al.*, 2018; Dubey *et al.*, 2019). As this was a real-world study not all patients received imaging of the whole neuraxis, but nonetheless there was no evidence of further clinical presentations suggesting that additional missed cases are likely to have been few.

Potential mechanisms of bladder dysfunction

How could it be that such clinically significant bladder dysfunction could arise in the absence of a clear pathophysiological cause in scan negative CES? There are several pymotential explanations.

- *Direct neural inhibition related to pain*. Pain from nerve root entrapment or muscle spasm, could cause sympathetic hyperactivity and increased inhibitory signals via the pelvic and hypogastric nerves impeding normal pelvic floor function and parasympathetic urethral sphincter relaxation and causing difficulty voiding. In the mixed group high numbers of patients had severe pain caused by nerve root entrapment and in the 'scan negative' group 70% of patients described the pain at onset as their worst ever back pain.

- *Effects of medication*. Medications such as pregabalin, gabapentin and benzodiazepines can cause or exacerbate urinary incontinence and opiates can affect bladder as well as bowel function causing voiding dysfunction and severe chronic urinary retention(Panicker *et al.*, 2012). Over eighty percent of patients in all groups were on more than one medication which can be associated with urinary retention or urinary incontinence.
- *Previous bladder dysfunction*. Patients may present with suspected CES due to an exacerbation of their underlying bladder dysfunction from pain, panic or medications such as stress incontinence, overactive bladder syndrome and voiding dysfunction. Stress incontinence is more common in patients with chronic back pain which affected >50% of patients in the mixed and 'scan negative' CES groups. Studies suggest that medically refractory overactive bladder syndrome symptoms may be due to an anxiogenic state and hyperawareness of normal bladder filling rather than an abnormality of the detrusor muscle (Klausner *et al.*, 2009). All types of bladder dysfunction were more severe in patients with 'scan negative' CES in the month before admission.
- *Shared mechanism with Fowler's syndrome and Paruresis*? Two urological conditions may cast further light on mechanism; Paruresis and Fowler's syndrome. Paruresis, also called "shy bladder syndrome", is a condition affecting 3-16% of the population causing intermittent inability to initiate or maintain urination due to failure of external urethral sphincter relaxation with additional inhibitory top-down brain-bladder signals. Patients are unable to void when aware of others around them. It is usually triggered in adolescence by an anxiety invoking experience in a public toilet, is associated with higher than population rates of psychopathology (5-70%) (Kuoch *et al.*, 2017) and responds to graded exposure therapy (Soifer *et al.*, 2009). Paruresis is an amplification of the normal inhibitory bladder responses to being in an unsafe voiding situation. The insula, medial and lateral prefrontal cortex and brainstem circuit are key components of the brain bladder network as well as the "fear network"(Sobanski and Wagner, 2017). In health, these brain areas are key to assessing the safety to void. However, during panic the fear network is engaged and abnormal voiding or lack of voiding can occur. Fowler's syndrome describes chronic urinary retention due to a primary failure of external urethral sphincter relaxation and is triggered by pain or medications. Patients with Fowler's syndrome have high rates of comorbid functional neurological disorders and pain (Hoeritzauer *et al.*, 2016). The aetiology of Fowler's syndrome is uncertain, but it may be a chronic model of the acute process affecting patients with 'scan negative' CES.

Is "scan-negative" CES largely a consequence of a functional disorder?

In keeping with our hypothesis, in comparison to 'scan positive' CES patients, patients with mixed and 'scan negative' CES had significantly more evidence of a functional neurological disorder (11% vs. 34% and 68%), despite having similar low rates of functional neurological disorders pre-admission (7% vs. 6% and 12%, p=0.8, p=0.5). Patients were also more likely to have predisposing factors for developing a functional neurological disorder: higher frequencies of functional disorder diagnosis on admission (24% vs. 64% and 81%) and more current psychiatric comorbidity (rates 44% vs. 75% and 90%). The specificity of symptoms of a functional neurological disorder on admission was 0.89 (0.57-0.97) sensitivity 0.68 (0.53-0.8) when comparing scan positive and scan negative CES groups.

The data builds on our pilot and retrospective studies suggesting that at least some patients with mixed and 'scan negative' CES have symptoms due, in broad terms, to a disorder of nervous system functioning, rather than pathophysiological disease, with functional or medication related urinary symptoms combining with pain and acute functional limb sensory loss and/or weakness.

Functional neurological disorders are diagnosed based on positive clinical signs with good diagnostic sensitivity and specificity (Daum *et al.*, 2015), such as Hoover's sign of functional leg weakness, weakness of hip extension which normalises with contralateral hip flexion. The understanding of what functional neurological disorders are has changed over the last decade. Previously thought of as primarily result of the physical conversion of traumatic emotional events, more recent work has led to a recognition of the disorder as being truly a brain-mind disorder with a Bayesian mechanism of 'top-down' expectation and abnormal self-directed attention overriding normal motor and sensory pathways(Edwards *et al.*, 2012; Van den Bergh *et al.*, 2017). It is an important diagnosis to make as without specific treatment, 80% of patients continue to have symptoms on 14 year follow up(Gelauff *et al.*, 2019) whereas tailored physiotherapy has the potential to improve outcome(Nielsen *et al.*, 2015, 2016)). Pain, panic and dissociative experiences are often triggers for functional neurological disorders. In a systematic review of 869 patients with functional neurological symptoms physical injury preceded onset in 37% (Stone *et al.*, 2009) and in another study panic was found to precede symptoms in 59% of patients with sudden onset functional neurological disorders(Stone *et al.*, 2012). Our study is the first to test the hypothesis that panic is more likely to occur in patients with functional neurological disorders compared with a control group with similar presenting symptoms. 57% and 70% of patients in the mixed and 'scan negative' groups had

symptoms of a panic attack at the onset of their symptoms compared with 37% of patients with 'scan positive' CES. Additionally, 70% of patients in the 'scan negative' group had their worst ever back pain.

A proposal for understanding the mechanism of mixed and 'scan negative' CES

We propose that some patients who have a vulnerability to functional disorders (including FND) with or without some underlying bladder problems who develop severe back/leg pain from nerve root entrapment or simply muscle spasm react with panic and dissociation(Perez *et al.*, 2018) There is abnormal bladder function due to inability to contract the pelvic floor (urinary incontinence) or relax the pelvic floor (urinary retention) and functional neurological symptoms such as leg weakness and numbness. Analgesics taken acutely or long term, particularly opiates, which >40% of patients were taking, could compound voiding dysfunction and medications such as gabapentinoids, which more than one third of patient were taking, could compound urinary incontinence. For a significant proportion pain may become chronic and when flare-ups of pain occur bladder and neurological symptoms reappear, and patients re-present with suspected. These patients may become trapped in a cycle of kinesiophobia, deconditioning, abnormal self-directed attention leading often to chronic pain from central sensitisation and functional neurological symptoms (Figure 2).

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

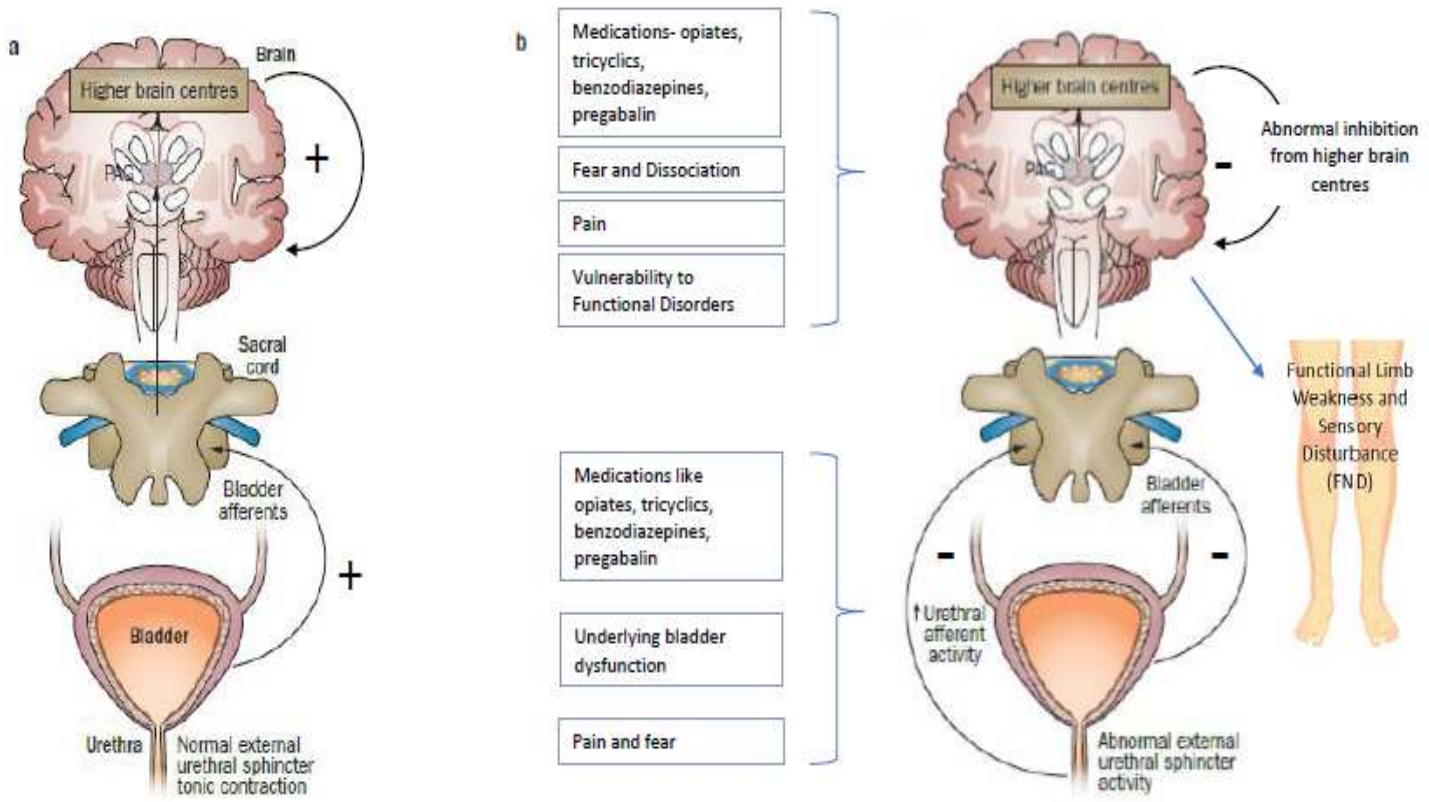


Figure Two: Proposed Mechanism of 'Scan-Negative' Cauda Equina Syndrome (CES) (adapted from Osman N and Chapple C, Nature Reviews Urology 2014 with permission)

a. In health, bladder filling leads to sacral cord activation and if safe and socially appropriate higher brain centres activate the PAG and voiding occurs.
b. In 'scan negative' CES both bladder and brain are affected by medications, pain and fear leading to inhibition of normal voiding, more pain and a negative feedback loop. The same brain processes also render individuals susceptible to functional neurological disorder causing motor and sensory dysfunction in the legs

Limitations

This was a real-world study which had limitations including case definition, blinding, potential bias in control and cases selection, questionnaire return rate, measures used and extent of investigations.

It was not possible to assess the majority of patients blind to the scan results due to the nature of patient recruitment and the urgent nature of the operation if a patient was diagnosed with 'scan positive' CES. The non-blinding of the examiner may have influenced the frequency of psychiatric diagnosis although all structured interviews were discussed with a blinded supervisor for the first twelve months. In Edinburgh there may be a higher frequency of patients admitted to the neurosurgery ward with 'scan negative' CES compared to other neurosurgical centres due to the reduced availability of out of hours MRI in the Edinburgh locality. However, literature suggests 'scan negative' CES occurs in the majority of patients scanned for suspected CES in UK centres(Hoeritzauer *et al.*, 2019).

Conclusion

We present the first well phenotyped, prospective information about patients with 'scan negative' CES, a common clinical neuroscience presentation which accounts for at least half of all patients presenting with suspected CES. We have provided evidence for understanding the nature of 'scan negative' CES based on a hierarchical model which takes in to account a range of probable physiological, psychological and "functional disorder" causative factors.

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Conclusion: Patients were again divided into three groups; 'scan positive' CES, a mixed group comprising nerve root entrapment or compression or 'impending' CES and patients with normal scans 'scan negative' CES. The prospective nature of the study allowed us to investigate our hypotheses by asking specifically about pain and panic at onset, examining for positive evidence of functional neurological disorders and asking about psychiatric symptoms, medication use and prior bladder dysfunction.

This study provided further evidence of the link between functional neurological disorders and patients with 'scan negative' CES. Patients with 'scan negative' CES were more likely to have evidence of a functional neurological disorder when examined during their admission. Their symptoms also provided support for a mechanistic hypothesis that pain and panic negatively affected the normal bladder-brain axis from both top down and bottom up ways. Pain and panic are also known triggers for functional neurological disorders. There was a stepwise progression of functional symptoms between groups, patients with 'scan positive' CES had the lowest and patients with 'scan negative' CES had the highest.

Predisposing factors such as higher levels of social functional impairment (Work and Social Adjustment Score), being off sick, pre-existing stress incontinence and high levels of pain medications which could affect bladder function were seen in patients with 'scan negative' CES. Precipitating factors such as a patients' 'worst ever' back pain and associated panic attack were more common in patients with 'scan negative' CES. Follow up investigation after 24 months for new diagnoses explaining clinical CES found only 4 patients who had partially or fully explanatory diagnoses. Therefore, the majority of patients do not have an underlying neurological disorder causing their symptoms.

There was only one structurally related urological disorder diagnosed on follow up. This was in the patient with a cervical inflammatory lesion. Other patients had urological diagnoses which would fall under category of functional urological diagnoses. As discussed earlier, the nomenclature around urology is different. However, the disorders diagnosed related most commonly to voiding dysfunction which is commonly associated with higher rates of psychological and psychiatric comorbidity[21]. The aetiology of these disorders is controversial and they are thought to reflect abnormalities of brain-bladder axis function not structure[21].

This study was the first deeply phenotyped study of patients with 'scan negative' CES. We were able to determine what proportion of patients with 'scan negative' CES had evidence of a functional

neurological disorder and were able to identify predisposing, precipitating and perpetuating factors relevant to the diagnosis and mechanism of 'scan negative' CES. We also found support for our hypothesis that at least some patients are best understood to have a functional disorder causing most or at least some of their symptoms. These findings, whilst still preliminary, allow the creation of a clinically useful narrative for patients who have thus far been a medical mystery which aims to help explain their symptoms and allow targeted physical, psychological and medical therapy (see patient information leaflet in appendix).

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Paper Five: Hoeritzauer I, Jon Stone, Clare Fowler, Suzy Elneil, Alan Carson, Jalesh Panicker. Fowler's syndrome of Urinary Retention: a Retrospective Study of Comorbidity. Neurourology and Urodynamics. 2016; 35(5): 601-603.

Introduction: To achieve **Aim 3:** *To determine what proportion of patients with urinary retention from Fowler's syndrome or idiopathic causes (chronic idiopathic urinary retention/dysfunctional voiding/bladder outlet obstruction) have comorbid functional neurological disorder* I carried out a retrospective study of comorbidity in 62 patients who were diagnosed with Fowler's syndrome between 2009-2013. There had been a suggestion clinically and from previous studies of vulnerability to psychological and functional comorbidity in patients with Fowler's syndrome, but this had not been directly investigated.

Fowler's syndrome of Urinary Retention: a Retrospective Study of Co-morbidity

Names of Authors withheld as per journal instructions

Abstract

Aims

To study the frequency of pain, psychological or functional disorders in patients with Fowler's syndrome.

Methods

We carried out a retrospective chart review of patients with a diagnosis of Fowler's syndrome attending the Uro-Neurology centre at the National Hospital for Neurology and Neurosurgery between 2009-2013 looking at triggering events, physical and psychological comorbidities.

Results

Of 62 patients with clinical and electromyographic diagnosis of Fowler's syndrome, 31 (50%) had unexplained chronic pain syndromes, 12 (19%) of these were taking opiates. 15 (24%) had "functional" neurological symptoms. Abdominopelvic surgery with general anaesthesia was the leading trigger (n=21, 35%).

Conclusions

We found high levels of co-morbidity with patients having some form of pain (50%), a probable functional disorder (24%) or psychological symptoms (31%). There are several potential explanations for this association including the effect of developing an apparently unexplained distressing condition, confounding effect of opiate use or referral bias. The findings suggest a need for prospective systematic study of comorbidity for this disabling condition.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Introduction

Urinary retention in young women is a disabling problem that often occurs in the absence of urological or clear cut neurological disease. In 1988, Fowler and colleagues(1) described in a group of young women in urinary retention, abnormal findings on urethral sphincter EMG, of complex repetitive discharges and decelerating bursts, suggesting a primary disorder of urethral sphincter relaxation; these findings were later shown to be associated with high urethral pressure profiles(2). Typically such women retained volumes of urine over a litre**,** but had impaired sensation of bladder fullness. Often, they described difficulties during intermittent catheterisation, particularly when attempting to remove the urinary catheter. This syndrome has become known as Fowler's syndrome (FS), and sacral neuromodulation has been found to be an effective treatment option(3),(4). Recent work has identified opiates as potentially exacerbating underlying physiological abnormalities leading to urinary retention both in patients with Fowler's syndrome and patients with unexplained urinary retention (without characteristic urethral EMG findings)(5).

The peak age of onset of Fowler's syndrome, in the second and third decades post menarche **(6)**, and the observation that urinary retention may be triggered after surgery, childbirth and minor medical procedures(6) remain unexplained. Recent studies have suggested a vulnerability to physical and psychological comorbidities but these have not been clearly reported(7). We therefore undertook a retrospective review of all patients with Fowler's syndrome attending our service to examine comorbidity more carefully.

Materials and Methods

A retrospective chart review of women referred to the tertiary referral Uro-Neurology centre at the National Hospital for Neurology and Neurosurgery between January 2009 to December 2013 for voiding difficulties or urinary retention and undergoing urethral sphincter EMG was carried out. Patients had been referred when local urological and local neurological investigations had been unable to find a cause for urinary voiding dysfunction.

Urethral pressure profile (UPP) was measured using the perfusion catheter technique, with a normal control range calculated as 92-patient age (years) in cm water, as established in a previous study**(8)**. Concentric needle EMG of the striated urethral sphincter using a technique previously described (1)was performed in all patients (JP or CJF) using an EMG machine (Keypoint®.NET, Alpine Biomed, Denmark). Patients with the characteristic abnormal EMG findings described above were diagnosed as having FS (1). From the charts, information about pain and non-urological symptoms such as psychological or psychiatric symptoms or diagnoses, functional or "unexplained" physical symptoms were noted.

Results

In total, 62 women were diagnosed as having Fowler's Syndrome. Mean age was 32 years (range 17-64); average duration of symptoms was 53 months (range 1-336).

All patients had complex repetitive discharges and decelerating bursts on urethral sphincter EMG. The UPP was elevated in 49 patients out of 52 in whom it could be measured (94%). Fifty patients (81%) were in retention at the time of assessment, 28 of whom spontaneously reported an uncomfortable gripping

sensation on withdrawing the catheter used for intermittent self-catheterisation. Thirty six patients (58%) had recurrent urinary tract infections.

Evaluating factors that triggered urinary retention

Twenty-one patients (35%) developed symptoms following anaesthesia all of whom had abdominal or pelvic procedures: laparoscopy/laparotomy (n=12), caesarean-section (n=2), hysterectomy (n=2) and post-partum (n=2), other procedures (n= 3) (colonoscopy, Mirena coil insertion under GA, colposcopy). Seven patients (11%) described the onset after experiencing acute pain or some other physical trigger (associated with unexplained abdominal, loin or perineal pain and numbness (n=2), fall against door frame, fall from horse, lifting heavy object, menstruation (each n=1), and pain and rash (n=1)). Six patients (9%) developed symptoms after a urinary tract infection of whom two volunteered a long prior history of poor voiding. Twenty-seven (44%) patients had no clear trigger for their symptoms of whom 14 volunteered a long history of voiding difficulties. No information on onset was available on one patient**.**

Physical and Psychological comorbidity

Eight patients (13%) had documented pelvic pathology, endometriosis (n=4), ovarian cysts (n=3) pelvic inflammatory disease (n=1).

Thirty one patients (50%) had unexplained chronic pain syndromes (abdominopelvic pain (n=22), back or leg pain (n=5), widespread or unspecified (n=4). Fourteen patients (23%), (6/31 with chronic pain syndromes), were taking opiates at onset of retention and 17 (27%), (12/31 with chronic pain syndromes), during follow up.

Fifteen patients (24%) had functional neurological symptoms with overlap of symptoms (loss of consciousness (n=7), limb weakness (n=6), sensory disturbance (n=6), memory impairment (n=3)).

Nineteen patients (30%) reported symptoms of anxiety/depression (n=18) or obsessive compulsive symptoms (n=3). In total only 19 (30%) patients had no pain symptoms or psychological co-morbidities.

Discussion

In this retrospective case note review, we found high levels of co-morbidity in patient with Fowler's disease. The most common comorbidities were pain (50%), functional neurological symptoms (24%) or psychological symptoms (30%) though a formal diagnosis was often lacking. It seems likely that these figures are an underestimate given the retrospective methodology of the study and the clinical focus of the uro-neurology service. Given the relative youth of the subjects, the presence of such high levels of co-morbidity is thought-provoking.

Several studies have hinted at high levels of comorbidity amongst women in urinary retention (7),(9),(10),(11) although these have used symptom scales and psychological assessments rather than describing comorbid diagnoses based on the patient's medical history. Fifty per cent of patients (n=31) in our review had unexplained pain syndromes, largely abdominopelvic but also back or leg pain, of which 12 (38%) had been started on tramadol or some similar oral opiates.

Patients presenting with the phenotype of Fowler's syndrome were previously often labelled as psychogenic or hysteric(12,13). The common psychoanalytic view that the symptom arose from sexual conflict or infantile guilt was understandably rejected by many clinicians (14). An equally unpalatable neurological view of psychogenic symptoms has been that they were feigned or 'not real'(15). Some older literature on 'psychogenic retention' made clinical connections between urinary symptoms and other physical and psychological comorbid symptoms(16) (12),(17)

From this chart review it appears that some women with Fowler's syndrome also have functional neurological symptoms such as non-epileptic attacks or leg weakness. Functional neurological symptoms are genuine disorders which can be understood as an interaction between physiological and psychological variable and are not just 'all in the mind'(18). A figure of 24% is higher than might be expected as a generic stress response, and warrants further investigation. Although common in neurology, functional neurological symptoms, e.g. seizures and leg weakness, are much less common in the general population. For example, dissociative attacks have a prevalence of 2 to 33 per 100, 000 (ie 0.002-0.03%). The prevalence of functional leg weakness is unknown but based on incidence of 3/100,000(16) and prognosis studies(19) is of a similar magnitude. However, the presence of a neurological disease is a risk factor for developing superimposed functional neurological symptoms, often typically related to the symptoms of that disease. For example in one study, 7% of patients with Parkinson's disease also had a somatoform disorder(20). Systematic reviews of comorbidity in irritable bowel syndrome and fibromyalgia have not reported on the frequency of functional symptoms such as seizures and leg weakness, even though they recorded numerous other functional symptoms such as fatigue and pain at high frequency giving further credence to the hypothesis that our figure of 24% is unusual(21)(22). Looking at things in reverse, bladder symptoms are common in patients with functional limb weakness (28%) (16) and anecdotally voiding dysfunction is over-represented in patients with functional neurological symptoms in general, although studies are lacking.

The study was limited by the retrospective methodology, history, examination and investigations were available only from letters sent by or received by the clinical team. Moreover, the clinical focus of the Uro-neurology service was on the management of voiding dysfunction, not the systematic collection of co-morbidities. Therefore, it is not possible to determine the true prevalence of co-morbidities in this population based upon the results of this study, or to draw causal inferences.

Nevertheless, the high levels of comorbidity in women with Fowler's syndrome is intriguing and several hypotheses can be considered. Firstly, it could be that the comorbidity that has been recorded is simply a result of the inevitable effect of a distressing medical condition in a population of young women. An earlier survey showed that on average these young women had been seen by three hospital consultants before a diagnosis was made (23)and levels of psychological morbidity were not that different to other neurological disorders in a tertiary setting. The resolution of some of these symptoms in patients who are treated with sacral neuromodulation would be in keeping with this. Secondly, it could be that Fowler's syndrome is triggered in some patients by the use of opiate based medication which exacerbates detrusor underactivity and reduced urge(5),(24). The association with functional neurological symptoms could simply be a confound related to opiates which are prescribed to patients who have a vulnerability to both chronic pain and functional disorders. Thirdly, it may be that patients with unusual or complex comorbidity are more likely to find their way to a tertiary Uro-neurology service whereas those that don't are more successfully managed in their local hospital. In favour of these hypotheses are the relatively specific neurophysiological findings which are not found in voluntary striated muscle under normal conditions, the raised urethral pressure profiles which are outwith the range for normal volunteers, and the presence of patients without comorbidity.

Knowledge of urethral sphincter EMG findings in women without urinary symptoms is limited but it seems likely that complex repetitive discharges and decelerating bursts are a not uncommon type of activity to occur in this muscle since two abstracts have reported its presence in healthy volunteers (25–27). The striated muscle of the female urethral sphincter has unusual properties: it has been demonstrated to be hormonally sensitive, undergoing atrophy with the menopause, and is almost continuously electrically active. The actual cause of CDRs and DBs is not known but this type of activity appears to be unique to the muscle. The "amount" of the activity in any one individual is difficult to

quantify, especially using the sampling technique of needle EMG which examines only a small volume of muscle, but it alone may not be the determinant of whether or not a women develops urinary retention. Based on the hypothesis that detrusor inhibition is the result of urethral afferent activation, some means of measuring that activity in women with the EMG activity, with and with bladder symptoms is needed before its significance to the cause of retention can be dismissed.

It is essential to formally evaluate functional neurological disorders and chronic pain in this population, exploring the behavioural underpinnings contributing to these, and the complex interplay, if any, that may exist between these and the underlying primary disorder of urethral sphincter relaxation.

If there is an association between functional neurological disorders and Fowler's syndrome, this could ultimately be of benefit to understanding both disorders and to patients with multiple comorbidities.

Our findings signal the need for prospective systematic study of comorbidity for this disabling problem. A detailed study of comorbidity which involves longitudinal understanding of the sequence of symptoms, interaction with medication, and response of those symptoms to successful treatment is required to test the hypotheses described above. The inclusion of a control group, for example patients in Uro-Neurology clinics without Fowler's syndrome or patients with defined disease causes for their symptoms would be particularly valuable in assessing the specificity of any associations.

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Conclusion: This was the first study demonstrating a higher proportion of chronic pain, functional disorders and psychological symptoms. Although retrospective, the study found evidence of a link between functional disorders and Fowler's syndrome. Almost one quarter (24%) of patients had evidence of a functional neurological disorder. We considered several hypotheses as to why this relationship occurred including the effect of opiates, which had previously been found to have a direct link in patients with idiopathic chronic urinary retention, the effect of bias from who is referred to quaternary referral centres with symptoms and the possibility that Fowler's syndrome or chronic idiopathic urinary retention may be due to a fixed, functional, external urethral sphincter dystonia.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Paper Seven: Lower Urinary Tract Dysfunction in patients with Functional Disorders attending neurology outpatient clinics. I Hoeritzauer[1], O Shipman-Sharma[1], J Stone[1,2], A Carson[1,2,3]

Introduction: This study was done to address **Aim 4** of the the PhD; **Aim 4:** *To determine what proportion of patients with functional neurological disorders have lower urinary tract dysfunction*. A prospective study of patients presenting to general outpatient neurology clinics over a one month period in the Western General Hospital in Edinburgh based on the Scottish Neurological Symptom Study was performed. The study asked patients about their bladder symptoms using the Urinary Symptom Profile questionnaire to gain information about the type of bladder dysfunction (stress incontinence, overactive bladder symptoms or low stream) and the short form-qualiveen to investigate effect on quality of life from any bladder dysfunction present. Patients were then rated by consultant neurologists along a four point Likert scale as having their neurological symptoms 'completely', 'largely', 'somewhat' or 'not at all' due to a functional disorder.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Lower Urinary Tract Dysfunction in patients with Functional Disorders attending neurology outpatient clinics

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Ethics approval:

South East Scotland Research Ethics Committee (Ref 16/SS/0107)

Abstract

Aims: To study the prevalence of urological symptoms in patients with functional disorders attending neurology outpatient clinics.

Methods: All patients attending general outpatient neurology clinics over one month were asked to fill in a questionnaire about urological symptoms (the Urinary Symptom Profile: subdivided into stress incontinence, overactive bladder and low stream scores) and distress caused by these (SF-Qualiveen). A consultant neurologist recorded how likely their neurological symptoms were to be due to a functional disorder; 'not at all', 'somewhat', 'largely' or 'completely'.

Results: 132 patients were included in the study (mean age 44yrs, 60% female), 33% of whom had symptoms judged as 'largely'/'completely' due to a functional disorder (n=44). Low stream symptom scores were higher in females with symptoms 'largely'/'completely' due to a functional disorder (0.3 vs. 0.85 p=0.005). Male and female patients with symptoms 'largely'/'completely' due to a functional disorder were more likely to report at least one significantly affected domain in SF-Qualiveen (66% vs 45%, p=0.03). However, symptom scores were low, and quality of life was only mildly affected.

Conclusions:

Females with functional disorders attending neurology outpatients have more low stream symptoms and are more distressed than patients with pathophysical diseases attending neurology.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Phenotyping Studies

Introduction

Lower urinary tract dysfunction (LUT) occurs frequently in patients with a wide range of neurological diseases. Despite the significant impact on quality of life, until recently it has received little attention in general neurology literature or practice. Increasing understanding of the complex brain-bladder axis and the anatomical networks linking emotion, attention and the bladder has led to greater interest in LUT dysfunction in neurological and psychiatric disease[1]. Patients with functional disorders, also called somatoform or psychogenic disorders, have also benefited from enhanced interest and understanding of brain-body networks, particularly the role that expectation plays in the interpretation and experience of bodily sensation[2].

In the Scottish Neurological Symptoms study, a large multi-centre study involving 3781 neurology outpatients, functional disorders accounted for the second most common reason why a patient was seen in neurology clinic (16% of all referrals). A smaller number (5.6%) had functional neurological disorders/conversion disorder[3]. Functional disorders refer to the whole range of functional disorders seen in neurological practice such as fibromyalgia, hyperventilation and chronic dizziness. The term functional neurological disorder is reserved for a subgroup of patients who have positive evidence of a functional neurological disorder causing motor, sensory or seizure symptoms as defined in DSM-5; for example, leg weakness with positive Hoover's sign.

In the Scottish Neurological Symptoms study the prevalence of the 13 most common physical symptoms which patients present to GPs with, such as back pain, headaches or fainting spells, were investigated using the PHQ-15. Patients in the functional group were found to have high rates of these comorbid physical symptoms. This proved useful in understanding the extent of the overlap between patients with multiple physical symptoms who also had functional disorders and in creating hypotheses about overlapping mechanisms of action[4,2,5].

However, although this study explored many physical symptoms it did not estimate the prevalence of LUT symptoms in patients with functional and pathophysiological disorders attending neurology. No other studies have investigated this question. LUT symptoms have long been hypothesised to be a common comorbidity of patients with functional disorders and neurological symptoms. 'Hysterical ischuria' (retention) was mentioned as far back as YEAR by Charcot and in the earlier 20th century there have been many case series and reports of 'psychogenic urinary retention' usually affecting females. In

the 1980s the criteria for DSM-IV somatisation disorder[7] included urinary retention and several studies have found some overlap between patients who have functional disorders such as irritable bowel syndrome and LUT storage symptoms[6]. Therefore, we hypothesised that the prevalence of LUT symptoms in patients with functional disorders attending neurology would be high and is likely to be distressing. We further hypothesised that females with a functional disorder would have more low stream symptoms.

Given the success of the Scottish Neurological Symptoms study in recruiting patients, the accuracy of diagnoses (only 4 out of 1144 patients' functional diagnoses changed over an 18 months follow up[7]) and the importance of a neurological control group to compare LUT symptoms with, our study utilized the same methods in a single centre to investigate prevalence of LUT symptoms in patients with functional and pathophysical neurological disease and levels of associated distress.

Our study aimed to assess a) type of LUT dysfunction based on our hypothesis that female patients would be more likely to have low stream symptoms and b) any associated distress, in patients attending general outpatient neurology clinics with functional and pathophysiological diagnoses.

Materials and Methods

A single centre study of consecutive patients attending general neurology outpatient appointments over a one month period was carried out at the Western General Hospital, Edinburgh. The study design was based on the Scottish Neurological Symptoms Study and used similar classifications to ensure diagnostic validity. Ethics approval was gained from South East Scotland Research Ethics Committee (Ref 16/SS/0107). All patients over 18yrs of age, attending a general neurology outpatient clinic during the study time, with capacity to consent and who could read the questionnaires in English were eligible for the study. Patients were informed of the study by information leaflet sent with their neurology outpatient appointment and then choose whether to take part on the day. If they expressed an interest, patients were consented by an author (OSS) and received questionnaires prior to their appointment.

Demographics and Urinary Symptom and Quality of Life Measures

Demographic data (age and sex) and was obtained from the questionnaire, opiate use from neurologist's clinic letter review. Bladder symptoms were assessed using the Urinary Symptom Profile which provides separate scoring for stress incontinence (Range 0-9), overactive bladder (Range 0-21) and low stream (Range 0-9). The Urinary Symptom Profile is best seen as a descriptive measure, demonstrating the three different types of urinary symptoms present with good clinical correlation compared with bladder diary and ICIQ-UI SF[8], but there are no cut-offs for scores denoting mild, moderate or severe urinary symptoms. Distress regarding urinary symptoms was measured using the Short Form Qualiveen (SF-Qualiveen). SF-Qualiveen is an eight item questionnaire used to assess the extent to which urinary symptoms impact on a patient's life in four domains: 'bother from limitations'; 'fears'; 'feelings' and 'frequency of limitations'. Minimally significant scores for each domain were defined as 0.82, 0.46, 0.51 and 0.42 respectively and for total scores was 0.93[9].

Neurological Diagnosis

When the patient attended their neurology appointment the consultant neurologist was asked to rate how likely the patient's neurological symptoms were due to a functional disorder with four options; not at all, somewhat, largely or completely. The definition included the same definition of functional disorders used in the Scottish Neurological Symptoms Study which has proven diagnostic accuracy[7]; 'tension headache, symptom syndromes (e.g. fibromyalgia, irritable bowel syndrome); physiologically explained processes which are thought to be linked to emotional symptoms (e.g. hyperventilation); chronic pain or dizziness which is unexplained by a clear structural cause' and also functional neurological disorders diagnosed according to DSM-5 criteria (functional neurological symptom disorder/conversion disorder). The DSM-5 criteria is a clinical diagnosis requiring positive evidence of a functional neurological disorder, such as the tremor entrainment test of functional tremor. As in the Scottish Neurological Symptoms Study for analysis, patients were grouped into two groups; 'not at all/somewhat' and 'largely/completely' due to a functional disorder. Neurologists also recorded their overall diagnosis of the patient's neurological problem.

Analysis

Comparisons of SF-Qualiveen and Urinary Symptom Profile scores between groups 'not at all/somewhat' and 'largely/completely' due to a functional disorder were conducted non-parametrically using a Kruskal-Wallis (multi-group) or Mann Whitney U test (two groups). Contingency tables for inter-group

prevalence of symptoms were analysed using a Chi-Square Test. Urinary Symptom Profile and SF-Qualiveen scores were analysed in two groups; 'not at all/somewhat' and 'largely/completely' due to a functional disorder and by gender within these groups. The role of opiates on bladder symptoms was explored by assessing urinary symptom scores with and without patients using opiates in both groups. Significance level was p=0.05 and adjusted for multiple comparisons, were appropriate, using Tukey's honest difference method. All analysis was undertaken in Statsdirect (www.statsdirect) or MATLAB 2015b using custom written scripts.

Results

(See **Figure One**). 230 patients attended neurology outpatient clinics over the month-long study duration. 165 patients were consented for the study of whom 132 correctly filled out the questionnaires. 88 (67%) of patients were classed as having symptoms 'not at all/somewhat' due to a functional disorder and 44 (33%) 'largely/completely' due to a functional disorder. There was a significant difference between genders across the four groups (p=0.01) with the highest proportion of females to males in the group with symptoms 'largely' due to a functional disorder (6.67:1).

Neurological Diagnoses

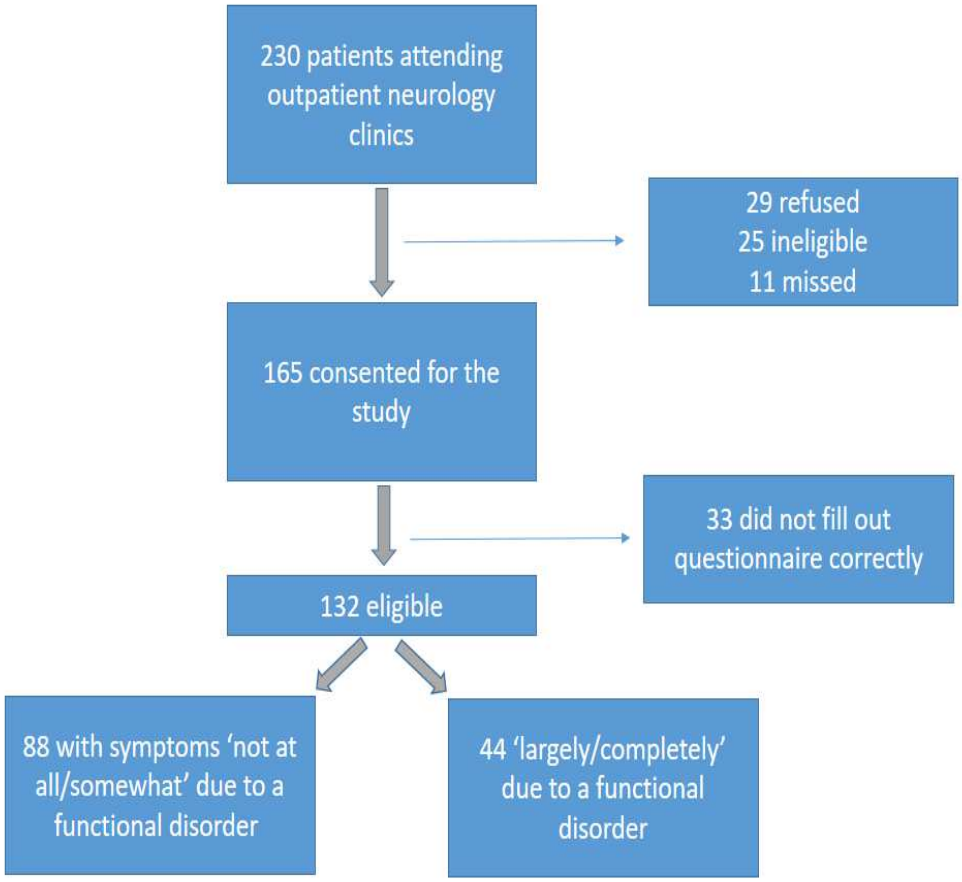
In keeping with the spectrum of functional disorders seen in the Scottish Neurological Symptom study a quarter of with symptoms 'largely/completely' due to a functional disorder were diagnosed with headache disorders (n=11; migraine n=7 and chronic daily headache n=4). Half of all patients with symptoms 'largely/completely' due to a functional disorder were given a diagnosis of a functional neurological disorder (FND) (n=22; general FND n=8, dissociative seizure n=7, functional sensory symptoms n=2, functional weakness, memory impairment, persistent postural-perceptual dizziness, functional gait disorder and dystonia, all n=1). The remaining quarter of patients were diagnosed with anxiety (n=4), chronic pain (n=3) and tic disorder, Insomnia, Chronic fatigue syndrome, Orthostatic hypotension (all n=1).

Only one patient had overlapping structural and functional disease diagnoses, this patient had an MRI scan suggestive of white matter inflammation but did not meet McDonald criteria for a diagnosis of multiple sclerosis. Her presenting symptoms at outpatient clinic were felt to be largely or completely

due to a functional neurological disorder and she was coded for this study as having a functional neurological disorder.

In patients with symptoms 'not at all/somewhat' related to a functional disorder the most common diagnostic criteria were headache disorder (n=26, 30% primary headache disorders) and seizure disorder (n=25, 29%). 13% of patients had neuropathy (n=11), 5% had demyelinating disease (n=4) and three patients (3%) each had Parkinson's disease, transient loss of consciousness or other neurological symptoms (atypical facial pain, facial twitching, tinnitus all n= 1). Other infrequent diagnoses were peripherally induced vertigo, degenerative disc disease, vasculitic disease or anxiety related (health anxiety or anxiety about family history) all 2% (n=2). One patient had each of: stroke, obstructive sleep apnoea, REM behaviour disorder, trigeminal neuralgia and motor neurone disease.

Figure One: Flow Chart of Patient Recruitment



Questionnaire Adjustment

There is only one question in SF-Qualiveen which is negatively phrased, Q8 "Can you go out without planning anything in advance?" During preliminary analysis we noted that this one question showed large inter-domain variance and a Cronbach's Alpha=0.29 and was answered by 17/132 (13%) of patients with "never" (the maximum score) despite them scoring 0 on all other SF-Qualiveen questions. We interpreted this as a problem with the questionnaire rather than a true effect. In the 16 patients (largely/completely n=3 (7%), not at all/somewhat explained n=13 (15%)) who scored 0 in all other SF-Qualiveen questions adjusting "never" to its corresponding score 0 score "always" increased the inter-domain agreement and Cronbach's alpha increased to 0.65. This may be a problem with the questionnaire, and we highlight it as a potential source of bias to other researchers. We removed these 16 patients' answers from our analysis. Bother with limitations and overall score was calculated on other 116 patients.

Urinary Symptoms and Distress due to Urinary Symptoms

See **Tables One and Two** Aside from gender there was no difference in measures between patients' in the largely/completely and not at all/somewhat groups. Over 80% of patients in both groups scored at least one point on the OAB section of the Urinary Symptom Profile (n=73, 83% and n=28,86%). When divided by gender women with symptoms largely/completely due to a functional disorder had significantly different low stream symptoms (0.3 vs. 0.85, p=0.0005) and were more bothered by limitations and fear (p=0.008 and p=0.03) and had higher opiate use (21% vs. 4%, p=0.03). When divided by gender over 80% of females in both groups scored at least one point on the OAB section of the Urinary Symptom Profile (n=38,83% and n=28,85%) but a higher proportion of patients in the largely/completely group scored more than one point in the low stream score (n=7,15% vs. n=15, 45%). However, when we excluded the seven patients taking opiates (widespread pain n=5, chronic back pain n=2) then there was no significant different between low stream rates (0.3 vs. 0.4, p=0.1) and the number of patients with low stream symptoms fell to nine (33%).

Distress

Patient with symptoms 'largely/completely' due to a functional disorder were significantly more likely to report at least one significantly affected domain in SF-Qualiveen (66% vs 45%, p=0.03). However,

despite more patients being distressed, levels were still 1 to 1.1 suggesting only slight reduction in quality of life.

Table One. Urinary Symptoms and SF-Qualiveen dichotomized

	Extent to which neurological symptoms explained by Functional Disorder				
	Not at all/Somewhat		**Largely/Completely**		P value
N	88 (67%)		44 (33%)		
Age	45		42		0.4
Sex	F:M = 1.91:1		F:M = 3:1		**0.01**
Urinary Symptom Profile (n(%) or mean +-SD					
	Mean Scores all patients **n=88**		Mean scores all patients **n=44**		
Stress Urinary Incontinence	0.72+-1.52		1.27+-2.29		0.3
Overactive Bladder	3.95+-3.57		5.55+-4.65		0.2
Low Stream	0.75+-1.42		0.95+-1.22		0.1
SF-Qualiveen					
	Not at all/Somewhat		**Largely/Completely**		P value
	n (%) with distress*	All patients (mean, +-SD)	n (%) with distress*	All patients (mean, SD)	
Bother with limitations	20 (23%)	0.47+-0.78	17 (39%)	0.76+-0.97	0.06
Fear	42 (48%)	0.53+-0.78	27 (61%)	1.08+-1.21	0.1
Feelings	22 (25%)	0.49+-0.88	18 (41%)	0.93+-1.21	0.06
Frequency limitations**	41 (55%)	0.86+-0.96	26 (63%)	1.22+-1.22	0.2
Overall		0.59		1	
P value compares the mean scores of patients in USP and % with distress in SF-Qualiveen *SF-Qualiveen scores above cut off ** 16 patients were excluded (see text)					

Table Two. Urinary Symptoms and SF-Qualiveen dichotomized, **Females only**.					
	Extent to which neurological symptoms explained by Functional Disorder				
	Not at all/Somewhat		**Largely/Completely**		P value
N	46 (53%)		33 (75%)		
Age	40		42		
Urinary Symptom Profile (mean, SD)					
	Mean Scores		Mean Scores		
Stress Urinary Incontinence	0.98+-1.65		1.24+-2.26		0.9
Overactive Bladder	4.33+-3.77		5.91+-4.87		0.2
Low Stream	0.3+-0.84		0.85+-1.25		**0.005**
Low stream ***when patients using opiates removed***	0.3+-0.65		0.42+-0.64		**0.1**
SF-Qualiveen (mean, SD)					
	n (%) with distress*	All patients (mean, SD)	n (%) with distress*	All patients (mean, SD)	
Bother with limitations	7 (15%)	0.3+-0.56	14 (42%)	0.86+-1.05	**0.008**
Fear	22 (48%)	0.58+-0.83	21 (64%)	1.21+-1.29	**0.03**
Feelings	12 (26%)	0.47+-0.87	14 (42%)	1.08+-1.32	0.09
Frequency limitations	21(46%)	0.8+-0.9	19(58%)	1.25+-1.28	0.2
Overall		0.53		1.1	
Opiate Use					
	Not at all/Somewhat		**Largely/Completely**		P value
Total	2 (4%)		7 (21%)		**0.03**
Co-codamol/ dihydrocodeine	1		4		
Tramadol oxycontin	1		2 1		
Low Stream Questions					
How would you describe your usual urination over these past 4 weeks?				P value	

Need to push with abdominal (stomach) muscles or learn forward (or require change of position) to urinate	4 (9%)	6 (18%)	0.2
Very slow from start to finish	0	1 (3%)	0.4
In general how would you describe your urine flow?			
Difficult to start then normal or easy at first but slow to finish	6 (13%)	12 (36%)	**0.02**
Very slow from start to finish	1 (2%)	2 (6%)	0.4
P value compares the mean scores of patients with USP and % with distress in SF-Qualiveen ^ Any symptoms= any USP scores >0 *SF-Qualiveen scores above cut off			

Lower Urinary Tract Dysfunction in patients with a functional neurological disorder

A small number of patients had a functional neurological disorder (n=22) and only preliminary observations can be deduced due to the sample size. Patients with a functional neurological disorder were 77% female and had significantly more bother with limitations and overall distress. Of the 16 female patients with a functional neurological disorder 50% (n=8) scored one or more on the Urinary Symptom Profile and two patients were taking opiates.

Table Three: Lower Urinary Tract symptoms in patients diagnosed with a functional neurological disorder			
	Extent to which neurological symptoms explained by Functional Disorder		
	Diagnosis of FND	**Not at all/Somewhat**	
N	22	88	
Age	42.5 +-15.68	44.9+-18.08	0.5
Sex	F:M= 2.67:1	F:M = 1.91:1	0.09
Urinary Symptom Profile (n(%) or mean (SD))			
	All patients	All patients	**P value**
Stress Urinary Incontinence	0.86 +- 1.91	0.72+-1.52	0.9
Overactive Bladder	5.63+- 4.86	3.95+-3.57	0.2
Low Stream	0.91+-1.06	0.75+-1.42	0.2
SF-Qualiveen (mean, SD)*			

	n (%) over threshold	All Patients	n (%) over threshold	All Patients	
Bother with limitations	11 (50%)	0.98 +- 1.13	20 (23%)	0.47+-0.78	**0.02**
Fear	13 (59%)	1.25 +- 1.34	42 (48%)	0.53+-0.78	0.35
Feelings	9 (41%)	1 +- 1.29	22 (25%)	0.49+-0.88	0.2
Frequency limitations	14(64%)	1.36+-1.3	41 (55%)	0.86+-0.96	0.2
Overall		1.14		0.59	**0.005**
P value compares the mean scores of patients in USP and % with distress in SF-Qualiveen					

Discussion

One third of patients presenting to neurology outpatients had symptoms largely or completely due a functional disorder and half of these (n=22, 16%) had a diagnosis of a functional neurological disorder. Overall, patients with symptoms 'largely/completely' due to a functional disorder scored had similar severity of symptoms and were similarly distressed. However, female patients with functional disorders reported more low stream symptoms and detriment to quality of life with respect to their urinary symptoms. Difference in low stream symptoms became insignificant when patients taking opiates were excluded.

Little is known about the severity of lower urinary tract symptoms in a typical range of patients with functional disorders and neurological symptoms who attend outpatients. There has been some exploration of lower urinary tract symptoms in functional disorders, including irritable bowel syndrome and fibromyalgia with patients commonly having storage symptoms[10]. Historically patients with functional neurological disorders, including those described previously as having "hysteria"[11] and DSM-IV somatisation disorder[12], were associated with the symptom of urinary retention. There have only been four studies systematically investigating urinary dysfunction, three in patients with functional neurological disorders and one on 'psychogenic' urinary dysfunction. One study of lower urinary tract symptoms in patients with functional movement disorders found that 20% of patients self-reported lower urinary tract symptoms. The majority of patients described overactive bladder symptoms (63.6%).

Patients with fixed dystonia had the most severe bladder symptoms and were more likely to be on opiates and have low stream symptoms[13]. The other two studies investigated the relationship between functional disorders and lower urinary tract symptoms indirectly. The first study of 107 patients with functional leg weakness asked patients if they suffered bladder symptoms at interview, these were found in 28% of patients [14]. Unfortunately, no other details about type or severity are available. In the other study, 62 patients with Fowler's syndrome 24% were found to have evidence of a functional disorder and half had some form of pain[15]. In the only recent study of psychogenic urinary dysfunction Sakakibara et al[16] defined it as exclusion of any urological, gynaecological and neurological causes in patients who had accompanying more obvious psychiatric/psychological features. The overall prevalence of psychogenic urinary dysfunction was 0.7% (n=16) in their specialist Uro-Neurological population. Sakakibara et al found that most patients with psychogenic urinary dysfunction had both difficulty urinating and overactive bladder symptoms. Most urodynamics were normal, although some patients demonstrated underactive/acontractile detrusor or had increased bladder sensation. In keeping with this our patients with functional disorders had high overactive bladder symptom scores and female patients with functional disorders had more low stream symptoms compared with other general neurology patients.

However, mean scores for all patients were not particularly high and were lower than had been found previously in patients with functional movement disorders, particularly if the means of the 'largely/completely' groups were compared. This may be because patients were only invited to take part in the study of functional movement disorders and LUT symptoms if they described LUT symptoms to their neurologist. Furthermore, although more patients in the functional disorders category met the criteria for distress caused by urinary symptoms their scores were also not high, with overall average in the group around 1. This may suggest a statistical but not clinically significant difference between the two groups as patients had varying levels of slight distress. Our study demonstrates that although LUT symptoms are often recorded by patients with functional disorders and functional neurological disorders, they may not be clinically of great importance to patients. The two specific features found to be positive, bother with limitations and bother with feelings, may be important as they enquire about distress caused by time spent passing urine or catheterizing and a feeling of bladder problems complicating their lives and feeling embarrassed and worried about bladder symptoms. These may be important questions to explore further with patients with functional disorders.

There are numerous reasons for low stream symptoms of which medications such as opiates and dysfunctional voiding are only two. Whilst there was a higher proportion of women taking opiates in the 'largely/completely' due to a functional disorder group, this still only amounted to less than one quarter of the group total. However, when these patients were excluded the symptom score was similar between groups. This highlights the importance of taking into account medications and other biological mechanisms which may impact on patients' symptoms and be readily treatable. Resolution of chronic idiopathic urinary retention has been reported with stopping opaties[17]. Alternative explanations include other medications, functional or structural bladder problems including dysfunctional voiding and undiagnosed Fowler's syndrome, which was found to have significant comorbid functional neurological disorders in a retrospective study[15,18]. These were beyond the scope of this small self-report study.

Limitations

This study was of self-reported lower urinary tract symptoms and did not explore the dysfunction through urodynamics. Assessing patients with urodynamics and post void residual using a bladder scanner or in-out catheterization in future studies would provide understanding of the mechanism of bladder dysfunction in patients with bladder symptoms, including the prevalence of dysfunctional voiding and urinary retention. Our study is limited by the small number of patients with a functional neurological disorder (n=22) and the lack of follow up to ensure diagnostic accuracy, although diagnoses made in this way have previously been found to be accurate on 18 month follow up. Additionally, age is likely to significantly affect the type and prevalence of lower urinary tract symptoms such as stress incontinence, that we did not find any correlation may be due to the small range of ages involved. The Urinary Symptom Profile, although a good tool for self-report of lower urinary tract dysfunction, is very sensitive[19] and does not have cut offs for symptoms which are mild, moderate or severe. Therefore, all we can say is that patients have certain symptoms, their severity is less easy to interpret. We collected information about opiate use but other medications are associated with urinary retention and urinary incontinence but this link was not testable in our study[20,21]. We do not feel our findings can be entirely explained by medications, but further studies should ask patients about a wider range of medication use.

Conclusions:

This study is the first to investigate bladder symptoms in a wide range of patients with functional disorders attending outpatient neurology clinics. It also compares these patients to a variety of patients attending general neurology outpatients. Despite the importance of symptoms and distress caused by them to patients affected by both pathophysical and functional neurological disorders, there have only been three other studies investigating lower urinary tract symptoms in patients with functional disorders in the last ten years. We conclude that bladder dysfunction in patients with functional neurological disorders is an unexplored, yet clinically significant problem.

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Conclusion: The study discovered that patients with functional disorders have similar levels of urological symptoms as patients with other neurological disorders but were more distressed by them. Females with functional disorders had more severe low stream symptoms (0.85 vs. 0.3). I discussed the small number of studies which address urological dysfunction in functional neurological disorders and current thinking about mechanisms causing voiding dysfunction which may be associated with medication, pain, trauma and higher psychological comorbidity than control urological populations. Opiates appeared to be a major factor in low stream symptoms in patients with functional disorders. When patients who were taking opiates were excluded, the symptom scores between groups was no longer significantly different. Similar findings in a cohort of patients with idiopathic urinary retention resulted in symptom resolution on stopping opiates and highlighted the need to investigate all biological factors which may be influencing urological function.

This study was limited by the questionnaire and by the lack of a simple question 'do you have any bladder problems?'. The lack of this step made the study less useful as the questionnaire does not have a cut-off point for normal/no symptoms. It was also limited by self-report methodology and lack of urological investigation but serves as a first step towards dedicated study of the relationship between functional disorders and urological symptoms.

Limitations Chapter

In this study there are a wide range of limitations and potential biases due to; the populations studied, recruitment mechanisms, blinding, the assessments used and the follow up rates achieved.

The chapter is a reflection of my learning about research methodology. It will focus on the prospective study although the methodological limitations apply to other parts of the study.

Case Definition and Sampling Bias

Scan positive CES

There were significant difficulties with defining both controls and cases. I will start with the definition of controls, patients with clinical and radiological evidence of cauda equina syndrome (CES). Cases were based on the definition of controls.

Difficulties with the definition of 'scan positive' CES

Despite patients with 'scan positive' CES being a seemingly well-defined control group there were major problems when it came to utilising a simple definition. First was the lack of any national or international consensus on what exactly CES is, either radiologically or clinically. There are at least 17 different clinical definitions of clinical CES and even after a systematic review of CES definitions[15], at least two more different definitions have been suggested with multiple sub classifications[19,22]. Debate rages over whether certain CES phenotypes require surgery urgently or whether surgery within 24 or 48 hours of symptom onset corresponds to long term outcome. Radiologically there is little guidance on what constitutes enough cauda equina nerve root compression to have symptoms. A famous animal study required >75% canal stenosis or lack of CSF around the CE nerve roots so we opted to use this definition with an awareness that it remains open for criticism.

Difficulties with the definition of the mixed group

The most scientifically controversial CES definition is 'suspected' (usually called impending in clinical settings) CES[23], which is described as "those with bilateral radiculopathy and/or subjective sphincteric problems with no objective evidence of CES, such as objective alteration of perineal sensation" [23]. There is no radiological definition of 'suspected' CES however, in clinical practice radiologically there is a large disc protrusion but no cauda equina nerve root compression seen. The clinical aspects of CES and concern about medicolegal consequences of missing an early CES

presentation mean that many patients with impending CES are treated as urgently as patients with 'scan positive' CES. It is often not possible to tell if patients with impending CES are included in 'scan positive' CES populations described in literature as definitions of CES even in large studies are usually "clinically determined"[24,25]. Whether this group of patients with impending CES is included within the 'scan positive' CES group is important in light of literature which shows that patient factors such as female gender, high somatic symptom score and treatment expectations influence how likely a patient is to be offered spinal surgery[26]. Given our hypothesis that some patients without 'scan positive' CES have a functional neurological disorder explaining some or all of their symptoms, and that patients with many types of functional disorder are more likely to be female and have high numbers of somatic symptoms[27], it was important to remove them from the 'scan positive' CES group in order to be able to study as pure a sample as possible.

What is 'scan negative' CES?

To create as pure a sample as possible, patients with clinical CES but normal scans *or* scans without any nerve root entrapment were placed into a 'scan negative' CES group. We hypothesised that these patients would be most likely to have predisposing, precipitating and perpetuating factors for FND and have evidence of functional disorders and FND.

Final Definitions

All patients had clinical features of CES as per the Fraser et al systematic review criteria; ≥1 of bladder, bowel, sexual dysfunction or saddle numbness +/- lower limb neurological dysfunction and were divided into three categories based on their radiology: 1) 'scan positive' cauda equina syndrome - defined as compression of the cauda equina nerve roots with >75% canal filling and/or no CSF around the cauda equina nerve roots on axial view[28]; 2) a 'mixed' category in which, patients who did not meet radiological criteria for cauda equina compression but did meet the clinical and radiological criteria for suspected/impending CES and had either a large disc with <75% canal narrowing or cauda equina "crowding" (reduced but not absent CSF volume around the cauda equina nerve roots on axial imaging and <75% canal narrowing), bilateral or unilateral nerve root entrapment which may have explained some of their symptoms and 3) 'scan negative' cauda equina syndrome with no nerve root compression or other radiological reason for their clinical CES symptoms.

This stratification was designed by my supervisors and I with input from the neurosurgeons and is open to the criticism that it has not been validated in prior studies.

Sampling Bias

Who makes it to neurosurgical wards with 'scan negative' CES

The diagnosis of 'scan negative' CES can only be made once MRI imaging has occurred and other conditions have been excluded. This necessitates studying patients in secondary care. Population studies are the best way to examine aetiological associations for a condition. Patients recruited from hospital settings may have features in common, such as depression or anxiety or geographical or socioeconomic factors that relate to referral rather than the underlying symptoms or may represent more "difficult" patients. Studying these patients may tell us more about the ability to get referred to secondary care than about patients with uro-neurological disorders and negative imaging. There may be many patients who have bladder symptoms and require urgent MRI imaging, however, only a small amount of patients will make it to the neurosurgical unit. This may be because patients who are admitted to neurosurgery present via their GP and get direct neurosurgery admission, present with more symptoms or are more likely to present overnight out of hours when MRI imaging is not available. These patients may be much more likely to have functional symptoms, panic and dissociation.

How have I dealt with this in my study?

This study aims to be representative of the patients who present as 'scan negative' CES, not the population of patients with uro-neurological disorders and negative imaging. It would be almost impossible to obtain a population-based sample of patients with 'scan negative' CES as patients would need to be investigated with examination, bloods and imaging, to ensure that they did not have another condition, particularly 'scan positive' CES.

The retrospective study showed that there were a large number of patients presenting with clinical CES to a regional neurosurgery unit. In order to be able to carry out a semi structured interview and examination the best way to access patients was via the inpatient neurosurgical ward. These patients may have had more symptoms than others but are representative of many patients, represent an unmet need in diagnosis and treatment and could be accessed and recruited in a standardised, consecutive way which allowed for additional information to be gathered about patients in the acute setting. Patients admitted to other wards in the Western general Hospital after

discussion with neurosurgery, and usually a normal scan, were also seen during their inpatient stay but it was more difficult to review and examine them and impossible to get the team responsible to do the additional MRI brain and lumbar puncture testing which lead to lower quality information about these patients.

Diagnostic suspicion bias

The problem

How do doctors choose which patients with back pain have possible CES? How much do they over diagnose it in patients with severe pain or prior bladder dysfunction or underdiagnose it when patients have bowel or sexual dysfunction or saddle anaesthesia but normal bladder function? How many patients are not asked about sexual dysfunction and are therefore not eligible for scanning? Do doctors over-investigate in patients with prior lumbar surgery? In how many cases are patients' pain or a functional disorder causing the majority of their symptoms, but they get an emergency operation anyway due to the distress they present with?

I have no doubt that there are considerable differences in the thresholds which A&E, GP and even differing consultant neurosurgeons involved in the study used to investigate or operate on patients with back pain and uro-neurological symptoms. Some GP and A&E staff will readily investigate for possible CES in anyone with back pain and any kind of bladder dysfunction, others require an abnormal saddle sensation or post void residual of >200mls. Some neurosurgeons will operate during the acute admission on anyone with a disc herniation and any bladder symptoms or if a patient is in severe pain whereas others will operate only if patients have both a convincing history in keeping with CES and no CSF around the cauda equina nerve roots on imaging. These more conservative surgeons will often watch and wait in patients with suspected CES and even in the presence of radiological but not clinical CES. The difficulty of diagnosing 'impending CES' has been previously highlighted. Impending CES symptoms may be caused by the pain, panic, medication or functional neurological disorders rather than due to cauda equina nerve root compression.

How have I dealt with this in my study?

These patients, and their care, represent the normal clinical course of patients presenting with suspected CES and whilst heterogenous, highlight the difficulties faced in observational clinical studies.

Diagnostic accuracy bias

The problem

How accurate is the diagnosis of 'scan negative' CES? What if many of these patients turn out to have a disease that explains their condition such as an inflammatory, infectious, vascular or neurodegenerative problem? Shouldn't all patients have an MRI brain and a lumbar puncture to ensure they don't have a disease?

How have I dealt with this in this study?

Both of my own retrospective and prospective studies have, for the first time, demonstrated a low misdiagnosis rate in patients with 'scan negative' CES of 1-4% on follow up on an average of 15 and 24months. This is in keeping with other studies of misdiagnosis in functional neurological disorders and is broadly comparable with all neurological diseases[29].

There are several reasons why I did not include neuroimaging as a prerequisite for entry into the study:

The study was aiming to be an observational case: control study so that results were generalisable to neurology services elsewhere. Compulsory neuroimaging would have interfered with this process and may have made neurosurgeons less likely to agree for me to see their patients.

A normal MRI brain fails to guarantee the absence of a wide range of neurological disorders such as neurodegenerative disorder (such as multisystem atrophy or progressive supranuclear palsy), some vascular malformations (especially spinal ones) or infectious lumbosacral polyradiculitis. When misdiagnosis did occur an MRI brain would not have changed initial diagnosis (sacral chordoma, cervical spine transverse myelitis, spastic leg with normal imaging and cervical spinal haematoma). Lumbar punctures in all patients would have strengthened our argument about lack of new neurological diagnosis, particularly of newer diagnoses such as anti-MOG antibody but we were concerned about iatrogenic implications for patients. Additionally, most patients were discharged before a lumbar puncture could be performed and neurosurgical teams were not keen for patients

to have them as they delayed discharge. Outpatient lumbar punctures could have been performed after discharge but infectious polyradiculitis such as Elsberg syndrome would no longer be detectable as CSF normalises within the first 48-72hours. There are also cost and resource implications for both MRI brain imaging and lumbar punctures and the resultant delay in discharge or use of outpatients.

In conclusion, on the basis of previous studies, as well as the retrospective and prospective study, I expect misdiagnosis to have occurred at a rate of 5-10% in the 'scan negative' CES group and 5-10% of patients in the mixed group who had radiologically unimportant MRI scan findings. I do not think neuroimaging or lumbar puncture would have significantly altered this rate. A re-analysis after 10years would clarify whether this conclusion is correct.

Control Definition and Sampling Bias

The incorrect control group can be the primary flaw in a case control study.

How have I dealt with this in the study?

The controls were selected to answer the questions I felt were most important in phenotyping and understanding mechanism in patients with 'scan negative' CES:

To what extent do the factors associated with 'scan negative' CES simply reflect a mixture of:

1. The impact of pain and medications on bladder dysfunction?
2. The complex process that leads some patients with back pain and bladder symptoms to being seen in A&E or by the neurosurgical team while others are not?

As the study was primarily aiming to phenotype patients with 'scan negative' CES, and a representative sample was required so that information could be generalisable to other neurosurgery centres, patients with complete cauda equina nerve root compression ('scan positive' CES) which would be expected to completely explain their pain, bladder, bowel and sexual dysfunction and lower limb symptoms and patients with nerve root compression which could explain some of their symptoms were the best control group possible. A control group of patients with 'scan negative' CES who had not been referred to hospital would be the ideal control group. As already discussed, this would have been an impossible group to identify and treat.

Confounding in the control groups

The problem

What if the factors being examined in this study were particularly prevalent for some reason in the neurosurgical controls compared to patients generally with CES symptoms? Did it matter that most patients with 'scan positive' CES had discogenic cauda equina compression? How does that affect the data?

How have I dealt with this in this study?

The criteria for the control groups were designed to be clinically useful. Patients in the 'scan positive' CES group were more likely to be males but this is useful information. Patients in the mixed group were similar in age, symptoms and sex to patients with 'scan negative' CES and were important in assessing whether stepwise functional predisposing, precipitating and perpetuating factors existed.

Selection bias of patients with functional weakness by referring neurologist

The problem

The biggest criticism that can be made of the recruitment methods of patients with 'scan negative' CES in this study is that they are not reliability consecutive since they depended on neurosurgeons telling patients about the study and patients choosing to take part.

There may be several additional reasons why recruitment may not have occurred.

- The neurosurgeon may have forgotten to mention it to the patient
- The neurosurgeon may not have wanted to involve the patient in case it created more work and ordering more scans, or been worried carrying out lumbar punctures may have prolonged inpatient stay
- The patient may not have been sent to the neurosurgery ward and may have been discharged directly from A&E or sent to a medical ward if the scan was done early
- There may have been too many patients to recruit all of them

How have I dealt with this in this study?

There were ethical and pragmatic reasons for choosing this method of recruitment. Ethically, patients had to be approached by a member of their clinical care team to ensure their willingness to take part in the study. Secondly, I wanted to see patients in the inpatient setting to phenotype the acute symptoms of patients with 'scan negative' to 'scan positive' CES and to interview and examine them looking for positive evidence of a functional neurological disorder.

Nevertheless, patients with 'scan negative' CES were admitted and not recruited to the study which could have biased the study in several ways.

Non-recruitment of cases of 'scan negative' CES from other specialists.

The problem

The majority of patients I recruited were from the neurosurgery ward and were seen as inpatients. There are patients who present to A&E with back pain and bladder dysfunction, or who develop these symptoms during their inpatient stays and are never discussed with neurosurgery. These patients may differ significantly from patients admitted to the neurosurgery ward. Patients who develop their symptoms in a less acute way may present to neurology or urology but never be referred to neurosurgery as their imaging will be normal.

How have I dealt with this in this study?

I am aware that the patients with 'scan negative' CES I have seen in the study represent an unknown proportion of the overall number presenting to general practitioners, A&E departments, in pain clinics, attending urology, orthopaedics etc. Since so many patients had resolution of symptoms, especially symptoms of a functional neurological disorder, on follow up, it follows that there must be patients who are never referred to neurosurgery. During my PhD I was asked to see several patients who were referred only to outpatient neurology as they had either never presented to A&E, had been discharged directly after MRI scanning or did not have severe enough symptoms to warrant MRI scanning in A&E. This is perhaps not a problem with this study given that the aim was to phenotype patients with 'scan negative' CES. It is, however, important to remember that the patients with 'scan negative' CES seen in this study are likely to be only a proportion of the incident cases in South East Scotland and may represent the most severe end of the symptom spectrum.

Selection bias in recruitment of controls

The problem

Controls were recruited from the same neuroscience centre. Patient factors could have influenced who was referred to neurosurgery with possible CES for an urgent MRI scan.

How have I dealt with this in this study?

This study reflects usual clinical practice. We are aware of patient factors which may influence which patient with nerve root compression are referred for an urgent scan and tried to assess these for differences in our study including assessing pain, panic, dissociation, somatic symptoms, quality of life, illness and treatment beliefs.

The overlap with pain and medications

The problem

The majority of patients with 'scan negative' CES had severe pain and were on medications which could impact on bladder function. Whilst Hoover's sign and thigh abductor have good sensitivity and specificity in other groups, including patients with stroke[30], it is unclear what effect pain will have on the reliability of the test. Many patients were on mediations which may have impacted on their ability to answer questions accurately by causing drowsiness or confusion. There was no way to control for strong medication use although all patients' medications were written down.

How have I dealt with this in this study?

I had planned on asking a blinded neurological consultant (JS) to check Hoover's sign and thigh abductor and also planned to use weighing scales to detect the difference in weight put through the leg on direct versus automatic hip extension. Unfortunately, I did not achieve either of these. Future studies will be designed to create a more streamlined way to get blinded assessment. Teaching the neurosurgeons how to do Hoover's sign would also be a way to have an additional assessor. Although they would be non-blinded to the history, they usually see patients before they have an MRI scan.

Medications which could affect bladder, bowel or sexual dysfunction were documented in all groups. Surprisingly, there was no significant differences between overall pain medications in type or

number between groups. On looking at medications individually patients in the mixed group were more likely to be taking gabapentinoids and patients in the 'scan negative' group were more likely to be taking benzodiazepines. This may have led to bias in the study results but reflect clinical reality.

Heterogeneity

The problem

Is it valid to study patients with urinary retention versus urinary incontinence or bladder, bowel and sexual dysfunction? Are the populations of scan negative CES too far removed from patients with mixed CES to be studied together? Are patients with functional symptoms brought on by severe pain and a panic attack similar to patients with life-long somatisation? Are transient signs of a functional neurological disorders the same as symptoms severe enough to warrant the diagnosis of a functional neurological disorder in outpatient clinic?

How have I dealt with this in the study?

The main aim of the study is to phenotype patients who present with 'scan negative' CES. Generalisability could only be persevered by a consecutive case control study of patients presenting with suspected CES. Rather than eliminate heterogenicity using a poorly tested construct, such as patients with only complete urinary retention, the study aimed to encourage it but remain aware of the problems, which include:

- Mixing patients with severe and mild bladder, bowel and sexual dysfunction and neurological deficit
- Mixing patients with transient (days/weeks) and enduring (years) symptoms e.g.
    - Acute Symptoms after bilateral S1 nerve root compression vs. acute worsening of chronic pain, functional weakness and bladder symptoms

Refusal rates (non-response bias)

The problem

Refusal rates introduces bias because patients who refused could have changed the results. In addition, patients who did not complete all the assessments, or only partially completed questionnaires introduce potential bias.

How I dealt with this in this study

Refusal to take part in the study total n=28 (12% total patients)

1. *Patients with 'scan negative' and mixed CES – response rate 84%; questionnaire response rate* 66%

   This study was done on patients who were admitted acutely to the neurosurgery ward having been brought into hospital in severe pain and who underwent scanning after being warned that they could lose bladder, bowel, sexual function and lower limb function. It was challenging to recruit patients particularly as I was allowed to approach them only after a member of their clinical team had discussed the study with them. The neurosurgeons were busy and would forget the study unless specifically reminded before the ward round. Even then some patients would have to be approached later by one of the nurses. All assessments including structured clinical interviews for DSM-IV psychiatric disorders had to be done by the bedside where there was very little privacy. However, few patients stopped the interview at that point. The questionnaire was returned in <70% of patients with 'scan negative' CES. Feedback I received was that it was too long and too psychological. I learned from this and only gave the questionnaire after we had completed the interview. The introductory leaflet was non-psychological.

It remains possible that the patients who did not take part had particularly low rates of emotional disorder or high rates of adverse childhood experiences. Their demographics are representative of the mixed and 'scan negative' CES groups. Their absence remains a source of potential bias. Possible directions of bias include:

- Patients with more emotional disorder may welcome the chance to talk about the way they have been feeling and agree to take part in the study more readily
- 'co-operative' or contented patients were more likely to be approached
- Or conversely patients who were upset by the lack of diagnosis were more likely to be offered information about the study
- Patients with emotional disorders are more likely to be approached because the doctor subconsciously thinks they would enjoy or benefit from the assessment

2. *Controls with 'scan positive' CES*

As described above, patients presented in pain and were often waiting for an emergency operation. I found that if patients were waiting for the operation then waiting until after the operation resulted in higher study response rate.

It remains possible that patients who did not take part in the study had different symptoms, evidence of functional neurological disorders or high levels of emotional disorder. This is a source of potential bias. Other sources of potential bias as the same as those for patients with 'scan negative' CES.

Refusal to complete all questionnaires

It was disappointing that despite many efforts, I was unable to get all the questionnaires completed. The non-completion rate was 0% to 28% for the various measures. The illness perception questionnaires and a question about whether sexual function had changed were particularly poorly answered (11% to 28% non-completion rate). There may have been systematic differences between those who did and those who did not complete the questionnaires- for example did the patients with 'scan negative' CES who did not complete the follow up questionnaires do so because they were much better or much worse? This is a potential source of bias.

How I dealt with this in this study

There were significant differences in the numbers of patients returning the questionnaire. It was unclear whether this was due to length, complexity or the particular components of the questionnaire. Because age of school leaving was not enquired about this could not be factored in. Some patients circled words they did not understand, such as defecate, and in feedback said they did not understand all the wording. There were also particular problems with some patients feeling the questionnaire was too psychological and therefore that I was insinuating it was "all in their head". Additionally, some components of the questionnaire such as the life events measurement questionnaire were so complex and so poorly performed as to be impossible to interpret. I shorted the follow up questionnaire and sent out only the key parts. This improved the response rate by 18% (n=20, total n=112) but the number from patients with scan -ve CES remained low (n=28,46%).

Little can be derived from the 'scan negative' follow up data so a notes review looking at new diagnoses, urological investigations and diagnoses and functional disorder diagnoses was carried out. This fulfilled the purpose of ensuring any new diagnoses were picked up and a more accurate whole group picture was available when assessing outcome of patients with 'scan negative' CES.

Assessment Bias

Non-blinding of the interviewer

The problem

As the interviewer I attempted to keep myself blinded to the diagnosis when patients were admitted the same day. However, often patients with 'scan positive' CES prior to surgery did not wish to take part in the study so information had to be gathered the subsequent day and the diagnosis was then known. This may have skewed the recording of information in the semi-structured interview, the examination and the psychiatric interview.

How I dealt with this in this study

Having considered this problem prior to starting the study there was no way to avoid this unblinding of the interviewer. I provided anonymised psychiatry data to Prof Carson when assessing DSM-IV diagnoses via the structured clinical interview. It is not clear whether the data indicates the presence of interview bias in the study of emotional disorder.

Psychiatry Diagnoses:

I interviewed all patients and provided the psychiatric details to AC in an anonymised way. However, the levels of psychiatric diagnoses are higher than would be expected from the retrospective study or from literature about patients with chronic pain. This may be due to overdiagnosis or overinterpretation during the semi-structured interview.

How I dealt with this in this study

Psychiatric diagnoses were made after the history was taken and the knowledge of whether patients were 'scan negative' or 'scan positive' may have impacted on the psychiatric diagnosis. However, there is a structured way to conduct the interview and all questions were asked to all patients.

Measurement Bias

Validity and reliability of the individual measurements

The problem

Urinary Symptom Profile: I used this questionnaire primarily because it was recommended to me. Learning more about the questionnaire and its lack of clinical correlation after I had incorporated it into my study was a somewhat painful experience, especially when I realised that the questionnaire was so sensitive that it may have over-represented the bladder symptoms of patients. Additionally, it was not possible to say whether patients were symptomatic or not using this questionnaire as it is not validated for this interpretation of the results. Colleagues have published reports counting how many patients had a score of zero but this may lead to overinterpretation of the results[31].

Timing: Questionnaires were included which are validated to ask about symptoms in a non-acute fashion; the Urinary symptom profile is designed to be used based on urological symptoms in the last month, the somatic symptom count asks about symptoms over the past month and the life events questionnaire asked about life events occurring in last year.

How have I dealt with this in this study?

I have recognised that this a potential source of bias. This was a learning experience and I will ensure that I research all questionnaires thoroughly before using them to ensure they are properly validated for the specific questions my research is asking.

The difference between categorical and dimensional measures of emotional disorders

The problem

There are both categorical and dimensional methods of assessing emotional disorder and it is not clear which is most valid.

How have I dealt with this in this study?

In this study I used a categorical measure (SCID) and dimensional measure HADS.

Anti-psychological response bias

The problem

Patients with physical symptoms often tend to be 'offended' if it is suggested that they are due to a psychological problem. They may therefore not take part in the study, answer interview questions or fill out questionnaires truthfully. This could have affected data on emotional disorder (SCID and HADS), distress (SF-36 physical function), dissociation, adverse childhood events, or thoughts about what is causing their symptoms.

How have I dealt with this in this study?

By assessing illness beliefs at the same time as emotional disorder it was possible to assess if this is still the case. Fewer patients completed the illness beliefs questionnaires (72% scan positive CES vs. 74% mixed and 67% scan negative CES) than the HADs (100% vs. 98% and 100%. Patients with 'scan negative' CES were surprisingly likely to agree that some symptoms may be due to stress (7% scan positive CES vs. 18% mixed and 44% 'scan negative' CES) and this question was answered by 85% of patients with 'scan negative' CES. The discrepancy in both cases and controls between dimensional (subjective HADS) and categorical (more objective SCID) measures supports the idea of 'anti-psychological bias'. It may therefore be operating regardless of the diagnosis, or alternatively the explanation for these differences is interview bias.

The difference between self-rated and actual disability

The problem

Patients with 'scan negative' CES may be over-or under-reporting their disability compared to controls with neurological weakness.

How have I dealt with this in this study?

Measuring objective disability, for example with activity monitors, was beyond the scope of this study and due to the short admission time would likely not have added much information as it would only have recorded atypical activity in the acute setting. I therefore only measured disability subjectively by asking about what a normal day at home is like and with SF-12 physical function score and the work and social adjustment questionnaire. A more prominent source of potential bias is the poor return rates of questionnaires which is discussed above.

Limitations of the Analysis

Inadequate correction for multiple comparisons

The problem

I have carried out multiple comparisons between cases and the two control groups. Therefore, some of the apparently significant results may have occurred by chance.

How have I dealt with this in this study?

Although I have attempted to separate out primary data (number of patients with abnormal post void residual bladder scanning, abnormal bowel and sexual function as per validated questionnaire cut-offs) from exploratory data (signs of functional neurological disorders, panic at symptoms onset) the study is still affected by multiple comparisons. Rather than attempt a complex Bonferroni correction I think it more appropriate to highlight this potential limitation and also state that an P value of less significance than $P<0.01$ should be treated with caution.

Low Sample Size

In any case control study, the sample sizes should be adequately powered to detect a difference. This presented a challenge as in the pilot study 90% of cases vs. 0% of controls had Hoover's sign of functional leg weakness. If this data was used to calculate sample size, then the required size was very small. However, we were unsure of the veracity of out pilot data given the small numbers involved (11 and 7). In order to get the most representative sample we divided patients into three discrete categories. This resulted in a lower than ideal sample size for the two gold standard categories ('scan negative' and 'scan positive' CES). Despite the low sample size estimated from the pilot work I hoped to obtain 100 patients in the 'scan negative' category (clinical significance set at $p<0.05$ with 80% power) using the example of detective a difference between 40% and 60%. I did not achieve this. Sixty-two patients were recruited from the 'scan negative' group, 76 from the mixed group and 47 patients from the 'scan positive' CES group.

How have I dealt with this in this study?

Allowing the categories to occur from consecutive patients hopefully demonstrates a representative breakdown of patients presenting with clinical CES and makes the data more clinically useful. However, the low sample size is a potential for bias and the low sample sizes tends to reduce the ability of the study design to detect a difference between groups.

Confounding

The problem

In any study of multiple variables, confounding may be an important source of bias. Confounding occurs when two variables A and B are not only related to the development of disease C but are also related to each other. For example, in this study, both DSM-IV disorders and prior functional disorders, particularly chronic pain, are associated with 'scan negative' CES. However, chronic pain occurs more frequently in patients with DSM-IV disorders. Therefore, the apparent association between 'scan negative' CES and chronic pain may be a spurious one which is confounded by psychiatric diagnoses.

How have I dealt with this in this study?

This was not a matched case control study, where common confounders such as age, sex, duration of symptoms can be controlled. The 'scan negative' and mixed groups were similar in these variables and the 'scan negative' and 'scan positive' groups were similar in symptom duration. These variables could be important confounders. However, the study was primarily to phenotype patients presenting with 'scan negative' CES.

Conclusions

There were many limitations to this study. Some of these reflect the nature of observational studies and many reflect the learning obtained in research methodology during my PhD. The acute, painful and distressing nature of the clinical symptoms affecting all patients and the new areas of phenotyping providing interesting and profound challenges for those doing future studies in this area.

Conclusions and Route Forward

This PhD has been the exploration of whether a relationship exists between bladder disorders and functional disorders more generally. I have identified academic work pre 1980 which demonstrates that this relationship was an uncontroversial one until relatively recently[32]. Numerous accounts of hysterical ischuria are recorded dating back to the time of Charcot and psychogenic urinary retention was one of the criteria for conversion in DSM III[33]. Functional neurological disorders have not been judged kindly by history and as the pathology of other disorders became clear, the lack of pathological findings on dissection or imaging became confused with a lack of 'realness' of the diagnosis. Moves in the 1980s by Claire Fowler and colleagues to reclaim patients diagnosed as psychogenic urinary retention were clearly, in part, done with the intention of validating patient's experience. The movement to define patients with idiopathic urinary retention according to replicable seemingly scientific data, the urethral sphincter EMG findings, meant patients were studied and new treatments sought. Recent studies, however, have shown that the urethral sphincter EMG findings occur in women without urological dysfunction. These women do not develop urology symptoms even on ten year follow up[34]. Treatment with sacroneuromodulation has been successful in many patients but the focus on a potential channelopathy or other pathophysical cause of urinary retention lead to a devaluing of the functional and psychological comorbidities in this patient group, which have gone undiagnosed and untreated.

The last decade has brought with it a renewed interest and appetite for scientific and clinical information on functional neurological disorders. Led by clear, open communication with patients, positive diagnoses and good clinical assessment the field has reopened to both academics and, for the first time, patients. This has been underpinned by imaging techniques such as fMRI and neurophysiological investigations which demonstrate mechanistically important differences when comparing patients with functional weakness or movement disorders and with feigning[3536–38]. In this context a re-exploration of bladder symptoms that may be related to a functional neurological disorder, particularly those associated with pain, is a logical and clinically useful next step.

This PhD has set out to explore past and current literature, devise a hypothesis about how functional bladder disorders may occur from retrospective case note reviews and test that hypothesis in a prospective study by addressing four aims:

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Conclusions

- **Aim1:** To determine what proportion of patients with 'scan negative' CES have a functional disorder by clinical consensus

- **Aim 2:** To describe associated clinical features relevant to diagnosis, mechanism and aetiology in patients with Scan negative and scan positive CES

- **Aim 3:** To determine what proportion of patients with urinary retention from Fowler's syndrome or idiopathic causes (chronic idiopathic urinary retention/dysfunctional voiding/bladder outlet obstruction) have comorbid functional neurological disorder.

- **Aim 4:** To determine what proportion of patients with functional neurological disorders have lower urinary tract dysfunction.

The literature review improved my understanding of the historical link between urological and functional disorders as well as demystifying the complex brain-bladder network in health and in disease.

The bulk of my research has involved patients with cauda equina syndrome. A clinical and radiological syndrome which I initially thought was a clear pathophysiological control group soon became a poorly studied, slippery collection of symptoms, with no accepted definition or incidence, almost no prospective research, and most importantly the same symptoms and radiology eliciting differing responses from differing neurosurgeons about the importance and urgency of operation. As my understanding of the condition grew from the ongoing prospective work and the retrospective notes review it became clear that I would have to divide patients in a way which had not previously been done in the literature. I found the hardest part was deciding where patients with 'impending' CES should go. Neurosurgically they are treated exactly the same as patients with radiologically confirmed CES and my instinct was to put them into the 'scan positive' group. But the definition of who has 'impending' CES is broad and is almost completely operator dependent. Watching senior neurosurgeons make different decisions than junior ones, I could not honestly say they presented a replicable category of patients. I wondered to what extent factors other than the scan findings such as medication, pain catastrophisation, panic and psychopathology were playing a role in who had an operation. These patients were important in my learning because they represent the difficulties we face when patients have pathophysiological disease which requires treatment and produces symptoms, but we need to consider functional comorbidity, panic, dissociation and psychopathology and use this knowledge to create the optimum care for the patient.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Conclusions

The retrospective review was strongest in showing that patients with 'scan negative' CES or mixed CES do not go on to develop pathophysiological neurological conditions. We provided evidence that these patients do not simply have Multiple Sclerosis or other neurological disease which is presenting in an unusual way. The retrospective study also found a stepwise progression of functional, psychological and functional neurological disorders from the 'scan positive' to the mixed to the 'scan negative' groups. It was also important to find that patients had a similar level of unpleasant symptoms at onset, especially given the lengths the health service has gone to in order to provide a rapid neurosurgical response to alleviate the symptoms of patient with 'scan positive' CES. Half of patients with 'scan negative' CES developed chronic pain on follow up.

Building on knowledge of the brain-bladder network this study allowed the exploration of a hypothesis about how patients could develop 'scan negative' CES. This was a hypothesis which attempted to identify the important predisposing, precipitating and perpetuating factors which ranged from medication to psychiatric disorders.

Further evidence of a link between functional neurological disorders and urological dysfunction was found in the prospective study. The data showed a 'dose-response' increase in pain, back pain, psychiatric disorders and positive signs of a functional neurological disorder in the mixed and 'scan negative' CES groups. The hypothesis of multiple factors affecting brain and bladder simultaneously, leading to functional neurological symptoms and bladder dysfunction had corroboration from the prospective study findings.

This information creates a new narrative for patients presenting with clinical CES who have normal or non-explanatory imaging. Following phenotyping there are interesting questions to be answered and research on treatment strategies is required.

Future Questions

A PhD is just a steppingstone of knowledge. Whilst phenotyping patients who present with suspected CES but have normal or non-explanatory imaging is a useful and worthwhile task, further questions abound. These can be roughly broken down into three main questions; Is it possible to create a sensitive and specific scoring system to predict who will have normal or non-explanatory imaging pre scanning?; What is the long term outcome for patients with 'scan negative' CES and; Are

there key advantages from being admitted to a neurosurgical unit which could be harnessed for treatment trials?

Regarding a scoring system, due to the devastating nature of 'scan positive' CES, clinically and medicolegally, and the large overlap of symptoms, there are unlikely to be symptoms or signs which are sensitive and specific enough to exclude 'scan positive' CES. It is therefore likely that patients will always require an MRI scan to exclude CES compression. There are, however, important questions which may be useful to answer to allow patients to gain appropriate treatment quickly. These include whether patients' symptoms gradually progress as they attend the GP and then A&E in keeping with increased abnormal self-directed attention[4,5], or whether they have fully occurred by the time the patient attends A&E. More important than this theoretically interesting question is whether A&E and neurosurgical staff can accurately and consistently test for positive evidence of a functional neurological disorder. This, along with other risk factors for poor outcome such as a history of chronic pain, kinesiophobia, normal MRI scan and significant current psychopathology such as obsessive-compulsive disorder, agoraphobia or post-traumatic stress disorder could be used to triage patients to those who need specialist early treatment. This type of post-imaging scoring system to assist the patients who are likely to have poor outcome may be a useful next research step.

It is unclear what the five to ten-year outcome for patients with 'scan negative' is. From our retrospective and prospective studies, we know that 11-13% have recurrent episodes of CES, sometimes repeatedly and 50% have chronic pain. We also know only a maximum of 4% go on to develop a neurological disorder which potentially explains their clinical symptoms. However, physical function, quality of life and social outcomes are unclear. A larger cohort with these endpoints would be helpful for predicting good and poor outcomes and targeting treatment early to patients with the poorest likely outcome.

From clinical experience, patients who were admitted to wards other than neurosurgery took longer to recover and had fewer positive outcomes. Patients on other wards were not as positively encouraged to move and normalisation of function; walking, as well as bowel and bladder, and early discharge was not expected. The way pain was managed was also very different on the neurosurgery ward. Patients were treated with quickly escalating doses of medications to a level where they no longer had pain. Pain was a major issue highlighted by this PhD. As well as patients

presenting with 'scan negative' CES who had their worst ever acute back pain in 70% and chronic back pain in 51%, patients with Fowler's syndrome had high levels of pain, both acute and chronic, which must be acknowledged as part of the context of their bladder disorders. The clinical experience of better outcomes after neurosurgery ward admission could be tested against patients admitted to other wards with a focus on which factors (if any) improved outcome.

Future Treatment Studies

Ideally these questions would lead to a multi-centre two step randomised-control study assessing whether patients can be accurately diagnosed with 'scan negative' CES and whether specialist treatment could improve outcomes. For any treatment trials a focus on early explanation, movement, pain relief and encouraging normal bladder and bowel function with early removal of catheters seems key. Particularly in this patient cohort, with over 80% having one psychological comorbidity and a high proportion having a panic attack at pain onset, a multi-disciplinary approach with physical and psychiatric/psychological input will likely be required. Whilst improving outcome with education, pain management and reducing unhelpful medications and function with physiotherapy we also need to consider creating an acute treatment plan for when back pain recurs, as it will in the majority of patients. Pain management often encompasses a biopsychosocial view of pain and is based on best current evidence[39] being likely to involve advice and education about staying active and fist line non-pharmacological therapy and avoidance of opiates and further imaging. However, it would be useful to compare patient diagnostic certainty and understanding with outcomes. Pilot treatment studies for motor functional neurological symptoms demonstrate that both understanding the diagnosis *and* having the correct type of physiotherapy is key in gaining the best outcomes[7]. This allows patients to engage in fear-exposure therapy they would otherwise avoid as they understand the diagnosis and know even if pain occurs that no further damage is ongoing. This also seems to be the case in small studies of patients with complex regional pain syndrome[40] but is often forgotten in clinical practice.

Conclusion

This PhD has been the exploration of the clinical features and outcomes of patients with uro-neurological conditions who have normal or non-explanatory imaging. I have demonstrated a link between patients with uro-neurological symptoms and functional neurological disorders in the acute and chronic context. I have laid out a mechanistic hypothesis as to how patients develop urological symptoms, combing endogenous and exogenous risk factors to create a model of predisposing

factors in addition to pain, panic and dissociation to trigger functional symptoms. Deep phenotyping has led to a better understanding of this vulnerable, large and untreated group of patients who until now have been ignored.

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Papers in Appendix with brief summary of my input:

Section 1: Cauda Equina Syndrome

- Julie Woodfield1,2, **Ingrid Hoeritzauer1**,2, Aimun AB Jamjoom2,3, Savva Pronin2, Nisaharan Srikandarajah4, Michael Poon1, Holly Roy5, Andreas K Demetriades1, Phil Sell6, Niall Eames7, Patrick Statham1, British Neurosurgical Trainee Research Collaborative (BNTRC.). Understanding Cauda Equina Syndrome: protocol for a multi-centre prospective observational cohort study. BMJ Open. 2018 Dec 14;8(12):e025230. doi: 10.1136/bmjopen-2018-025230.
    - *With a neurosurgical colleague (JW) I wrote the BNTRC application and designed the project. I am on the steering committee and together with JW and PS I did the ethics application, designed the questionnaires and have been running the project.*

- Daniel M. Fountain, Simon Davies, Mohammed Kamel, Paulina Majewska, Julie Woodfield, Ellie Edlmann, Aimun A.B. Jamjoom, **Ingrid Hoeritzauer**, Mueez Waqar, Dominic Mahoney, Dillon Vyas, Moritz Schramm, Georgios Solomou, Francesca Dawkes, Heidi Grant, Jonathan Attwood, Alexandros Boukas, Dominic Ballard, Emma Toman, Matthew Sanders, John E. Lawrence, Beverly Cheserem, Saurabh Sinha, Patrick Statham, Neurology and Neurosurgery Interest Group, British Neurosurgical Trainee Research Collaborative Evaluation of Nationwide Referral Pathways, Investigation and Treatment of Suspected Cauda Equina Syndrome in the United Kingdom. Br J Neurosurg. 2019;0(0):1-11. doi: 10.1080/02688697.2019.1648757.
    - *I was in the steering committee for this study and assisted with study design, feedback on results analysis and write up of paper.*

- Hazelwood JE[1,2,3,4], **Hoeritzauer I**[5,6,7], Pronin S[5,6,8,7], Demetriades AK[5,6,8,7].An assessment of patient-reported long-term outcomes following surgery for cauda equina syndrome. Acta Neurochir (Wien). 2019 Sep;161(9):1887-1894. doi: 10.1007/s00701-019-03973-7.
    - *I came up with the project, supervised the medical student and assisted with the writing of the paper.*

Section2: Defining new phenotypes

- **Hoeritzauer I**[1], Carson AJ[1,2,3], Stone J[1,3]. 'Cryptogenic Drop Attacks' revisited: evidence of overlap with functional neurological disorder. JNNP 2018 Jul;89(7):769-776.
    - *JS designed the study and formulated the hypothesis. I gathered the information, did the statistics, reviewed the literature and wrote the paper*.

- Stone J[1], **Hoeritzauer I**[1], Tesolin L[2], Carson A[1,3] Functional Movement Disorders of the Face: A Historical Review and Case Series. J Neurol Sci. 2018 Sep 26;395:35-40.
    - *JS designed the study and formulated the hypothesis. I finalised the information, reviewed the literature and helped write the paper.*

- Popkirov S, **Hoeritzauer I**, Colvin L, Carson A, Stone J. Complex Regional Pain Syndrome and Functional Neurological Disorders - time for reconciliation. J Neurol Neurosurg Psychiatry. 2018 Oct 24. pii: jnnp-2018-318298
    - *JS and AC formulated the hypothesis. Together with SP I reviewed the literature and wrote the paper.*

Paper Two: Julie Woodfield1,2, **Ingrid Hoeritzauer1**,2, Aimun AB Jamjoom2,3, Savva Pronin2, Nisaharan Srikandarajah4, Michael Poon1, Holly Roy5, Andreas K Demetriades1, Phil Sell6, Niall Eames7, Patrick Statham1, British Neurosurgical Trainee Research Collaborative (BNTRC.). Understanding Cauda Equina Syndrome: protocol for a multi-centre prospective observational cohort study. BMJ Open. 2018 Dec 14;8(12):e025230. doi: 10.1136/bmjopen-2018-025230.

Understanding Cauda Equina Syndrome: protocol for a United Kingdom multi-centre prospective observational cohort study

ABSTRACT

Introduction

Cauda equina syndrome (CES) is a potentially devastating condition caused by compression of the cauda equina nerve roots. This can result in bowel, bladder and sexual dysfunction plus lower limb weakness, numbness, and pain. CES occurs infrequently but has serious potential morbidity and medico-legal consequences. This study aims to identify and describe the presentation and management of patients with CES in the United Kingdom (UK).

Methods and Analysis

Understanding Cauda Equina Syndrome (UCES) is a prospective, collaborative, multicentre cohort study of adult patients with confirmed CES managed at specialist spinal centres in the UK. Participants will be identified using neurosurgical and orthopaedic trainee networks to screen referrals to spinal centres. Details of presentation, investigations, management and service usage will be recorded. Both patient and clinician reported outcome measures will be assessed for one year after surgery. This will establish the incidence of CES, current investigation and management practices, and adherence to national standards of care. Outcomes will be stratified by clinical presentation and patient management. Accurate, up to date information about the presentation, management, and outcome of patients with cauda equina syndrome will inform standards of service design and delivery for this important but infrequent condition.

Ethics and Dissemination

UCES received a favourable ethical opinion from the South East Scotland Research Ethics Committee 02 (Reference: 18/SS/0047; IRAS ID: 233515). All spinal centres managing patients with CES in the UK will be encouraged to participate in UCES. Study results will be published in medical journals and shared with local participating sites.

Registration Details

UCES is sponsored by NHS Lothian (Reference: AC18017). UCES is registered at ClinicalTrials.gov (160318) and ISRCTN (ISRCTN16828522).

ARTICLE SUMMARY

Strengths and Limitations of this Study

- This UK wide study will be the largest prospectively established cohort of patients with CES.
- The collection of detailed clinical data will describe the range of presentations treated as CES in the UK in current practice and allow stratification of findings by clinical presentation.
- Validated outcome measures will be used to assess pain, disability, and bladder, bowel, and sexual function one year after treatment.
- Participant identification and recruitment will be efficiently carried out using trainee research networks to identify participants when referred urgently to specialist spinal centres.
- The relationship of timing of investigation and decompression to patient outcome will be limited by patient and clinician reporting of the timing of symptom onset.

INTRODUCTION

Cauda equina syndrome (CES) is a rare but potentially devastating condition caused by compression of the cauda equina nerve roots. This most commonly occurs due to a prolapsed intervertebral disc. The clinical syndrome includes any of bilateral sciatica, saddle anaesthesia, bladder, bowel, or sexual dysfunction.[1-3] The disabling nature of these symptoms causes significant medical and social morbidity and high health and social care costs. In addition, litigation related to the management of CES leads to significant medico-legal workload and costs.[1,4,5]

Due to the consequences of CES for patients and society, several groups have issued clinical guidance or standards of care for CES.[1,6-8] However, the evidence base for current clinical guidance consists of small retrospective single centre case series.[1,9,10] Even systematic reviews of outcomes in CES have included relatively few patients, with the largest including 464 patients.[9,11] Lack of a clear definition of CES has hampered comparative analysis of historic studies, and different interpretations of the available evidence have been offered.[10,12] A diagnosis of CES encompasses patients presenting with mild to severe urinary and bowel symptoms, perineal or perianal numbness, sexual function disturbance, or bilateral sciatica, and patients may also experience lower limb weakness, numbness, or unilateral sciatica.[2,3,13] Outcomes for different presentations vary, and accurate division by presentation may help to clarify the understanding of outcome studies and develop care standards appropriate to the presentation.[1,14]

Retrospective case series in the United Kingdom (UK) have identified approximately 15-31 patients per year per specialist neurosurgical or spinal centre with confirmed CES.[3,13,15,16] Published estimates of the incidence of CES are fewer than one case per 100,000 population.[17,18] However, in 2010-2011 in England, 981 surgical decompressions were performed for CES,[19] and the population was estimated at 52,234,000,[20] giving an incidence of 1.9 per 100,000. Therefore, there may be over 1000 patients managed for CES in the UK each year. Accurate data on the presentation and management of these patients would establish current management plus adherence to and feasibility of care quality statements as well as potentially informing the revision of guidance based on accurate and current data.

The British Neurosurgical Trainee Research Collaborative (BNTRC) has previously successfully used a network of neurosurgical trainees across the UK and Ireland to identify cases via local tertiary referral

systems in conditions such as chronic subdural haematoma.[21] As CES is managed in the UK by specialist spinal services, similar case ascertainment via specialist referral systems to neurosurgical, orthopaedic, or joint spinal services provides a method of accurately identifying patients with CES during hospital admission. We propose to carry out the first national cohort study of the presentation and management of CES in the UK and establish the largest prospective series of patients with CES. This will provide data on CES incidence, epidemiology, presentation, management, and outcomes. This will inform the development of clinical guidance and identify areas for future research in CES.

This prospective observational cohort study aims to:

- Identify the number of cases of CES in the UK in all collaborating centres
- Describe the presenting symptoms and signs in patients with CES
- Describe the pathways of presentation to specialist spinal services for patients with CES in the UK
- Describe the type, timing, and findings of investigations in patients with CES
- Describe the medical and surgical management of CES
- Compare current practice to standards of care for CES
- Describe clinical outcomes for patients with CES using validated patient reported outcome measures, stratified by presentation, investigation findings, and management
- Demonstrate the ability of neurosurgical and orthopaedic surgical trainee networks to collaborate successfully on a prospective cohort study

METHODS AND ANALYSIS

Understanding Cauda Equina Syndrome (UCES) is a prospective cohort study of patients with confirmed CES managed at specialist spinal centres in the UK. Cases will be identified by neurosurgical or orthopaedic trainees in each specialist centre through daily screening of tertiary referrals and admissions to specialist spinal services. All patients managed as CES by the treating team will be included in this study.

Data regarding timing and type of symptom onset, referral, investigation, management, and outcome will be recorded anonymously on a secure database by the local trainee investigator during the patient's hospital admission and after discharge. Patient consent will be sought for the use of their

data and patients will be asked to complete patient reported outcome measures representing their condition before surgery and up to one year after surgery. Imaging at presentation will also be collected. This data will be compared with care quality statements and published outcome data for CES. This is an observational study. No changes to routine patient care will occur during this study.

Participant Selection

The study will recruit for one year. Cases will be identified from admissions to spinal units between 1st June 2018 until 31st May 2019. The last one year follow up assessments will be sent to participants on 31st May 2020.

For inclusion in this study, the patient must:

- be over 18 years old;
- be admitted to a specialist spinal service in the UK between 1st June 2018 and 31st May 2019;
- have capacity to provide informed consent for participation in this study; and
- have a diagnosis of clinical CES and structural compression of the cauda equina on imaging as determined by the treating clinician.
    - Clinical CES includes any of: altered saddle sensation; bladder dysfunction; bowel dysfunction; sexual dysfunction; or bilateral sciatica. This should be associated with radiological compression of the cauda equina. The cauda equina compression can be due to any cause, including, but not limited to, disc, tumour, infection, etc.

There is no upper age limit as we aim to establish the demographics of those presenting with CES.

The exclusion criteria are:

- Children under 18 years old.
- Patients undergoing emergent decompression for unilateral motor or sensory symptoms (such as foot drop), without clinical evidence of CES.
- Patients referred with suspected CES where the diagnosis is not confirmed, for example patients with the clinical symptoms and signs of CES without radiological evidence of cauda equina compression.
- Patients not admitted to participating spinal centres in the UK.

- Patients admitted to a participating spinal centre before 1st June 2018 or after 31st May 2019.
- Patients who are unable to provide informed consent for participation in this study.

Capture-recapture methods will be used to ensure complete case ascertainment. In December 2018, June 2019, and December 2019 all local investigators will check their case ascertainment by asking their local coding departments for all discharges coded as CES using the diagnostic code ICD-10 G83.4. Any additional patients identified through this method that meet the inclusion criteria will be invited to participate.

Data Collection

Data relating to presentation, hospital admission, investigations, and follow up will be collected by the local trainee investigator. Data will be collected from the patient's notes, through routine interaction with the patient as part of clinical care, and through interaction with other staff members caring for the patient. All clinical and demographic information collected for this study by the local investigators is collected routinely. No extra assessments will be performed.

Study participants who have consented to participate will also be asked to fill out details about their patient journey, their symptoms, patient reported outcome measures, and service usage. These will be collected electronically anonymously via the electronic database and linked to the patient record. Patient reported outcome measures will include visual analogue scores for back and leg pain plus the relevant sections of the Oswestry Disability Index,[22] the neurogenic bowel dysfunction score,[23] the short form incontinence questionnaire,[24] and the Arizona sexual experiences scale.[25]

All patients who are eligible for inclusion in the study will have basic anonymous clinical data collected as part of the screening log to establish participation rates and incidence at each centre. This will allow accurate assessment of the incidence of CES. Patients who do not wish to participate in the study will not be contacted further for the completion of patient reported outcome measures.

The timing and type of clinician reported and patient reported data that will be collected for UCES is shown in Figure 1: Study Flow Diagram.

Clinician entered data will be entered directly into the database using the participant's unique study number. Imaging will be reviewed on local PACS systems and transferred to the study team for review. Participant questionnaires will be sent out by email using unique links for each participant. If participants do not have an email address or prefer to fill out questionnaires on paper, paper or telephone versions of the questionnaires will be used. If participants do not respond to the email invitations, they will be contacted to find out whether they wish to continue with the study and to complete the questionnaires when willing. Where patient data is routinely entered into spinal databases, surgical and outcome data from those databases will be linked anonymously to the patient record by the clinical team using the patient's unique identifier for that database or registry.

Data Analysis

This study aims to establish the number of patients presenting with CES in the UK over one year. We expect approximately 20 patients per spinal centre per year depending on the population served, and a total of approximately 600-1000 patients in one year across the UK. The incidence of CES will be established based on the number of patients identified at each unit and the catchment population of that unit. If all units in the UK participate, incidence will be calculated based on UK population estimates. Incidence will be calculated from all patients identified as being eligible for the study from referral screening and local coding departments even if they do not consent for further participation.

A descriptive analysis of the clinical and demographic characteristics of presenting symptoms, signs, and outcomes of patients with CES will be performed. This will be determined from both clinician reported and patient reported data. CES incidence and characteristics will be broken down into categories such as suspected (CESS), incomplete (CESI), with retention (CESR), and early (CESE) based on the clinical data. The categorical and quantitative findings on imaging will also be described. Methods of patient presentation to specialist services will be described. Type, timings, and findings of investigations in patients presenting via different routes will be compared. The investigation and management of patients with CES will be described and compared to that laid out in current care quality standards. Proportions meeting the standards will be reported. Patient outcomes will be assessed and analysed using both clinician and patient reported outcome measures at six months and one year. Patient outcomes will be stratified by demographics, presenting features, causative pathology, timing and findings of investigations, and timing and type of surgery. Patient usage of

healthcare services over the year following diagnosis and management of CES will be assessed using both patient reported service usage and electronic records.

Patient and Public Involvement

The design and aims of this study were discussed with current patients being investigated for CES and those who had previously been treated for CES. Patients trialled the questionnaires and provided feedback on the questionnaires and patient information leaflet. The length and content of the questionnaires and information leaflet were altered in response to patient feedback. All participants will receive a summary of the results of this study. Patients are not involved in recruitment to this study as this occurs during or after emergency admission to hospital with CES.

ETHICS AND DISSEMINATION

Patient Consent

Once patients have been identified as being eligible to participate in the study, they will be asked by a member of their clinical team whether they would be willing to receive further information about the study. For the majority of patients this will occur during their admission to the spinal unit, and the approach will be made by a member of ward medical or nursing staff. Once verbal consent has been gained to give further information about the study, patients will be provided with the information leaflet for the study. Patients who indicate that they are happy to have further discussions regarding the study will be visited in hospital by a member of their clinical team to complete the written consent process. The person undertaking written consent will be adequately trained to do so, and have a good knowledge of the study protocol, aims, and processes. The participant will be informed about and consent to their medical records being inspected by regulatory authorities and representatives of the sponsor. Both the participant and the person undertaking consent will sign and date the informed consent form to confirm that consent has been obtained. The participant will receive a copy of this document and a copy will be filed in the Investigator Site File.

Decompression surgery for CES takes place as an emergency, and admissions occur at all times of day and night throughout the week and weekend. Following decompression the length of stay in hospital wards may be as short as one to two days, or may be longer than a week when there are ongoing bladder or bowel problems. All patients will be given adequate time to read the information leaflet with a minimum time period of six hours. Some patients will be discharged prior to being identified as

being eligible for the study. These patients will be contacted by telephone by a member of the clinical team and asked if they would be willing to receive information about the study by post or email. If they agree, the information leaflet and consent form will be sent to them, and they will be re-contacted to go through the consent process over the telephone at least 24 hours after receiving the information.

When participants prefer to fill out paper questionnaires or do not respond to the email link, their contact details (name, address, telephone number) will be passed to the central study team at NHS Lothian using the NHS email system with the consent of the patient. The central study team will contact the participants to find out whether they still wish to take part in the study. Those who wish to continue with the study will be sent the questionnaires by email, by post, or they can be completed over the telephone with a member of the central study team depending on the preference of the participant. If participants do not wish to continue with the study, they will not be contacted further.

Participants are free to withdraw from the study at any point. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's electronic case report form. The participant will not be contacted any further for outcome measures but their basic anonymous clinical details will be retained to allow accurate epidemiological assessment of the incidence of CES. If a patient loses capacity to consent for ongoing participation during the course of the study, the data they have already submitted or has already been submitted by their clinical team with their consent will continue to be used in the study, but they will not be contacted with further questionnaires.

Data Protection

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor and representatives of regulatory authorities. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

All clinical details will be entered into a database hosted by Castor EDC. Castor EDC complies with all applicable laws and regulations: Good Clinical Practice (GCP), European Union (EU) Annex 11, and the European Data Protection Directive. Clinician entered data will be entered directly into the database using the participant's unique study number. The clinical team can only view the records of patients from their own centre. Once a participant has consented for their email address to be stored, this will be entered into the Castor database by the local clinical team. The email address field is stored securely and is encrypted and cannot be viewed by anyone outside of the patient's local centre.

All local investigators will store a copy of the link between the patient's unique study number and their contact details, National Health Service (NHS) number, hospital number, Community Health Index (CHI) number, unique identifiers for spinal databases or registries, or other identifying details on a secure password protected NHS computer. Consent forms and paper completed questionnaires will be stored securely in a locked NHS office. No identifying information will be entered into the secure database except the email address.

All identifiable scans will be stored and transferred within the NHS PACS network. Only anonymised scans will be processed outside the NHS PACS network. Anonymised imaging data will be labelled only with the study number and stored on anonymised CDs or on encrypted hard drives.

Data Retention

All study documentation will be kept for a minimum of 5 years from the end of the study. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor. The end of the study is 18 months after the enrolment of the last participant.

Insurance and Indemnity

Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

Ethical Review

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (GCP). All researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement. GCP training status for all investigators should be indicated in their respective CVs.

UCES received a favourable ethical opinion from the South East Scotland Research Ethics Committee (REC) 02 (reference 18/SS/0047, IRAS reference: 233515, sponsor reference: AC18017). Local management approvals must be in place at each site prior to recruitment of patients to this study. This study is registered with ClinicalTrials.gov (160318) and at ISRCTN (ISRCTN16828522). The most recent version of the protocol will be available on the website of the BNTRC at www.bntrc.org.uk. This study is sponsored by NHS Lothian.

Peer Review

The concept for this study was selected by a panel of judges in an open competition for support from the BNTRC. The protocol has been reviewed and approved by the steering committee for this study and reviewed by the British Orthopaedic Trainees' Association, the British Association of Spine Surgeons, and the BNTRC committee.

Publication

Ownership of the complete dataset arising from this study resides with the steering committee and the BNTRC. On completion of the study, the data will be analysed and tabulated, and a report will be prepared. A summary report of the study will be provided to the REC within one year of the end of the study. Local data collected as part of this study belongs to the local team collecting that data. The study report will be used for publication and presentation at scientific meetings. Summaries of results will also be made available to local investigators. Following the initial analysis and publication, study data will be made available to those who submit successful peer-reviewed proposals for use of the data to the steering committee via the BNTRC.

All local investigators who enter data for at least one case will be named as contributors on publications arising from this study and will receive a certificate of collaboration in this study. Authorship of publications arising from this study will be determined in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE).[26]

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Paper Two: Evaluation of Nationwide Referral Pathways, Investigation and Treatment of Suspected Cauda Equina Syndrome in the United Kingdom. Daniel M. Fountain, Simon Davies, Mohammed Kamel, Paulina Majewska, Julie Woodfield, Ellie Edlmann, Aimun A.B. Jamjoom, **Ingrid Hoeritzauer**, Mueez Waqar, Dominic Mahoney, Dillon Vyas, Moritz Schramm, Georgios Solomou, Francesca Dawkes, Heidi Grant, Jonathan Attwood, Alexandros Boukas, Dominic Ballard, Emma Toman, Matthew Sanders, John E. Lawrence, Beverly Cheserem, Saurabh Sinha, Patrick Statham, Neurology and Neurosurgery Interest Group, British Neurosurgical Trainee Research Collaborative

Evaluation of Nationwide Referral Pathways, Investigation and Treatment of Suspected Cauda Equina Syndrome in the United Kingdom

ABSTRACT

Purpose: Cauda equina syndrome (CES) is a spinal emergency with clinical symptoms and signs that have low diagnostic accuracy. National guidelines in the United Kingdom (UK) state all patients should undergo an MRI prior to referral to specialist spinal units and surgery should be performed at the earliest opportunity. We aimed to evaluate the current practice of investigating and treating suspected CES in the UK.

Methods: A retrospective, multicentre observational study of the investigation and management of patients with suspected CES was conducted across the UK, including all patients referred to a spinal unit over 6 months between 1st October 2016 and 31st March 2017.

Results: A total of 28 UK spinal units submitted data on 4441 referrals. Over half of referrals were made without any previous imaging (n=2572, 57.9%). Of all referrals, 695 underwent surgical decompression (15.6%). The majority of referrals were made out-of-hours (n=2229/3517, 63.4%). Patient location and pre-referral imaging were not associated with time intervals from symptom onset or presentation to decompression. Patients investigated outside of the spinal unit experienced longer time intervals from referral to undergoing the MRI scan.

Conclusions: This is the largest known study of the investigation and management of suspected CES. We found that the majority of referrals were made without adequate investigations. Most patients were referred out-of-hours and many were transferred for an MRI without subsequently requiring surgery. Adherence to guidelines would reduce the number of referrals to spinal services by 72% and reduce the number of patient transfers by 79%.

INTRODUCTION

Cauda equina syndrome (CES) occurs due to compression of the lumbosacral nerve roots that can lead to a constellation of symptoms including sphincter disturbance alongside lower limb motor and sensory deficits [1]. It is a common neurosurgical emergency with an incidence of approximately 0.3-0.5 per 100,000 per year [2–4]. Clinical features of CES have low sensitivity and specificity necessitating imaging early in the diagnostic pathway [5–8].

Compounding these challenges is the current lack of consensus on how urgently decompressive surgery should be performed. There is no class I evidence to support emergency decompression at any time point. Meta-analyses have separately demonstrated statistically significant benefits of surgery within 24 hours [9–11], within 48 hours [12], and within 72 hours when treated as dichotomous variables [11]. Areas of contention leading to conflicting evidence include from what starting point the "time to surgery" should be determined [13], and whether patients experiencing a complete injury with retention and overflow incontinence should be considered for emergency decompression [9–11].

In the United Kingdom (UK) guidelines from the Society of British Neurological Surgeons (SBNS) and British Association of Spinal Surgeons (BASS) advise that patients presenting with acute back and/or leg pain with any bladder or bowel disturbance and with or without saddle sensory disturbance should be suspected of having CES. There should be a low threshold for investigation with emergency MRI at the hospital receiving the patient prior to referral to ensure timely diagnosis, referral and transfer to a specialist spinal unit where appropriate. Spinal units should not be considered a scanning service and out-of-hours MRI scanning should be considered routine practice to prevent needless and potentially harmful transport of patients for diagnostic imaging. If cauda equina compression is confirmed, guidance is that decompressive surgery be performed at the earliest opportunity [14–17].

There is a paucity of literature regarding current service delivery against these standards. Consequently, we sought to investigate the current service provision for the diagnosis and management of CES across specialist units in the UK.

MATERIALS AND METHODS

A retrospective, multicentre observational study of the investigation and management of patients with suspected CES was conducted across neurosurgical units in the UK. Departments at each neurosurgical unit providing emergency spinal surgery (whether neurosurgery, dedicated spinal surgery, or orthopaedic surgery) were included and hereafter known as "spinal units". All patients

with suspected CES referred within the six-month data collection period of 1st October 2016 to 31st March 2017 were included. The study protocol was approved by the audit and clinical governance committee of each participating hospital where required, the SBNS, and published on the website of the British Neurosurgical Trainee Research Collaborative (BNTRC) [18]. Patient consent was not required due to the fully anonymised collection of data without any patient-identifiable information. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data collection

Data were collected in each spinal unit using a standardised proforma by teams consisting of consultant surgeons, trainees, junior doctors, and medical students. Data were entered electronically into Castor EDC (Castor EDC, Amsterdam, Netherlands), which complies with all applicable laws and regulations (Supplementary Material Figure S1).

Demographic data included the spinal unit, age, gender, source of referral and presentation categorised as incomplete CES (CESI) or CES with retention (CESR) (**Table 1**) [19], or "Other". Referrals for patients with isolated back pain or unilateral leg symptoms were subsequently excluded from calculation of referral timings. Imaging modality, imaging findings, imaging availability, purpose of referral, outcome of referral, patient transfers, surgical decompression, length of stay, and discharge destination were also recorded. Date and time information was collected for each step in the referral pathway (onset of symptoms, presentation to healthcare professional, referral to the spinal unit, MRI before or after referral, transfer, decompression and discharge including discharge destination). For the purposes of evaluating out-of-hours service provision, out-of-hours was defined as outside the hours of 9am-5pm Monday-Friday.

Statistical analysis

Categorical comparisons on pair-wise data were undertaken using Fisher's Exact testing. Continuous data excluding time intervals were analysed using Kruskal-Wallis testing. Time interval data were analysed using generalised linear modelling with logarithmic transformation of the timing variables following visual inspection of Q-Q plots. Univariable analyses were performed based on referral pathways. Multivariable analyses were performed including age, gender, presentation, timing of referral (dichotomised into in-hours and out-of-hours), pre-referral imaging and the referrer. Length of stay was calculated based on time from MRI to discharge if transferred to the spinal unit for an MRI, or time from decompression at the spinal unit to discharge. Variables evaluated for length of stay for

those transferred for an MRI included age, gender, presentation, timing of referral, the referrer, whether or not the patient underwent decompression after the MRI, and discharge location. Cases with specified dates and times were used to analyse time intervals in hours, while all cases with dates submitted were included to analyse time intervals in days. Bonferroni correction was implemented to account for the multiple time points tested in the referral pathway, with a resultant threshold p-value of 0.007 (0.05/7) used to denote statistical significance. All statistical analyses were performed in R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 4441 referrals across 28 UK spinal units (coverage 93%) were included in the study during the six-month period. Median patient age at referral was 47 years (IQR 36-61). The majority of referrals were for female patients, and from a hospital other than the spinal unit (**Table 2**). Nearly half of the patients presented with CESI, and of those submitted as presenting with "other" symptoms, lower back pain was the most common (Supplementary Material Figure S2). Of all referrals, 3679 (82.8%) were made on a weekday. For referrals where time of referral were submitted, the majority were made out-of-hours (n=2229/3517, 63.4%). This is in contrast to the time of presentation where available where less than half of patients presented out-of-hours (n=622/1261, 49.3%) (**Figure 1**).

Referral and Treatment Characteristics

In total, 1628 referrals (36.6%) were made with an MRI completed prior to referral. Twenty percent of patients were referred with reported MRI evidence of cauda equina compression (n=918/4441, 20.7%). Of the 878 cases with an MRI report, the most common causes included disc prolapse (n=470/878, 53.5%), spinal stenosis (n=205/878, 23.3%) and spinal metastases (n=78/878, 8.9%).

When referrals were made without an MRI, the purpose of the referral was for imaging advice (n=1564/2813, 55.6%), the lack of availability of an MRI scanner out-of-hours (n=551/2813, 19.6%) and the absence of an available MRI scanner to the referrer (n=265/2813, 9.4%). Referrals from other hospitals were more likely to be made with a completed MRI (n=1033/2485, 41.6%) than referrals from other specialties on the same site as the spinal unit (n=436/1194, 36.5%, p<0.001), or referrals from primary care (n=153/715, 21.4%, p<0.001) (Supplementary Material Figure S3 and Table S1).

Graphical depiction of the outcome of referrals is shown in **Figure 2**, demonstrating the pathways for patients with suspected cauda equina syndrome. Of the 2813 referrals made without an MRI, in 2336 cases the referral outcome was to perform an MRI scan (83.0%). In total, 695 patients referred

underwent surgical decompression (15.6%). Of the patients referred with an MRI, 474/1628 (29.1%) underwent decompression. A significantly smaller proportion of referrals made without an MRI resulted in surgical decompression (n=221/2336, 9.5%, *p*<0.001). Causes were not significantly different between cohorts undergoing decompression with an MRI before or after referral which was performed most commonly for a disc prolapse (n=532/695, 76.6%), spinal stenosis (n=96/695, 13.8%), and infection (17/695, 2.4%).

Out-of-hours Service Provision in Other Hospitals

In other hospitals receiving patients with suspected cauda equina syndrome, the majority of referrals to the spinal unit were made out-of-hours (n=1529/2485, 72.7%, Supplementary Material Table S1). Out-of-hours referrals were more likely to be made without a completed MRI scan (out-of-hours n=991/1529, 64.8%, vs. in-hours n=202/575, 35.1%, *p*<0.001, **Figure 3**). Of the referrals made without an MRI scan, referrals out-of-hours were more likely to result in the transfer of the patient for an MRI scan (out-of-hours n=370/991, 37.3%, vs. in-hours n=38/202, 18.8%, *p*<0.001). Overall 2.9% of all out-of-hours referrals from other hospitals underwent an MRI following referral which led to surgical decompression.

Referral Timings

Time intervals were available for 3168 (71.3%) of referrals (**Table 2**) with analysis based on the pathways outlined in **Figure 2**. Comparisons were made for each stage in the referral process with each pathway relative to the most common (MRI not done, MRI at other hospital) (**Figure 4**, **Figure 5**). Full results including effect sizes and confidence intervals can be found in the Supplementry Material (**Table S2**).

There was a significantly longer time interval from presentation to referral for patients undergoing an MRI prior to referral (median 6.1 vs. 1.5 hours, p<0.001). Conversely, the time interval from presentation to MRI for patients referred with an MRI was significantly shorter than patients referred before an MRI (median 3.1 vs. 13.9 hours, p<0.001). Of those cases referred before an MRI was completed, the time interval from referral to MRI was significantly shorter if the patient underwent the MRI at the spinal unit even if transferred from another hospital (median 7.2 vs. 13.3 hours, p<0.001). Moreover, for patients referred from another hospital, the time interval from MRI to decompression was significantly longer in patients referred with an MRI compared to if referred before an MRI was completed (median 23.2 vs. 9.7 hours, p=0.003). These results were consistent when repeating the analysis for time intervals expressed in days (Supplementary Material Table S3).

Full multivariable results are shown in Supplementary Table S3. Cases submitted with an MRI prior to referral reported a significantly longer time interval from presentation to referral and shorter time from presentation to MRI than cases referred without imaging. Referrals in-hours were associated with a shorter time from presentation to MRI, while patients presenting to primary care (GP) were referred earlier than patients from hospitals other than the spinal unit. Cases referred from the hospital in the same site as the spinal unit reported a significantly shorter time interval from presentation to MRI and presentation to decompression. Increasing age was associated with a longer time interval from MRI to decompression and referral to decompression. These results were consistent when analysing time intervals expressed in days (Supplementary Material Table S5).

Length of Stay

Median length of stay for patients transferred for an MRI was 17.9 (IQR 4.5-70.3) hours. Median length of stay for patients transferred not requiring surgery was 11.1 (IQR 3.6-48.6) hours compared to 75.6 (41.9-116.5) hours for those requiring decompressive surgery. A quarter of patients transferred for an MRI scan not requiring surgery were admitted for over 24 hours (n=78/330, 23.6%). Length of stay was significantly shorter if patients not requiring surgical decompression were transferred back to their referring provider (median 7.2 (IQR 3.0-15.4) hours) rather than their original place of residence (median 16.8 (IQR 4.0-59.9) hours, $p<0.001$). For all patients undergoing surgical decompression, multivariable analysis demonstrated a longer admission was associated with increasing age (Wald Z = 2.94, $p=0.003$), and diagnosis of an infection (Wald Z=2.86, $p=0.004$) or spinal stenosis (Wald Z=3.03, $p=0.003$). A shorter admission was associated with referrals from primary care compared to other hospitals (Wald Z=-2.35, $p=0.019$, Supplementary Material Table S7).

DISCUSSION

In this retrospective multi-centre study of 4441 referrals for suspected CES, substantial deviations from UK guidelines were identified. While the SBNS and BASS recommend that local hospitals should investigate patients thoroughly prior to referral to spinal services, in this study only a minority of cases were referred with diagnostic imaging completed (n=1628/4441). Guidelines also state that spinal units should not be considered a scanning service, but due to the majority of referrals being made out-of-hours (n=1529/2104, 72.7%) a proportion of patients were transferred to the spinal unit for an MRI scan (n=370/1529, 24.2%). Importantly, of these referrals a fraction required surgical decompression (n=45/1529, 2.9%).

Referral Pathway

Referrals made without an MRI were most commonly made for advice on whether an MRI was indicated. Existing guidelines already include specific signs and symptoms suggestive of CES available for all practising physicians that should prompt an emergency MRI. A proposed diagram based on these guidelines is shown in **Figure 6**, including where the MRI should be performed and what MRI findings require an emergency referral to spinal services. Based on a six-month period, implementing this pathway would reduce the number of referrals to spinal services by 72% (4441 to 1224) and reduce the number of patient transfers by 79% (739 to 156). This pathway should be incorporated into local and regional protocols with dissemination in key departments particularly Emergency Departments. Due to the possibility of self-referral, direct-to-patient education leveraging existing organisations such as Cauda Equina UK could also be made to improve detection of red flag symptoms early on in the disease [20]. Given that the majority of patients presented in-hours and were only referred out-of-hours, work to improve triage of these patients will also improve the burden of undertaking diagnostic imaging for these patients out-of-hours.

In other countries, guidelines are less specific on when and where an MRI should be undertaken. In the Netherlands, referral to specialists should be considered when the general practitioner is not sure about the diagnosis or considers surgical intervention.[21] In Norway and Denmark, guidelines for degenerative spinal conditions recommend referral to neurosurgery after an MRI is completed, but in the case of suspected CES early referral is recommended without specific guidance on where diagnostic imaging should be performed.[22, 23] In Germany, acute inpatient admission is required in patients with “red-flag” symptoms but again no specific guidance on location for diagnostic imaging is given.[24] Overall, no study of referral patterns or pathways for suspected CES in other countries was identified.

Diagnostic Imaging Availability

Part of the problem with implementing the pathway outlined in **Figure 6** lies in the availability of diagnostic imaging. Numerous national guidelines and protocols recommend that emergency MRI scanning is available 24/7 in all UK district general hospitals [25–27] and yet UK survey data showed only 14% of hospitals providing access to MRI 24 hours a day [28]. Although costs and staffing levels are often cited as the challenge, there are examples of cost neutral solutions without increased staffing, such as arranging out-of-hours CT radiographer training in basic brain and spine MRI scanning with rotations through MRI one week in every twelve [28].

Any associated cost increase will have to be balanced against two current significant cost burdens. First, the costs associated with the transfer of patients for an MRI scan which one hospital estimated at £6,000 per referral. Such is the cost that if only two referrals were made from one district general hospital it would be more cost effective for the trust to have their own dedicated radiographer on call [29]. Second, the clinical and financial implications of inadequate investigation and management of CES are an important consideration [30]. Around 10% of CES cases involve litigation [1]. Average claims range from £117,331, to £211,758 per case and a highest settlement of £2,041,000 [31].

Timing of Surgery

Although the decision to perform decompressive surgery for confirmed CES is a recognised emergency, the decision as to how quickly this should be performed is unclear. Guidelines are based on balancing the duration and clinical course of symptoms and signs alongside potentially greater risks of operating out-of-hours. No specific standards on time intervals have been published due to the absence of consistent results in published studies. The literature is also unclear with regards to the defined starting points used to calculate "time to surgery", with studies reporting the time from the first urinary symptom, time from bladder paralysis, or the time from admission to hospital [13].

This study revealed no significant differences between referral pathways and the time of onset of symptoms or presentation to decompression. However, pathways of patients referred outside the spinal unit were associated with significantly longer time intervals from referral to MRI if undergoing the MRI outside the spinal unit after referral. Furthermore, time intervals from MRI to decompression were significantly longer for patients with a confirmed CES undergoing an MRI before referral. Both represent the proposed pathway for managing patients with suspected CES in the UK. These results therefore have important implications for service delivery, particularly with efforts to increase the proportion of patients investigated through this pathway. Any policy changes to reduce the referral burden on specialist spinal units will need to ensure this does not result in an increase in the length of time patients with suspected cauda equina syndrome are being investigated and treated.

Future Directions

The comparative epidemiology and referral patterns between countries for suspected CES requires further investigation. The Getting It Right First Time (GIRFT) is a programme delivered in the United Kingdom to improve the quality of care within the National Health Service by reducing unwarranted variations. Data from this study will inform work to review local policies related to out-of-hours arrangements for radiography to ensure compliance with national guidelines and delivering of 24-

hour local MRI scanning [29]. This study has also informed an ongoing large prospective study of the investigation, management and outcome of patients with confirmed CES in the UK (Understanding Cauda Equina Syndrome or UCES) where comprehensive presenting symptomatology, timings, and outcome data will be collected [32]. The results of UCES will contribute to existing work developing tools to improve the clinical assessment and investigation of patients with suspected CES. [26, 33].

LIMITATIONS

This study covered a large number of referrals to spinal centres within the UK over the six-month study period and 28 out of the 30 UK neurosurgical centres participated. However, the absence of two neurosurgical centres and smaller orthopaedic centres that did not participate, means that this does not cover the whole population of the UK. Despite these limitations, we think that the large number of cases in this study should be representative of those referred across the UK. There may be a variability in data collection between centres which could not be centrally verified by the primary investigators due to the anonymous nature of data collection. This study only addressed cases which were referred to a spinal unit, missing patients who were managed without an MRI or who underwent MRI scanning locally which was normal without referral to the spinal unit. Outcome data was not collected in this study; the aforementioned future prospective study of confirmed CES in the UK (UCES) will collect outcome data and its relationship to presenting symptoms and the referral pathway including timings will be identified [32].

CONCLUSION

Guidelines in the UK for the investigation and management of patients with suspected cauda equina syndrome emphasise the importance of thorough investigation in the receiving hospital prior to referral to specialist units. This national retrospective multi-centre study of 4441 referrals has identified deviation from national guidelines. Currently the vast majority of referrals for suspected CES are made without an MRI out-of-hours with specialists subsequently recommending an emergency MRI that in a proportion requires a transfer to the spinal unit. Adherence to guidelines would reduce the number of referrals to spinal services by 72% (4441 to 1224) and reduce the number of patient transfers by 79% (739 to 156). Changes required to adhere to guidelines will need to acknowledge the identified longer time intervals for diagnostic imaging if patients are investigated locally without transfer to ensure the best care for patients with suspected CES in the future.

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An assessment of patient reported long-term outcomes following surgery for Cauda Equina Syndrome

SUMMARY

Background Data regarding long-term outcomes following surgery for cauda equina syndrome (CES) is scarce. In addition, these studies rely on patient descriptions of the presence or absence of symptoms, with no gradation of severity. This study aimed to assess long-term bladder, bowel, sexual and physical function using validated questionnaires in a CES cohort.

Methods A pre-existing ethically approved database was used to identify patients who had undergone surgery for CES between August 2013-November 2014. Patients were contacted over a one-month period between August – September 2017 and completed validated questionnaires via telephone, assessing bladder (Urinary Symptom Profile), bowel (Neurogenic Bowel Dysfunction Score), sexual dysfunction (Arizona Sexual Experiences Scale) and physical function (Physical Component Summary of SF-12 Questionnaire). Patients were also asked which of their symptoms currently they would most value treatment for and what healthcare services they had accessed post-operatively.

Results Forty-six of 77 patients (response rate 72%, inclusion rate 60%) with a mean age of 45 years (21-83) and mean time since admission of 43 months (range 36-60) took part in the follow up study. The prevalence of bladder dysfunction was 76%, bowel dysfunction 13%, sexual dysfunction 39% and physical dysfunction 48%. Pain was chosen as the symptom patients would most value treatment for by 57%, but only 7% reported post-operative pain-management referral.

Conclusions With a mean follow up time of 43 months**,** these findings confirm the high prevalence of long-term bladder, sexual and physical dysfunction in CES patients and provide useful data to guide the expectations of patients and clinicians.

Introduction

Cauda Equina Syndrome (CES) is a neurosurgical and spinal orthopaedic emergency with potentially significant clinical and medicolegal consequences for both the patient and the medical team managing the condition. It is a relatively rare occurrence with an incidence of 0.3-1/100,000 in the general population and accounts for 2-6% of lumbar spine procedures [7]. However, it is difficult to establish the true incidence of the condition due to a lack of consensus on an exact definition of the syndrome and its sub-classes [6].

CES involves compression of the nerves of the cauda equina, most commonly caused by the herniation of an intervertebral disc [6]. This results in a constellation of symptoms related to a loss of cauda equina neural function including bladder, bowel and/or sexual dysfunction along with loss of saddle sensation, motor control or reflexes of the lower limbs [6]. The aim of surgical management is to restore normality of function by urgent decompression of the cauda equina nerve roots, but there is a risk that recovery may be only partial or absent entirely. It is these debilitating residual symptoms that contribute to the serious physical and socioeconomic consequences that can arise following CES.

The main body of research into CES has attempted to elucidate factors affecting post-operative outcomes, such as presentation characteristics and time to decompression[5, 8, 11, 14, 20]. Individual studies are largely equivocal, but meta-analyses conclude that earlier surgical decompression is beneficial for the patient, and that patients with urinary retention and overflow incontinence have poorer outcomes than those without [1, 3]. However, because the main area of investigation is prognostic factors *prior* to surgery, outcomes following surgery are understudied.

The few studies that do assess outcomes generally focus on mobility, pain or bladder function, with bowel or sexual function rarely investigated. Furthermore, they tend to be short term in design, with data collection limited to the first routine follow-up appointment, leading to a paucity of data regarding the long-term outcomes following CES surgery. For example, Srikandajarah *et al* assess bladder outcome but only at around 3 months, with Korse *et al* (2017a) investigating bladder, bowel and sexual function but only at 6 weeks [12, 23]. This is a short time into the patients' recovery journey and means that both clinicians and patients have little data on which to base long-term recovery expectations.

When long-term bladder, bowel and sexual function are measured, such as Korse *et al* (2017b), studies rely on patient reported data, with outcomes often not defined or measured using validated assessment tools[13, 24]. This dichotomises symptoms into functional or dysfunctional

with no gradation of severity and means the data may not reflect the diverse range of residual symptoms which may be present.

Aims

This study used validated questionnaires to objectively assess a range of long-term outcomes following CES surgery. The primary aim was to assess the patients' current bladder, bowel and sexual function. Secondary aims assessed quality of life related to physical function, ability to return to work, what symptom patients would most value treatment for currently, and long-term healthcare service use as reported by the patient.

Materials and Methods

Participants and procedures

Seventy-seven patients who had attended the regional neurosurgical centre of the Western General Hospital, Edinburgh, between August 2013 and November 2014 were identified from a pre-existing ethically approved database of patients with suspected CES. After University of Edinburgh ethical review, the participants were contacted via telephone, gave informed consent and completed the questionnaire delivered by the author (JEH). Patients were included in CES caused by degenerative disc disease and excluded in cases of CES secondary to intradural or extradural tumours or if unable to complete the questionnaire due to death, insufficient English or untraceable contact details (Figure 1).

Following completion of the questionnaire, electronic records were used to confirm age and gender, and to assess whether the patient had incomplete CES (CES-I), with altered urinary sensation or loss of desire to void, or CES with retention (CES-R), with painless urinary retention and overflow incontinence [8].

Questionnaire

The questionnaire contained two sections; validated and unvalidated. In the validated section, *bladder dysfunction* was assessed using the *Urinary Symptom Profile (USP)* with dysfunction defined by a score ≥1. This allows the breakdown of urinary symptoms into 3 domains of stress incontinence, overactive bladder (OAB) and low stream. Increasing scores indicate worsening dysfunction [9]. *Bowel dysfunction* was assessed using the *Neurogenic Bowel Dysfunction (NBD) Score*, which categorises bowel dysfunction into "very minor" (score 0-6), "minor" (7-9), "moderate" (10-13) and "severe" (14+), and rates overall bowel satisfaction out of 10 [15]. *Sexual dysfunction* was assessed using the *Arizona Sexual Experiences (ASEX) Scale*, where dysfunction is described by an overall score of ≥19, one domain ≥5 or 3 domains ≥4 [17]. Lastly, physical functioning was assessed using the Physical Component Summary (PCS) of the Short-Form 12 (SF-12) questionnaire with scores compared to the Scottish adult average data [26].

The unvalidated section was a semi-structured interview conducted by JEH. This assessed occupation status prior to CES; return to work following surgery; current status including any residual weakness/numbness/pain; whether pain prevents them from doing daily activities; use of any mobility aids; which of their symptoms they would most value relief from, and healthcare service use.

Statistical analysis

Statistical analysis was performed using SPSS version 22 for Mac OS X (SPSS inc., Chicago, IL). Independent T-tests were used to analyse mean differences between the CES-I and CES-R, with statistical significance determined by a p-value <0.05.

Results

Overall 46/77 participants completed the study, generating a response rate of 72% and an inclusion rate of 60% (Figure 1). The group comprised of 19 males and 27 females with a mean age of 45.4 years (range 21-83) and mean time since admission of 43.4 months (range 36-50). In total, 83% (n=38) of participants had (CES-I) and 17% (n=8) had CES-R. This proportion is similar to that of the intial cohort of 74 patients, which had 81% with CES-I and so is representative.

** Figure 1 here**

Bladder function

On follow-up, 76% (n=35) of patients suffered bladder dysfunction as defined by the USP (Table 1). Overactive bladder was the most frequently described symptom (72%), with stress incontinence (39%) and low stream (41%) affected at similar rates. The mean total USP score for all participants was 7.15 (±7.17), with breakdown mean scores of Overactive Bladder 4.37 (±4.72), Low Stream 1.59 (±2.70) and Stress Incontinence 1.20 (±2.07). Patients with CES-R demonstrated significantly more dysfunctional Low Stream scores (+2.77, p=0.007), with no significant differences in the other USP domains.

Table 1 here

Bowel function

On follow-up, 13% (n=6) of participants reported bowel dysfunction with a severity of “minor” or greater as defined by the NBDS. The mean score for satisfaction was 7.7/10, the median 9/10, and the mode 10/10. Bowel function was significantly worse in patients with CES-R, with a mean difference of +4.13 compared to those with CES-I (p=0.012).

Sexual Function

At follow-up 39% (n=18) of patients reported sexual dysfunction as defined by the ASEX

questionnaire. Patients were most commonly dysfunctional in the domains of sex drive (35% n=16), ease (37% n= 17) and maintenance (35% n=16) of arousal and ease of orgasm (39% n=18) with orgasm satisfaction less affected (23% n=11). Patients with CES-R had significantly worse sexual function, with a mean difference of +6.76 (p=0.009)

Physical function and Employment

The SF-12 demonstrated 48% (n=22) of patients to have statistically significant poorer physical function than the Scottish adult average of 49 (±10.3) and the group mean Physical Component Score of 39.2 (±11.3) to be markedly lower than this too (Figure 2). Prior to admission 74% (n=34) patients were in employment, with 15% (n=7) unemployed and 11% (n=5) retired. At follow-up, 71% (n=29) of those of a working age were able to return to full employment, with 15% (n=6) returning in a reduced capacity and 15% (n=6) unable to work. The number of retired patients remained n=5. There was no significant difference between CES-I and CES-R in the Physical Component Summary.

Figure 2 here

Semi-structured interview

Residual symptoms were present in many with 70% (n=32) reporting areas of sensory loss and 44% (n=20) reporting current leg weakness, including 13% (n=6) requiring walking aids to mobilise. Additionally, 70% (n=32) of patients described themselves as suffering pain, of which the majority was back pain (35%, n=16). This pain represents a significant barrier in 57% (n=26) who state that pain prevents them from doing things in their daily lives.

Despite a variety of residual symptoms, the majority of patients chose pain as the symptom that they would most value treatment for (57% n=26). Back pain was highlighted as more important than leg pain with 35% (n=16) stating it to be the symptom that they would most like to remove (Figure 3).

Figure 3 here

Review after discharge

Following hospital discharge, 85% (n=39) of patients reported having contact with the healthcare service, the most common being community-based physiotherapy (76% n=35). Fewer patients, 20% (n=9) stated they had been referred to specialist urology services and fewer still 7% (n=3) had been referred to the pain management team (Figure 4).

Figure 4 here

Discussion

This study aimed to assess the long-term outcomes following CES surgery by using validated questionnaires to quantify the symptoms currently experienced by a cohort of previous CES patients. Results demonstrated bladder, bowel and sexual dysfunction to be common problems within this population. Physical function was also shown to be significantly reduced in a large proportion of the patients, with many reporting persistent pain, sensory loss or weakness. Patients who had CES-R had significantly more stream-related bladder dysfunction, bowel dysfunction and sexual dysfunction, but no difference in physical functioning. Service use was assessed through semi-structured interview, with the majority of patients obtaining post-discharge physiotherapy, but few accessing urology or pain management services.

The main limitation of this study is the relatively small sample size (n=46) and the risk of selection bias and social desirability bias when sourcing data from voluntarily responding patients. However, we achieved a follow-up rate of 71% using telephone interviews and attempted to minimise social desirability bias through a semi-structured interview approach. We feel our sample size to be satisfactory, since the median number of participants in CES studies is n=14, and consider our inclusion rate to be adequate give the personal and invasive nature of the questionnaires [24]. Whilst the USP is useful for determining the number of patients affected by bladder symptoms and in what way, it does not provide a scale to assess the impact of the symptoms on quality of life. As such, future studies could assess this through combining the USP with the recently validated SF-Qualiveen [13, 21]. Use of services post discharge was patient reported. This was impossible to confirm due to patients coming from many regions with differing online record systems which may have impacted on the figures. However, urological and pain management interventions are often quite invasive or time intensive and the high rates of reported physiotherapy usage gives us confidence that these figures are unlikely to be grossly underestimated.

In highlighting the large burden of disease present in this patient population, our results broadly agree with previous literature in this area. However, the proportions of patients with residual symptoms differ in some categories.

Our study noted a much higher rate of bladder dysfunction (76%) than previous investigations, with Mccarthy *et al* finding 43% of patients to have bladder dysfunction at 5 years and Korse reporting 47% reducing to 41% on long term follow-up [13, 16]. We hypothesise that this difference may be explained by the use of the objective USP score which is known to have a high sensitivity to a range of urological symptoms and patients would often report a symptom-free bladder, only to show dysfunction on the USP [27]. This conjecture is supported by the findings of Hellström *et al* who describe how although only 41% of CES patients complained of bladder dysfunction, urodynamic findings were abnormal in 76% [10]. This potentially demonstrates an opportunity to improve symptoms in patients who are not aware of the possibility. The majority of bladder dysfunction was in the overactive bladder domain (72%), with less dysfunction related to stress incontinence or low stream. This is likely due to the neural damage sustained in CES that would preferentially affect detrusor innervation and function over pelvic floor strength or urethral patency [2].

Bowel dysfunction is the symptom with the greatest variation of reported prevalence in the literature and the results from this study continued this trend, describing a much lower rate than previously reported. Korse *et al* describe a higher prevalence of 47% on initial follow-up, reducing to 43% over 13 years [13]. The rates reported by McCarthy *et al*. were higher still with 60% reporting "bowel disturbance" as they were by Podnar, however this study did not use validated questionnaires in data gathering [16, 19]. Using the neurogenic bowel dysfunction score allowed us to assess the degree of dysfunction present. Results showed that although the literature describes patients who complain of bowel disturbance following CES, few are affected to a quality-of-life-reducing level when investigated using validated methods. This is further supported by the high median and mode average in "bowel satisfaction" with a lower mean value.

In regards to sexual function our results demonstrated a lower prevalence of dysfunction (39%) compared to prior research, again likely caused by the method of outcome measurement. Mccarthy *et al* reported that 50% of patients had some degree of dysfunction, with Korse *et al* finding dysfunction prevalence to be 56% at 2 months, marginally improving to 53% at 13 years [13, 16]. However, Mccarthy *et al* used different questionnaires to assess outcomes in males and females including the unvalidated Female Pelvic Floor Questionnaire. In Korse *et al*, the outcome was patient reported, not objectively assessed, and 11/19 were coded as "dysaesthesia of genital region" or "not

specified". Whilst this may represent abnormal sexual function it does not necessarily imply dysfunction and may lead to an inflated prevalence.

Physical function is rarely objectively assessed in CES patients, but previous research agrees that the majority of patients score lower than the population average. McCarthy *et al* assessed physical function using the Short-Form 36 questionnaire, a longer questionnaire from which the SF-12 was adapted and found CES patients to have significantly reduced function in the "Physical" and "Role Physical" domains [16].

Patients with CES-R demonstrated significantly poorer Low Stream bladder function, bowel function and sexual function in comparison to those with CES-I. This is likely due to the more serious nature of CES-R, which indicates compression and damage to nerves of the lumbo-sacral plexus and therefore more likely subsequent permanent damage the nerves supplying bladder, bowel and sexual function as a result. Specifically, the Low Stream USP domain was worse in these patients due to some needing to self-catheterise as a result of CES. Few studies directly compare long-term outcomes between patients with CES-I and CES-R, with none to our knowledge assessing bladder, bowel, sexual and physical function. Gleave and Mcfarlane feel those with CES-R often have worse outcomes and this is supported by Kennedy et al note that all 5 patients in a 19 patient study who had residual impairments at 2 years follow-up had urinary retention at presentation [8, 11]. However, McCarthy et al found no significant differences between CES-I and CES-R in a range of outcomes [16]. A Meta-analysis was performed, but was only able to report on urinary outcomes due to a lack of data present for other functions. This showed that patients with CES-R had relative risk of 2.58 of having bladder dysfunction, although this result was not significant (95%CI 0.59-11.31)[4]

In a holistic approach we also assessed function through the patients' occupation status, symptom they would most value treatment for, and NHS service use post-discharge. In patients of working age we found 71% were able to return to full employment, roughly matching the data from previous studies regarding spinal surgery which found 67% patients were able to return to work over a 3-month to 5-year follow-up [25].

Overall, 70% of patients declared that they suffered pain on follow-up, with 57% (n=26) stating that it stops them from doing things in their daily lives. Furthermore, when asked to decide which symptom they would most value treatment for, the most commonly chosen option was pain, with back pain more important than leg pain. This is a considerably higher rate of pain than would be

expected, given that the proportion of patients reporting leg or back pain 2 or more after discectomy for radiculopathy 17% [18]. Furthermore, little literature has assessed the prevalence of pain as a long-term outcome, preferring to focus on other functions. However, a small study of 14 CES patients by Shapiro found that 28% suffered from chronic pain at 6-60 months follow-up [22].

The patient-selected most important symptoms did not correlate with the patients' stated use of NHS services. Despite 57% of this population describing their lives to be limited by pain and it being their chosen symptom for treatment, only 7% (n=3) reported contact with the pain management team post-discharge suggesting that greater utilisation of this service could benefit this population.

Future studies should continue to follow this cohort and reassess for any future improvement in bladder, bowel, sexual or physical function using the questionnaires utilised by this study. Additional work could further investigate pain as an outcome in this population, using validated questionnaires.

Conclusion

This long-term outcomes investigation of CES post-surgery patients has identified continued abnormal bladder, bowel, sexual and physical dysfunction in patients at a mean follow-up of 43 months. Almost three quarters of patients continued to have bladder symptoms at long term follow up and almost 40% had sexual dysfunction. Bowel dysfunction was found to have less of an impact than previously suspected, and pain was identified as the symptom patients would most value treatment for. However, referrals for pain management did not correlate with the importance given to this symptom, highlighting the necessity of global assessment and management in this complex patient group.

We believe this to be the largest cohort of patients with CES investigated for long-term outcomes using validated questionnaires and, although a relatively small sample, we hope this will provide some much needed data to guide the expectations of clinicians and patients throughout their CES diagnosis, operation and recovery process.

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Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables and Figures

Fig 1 Patient Inclusion

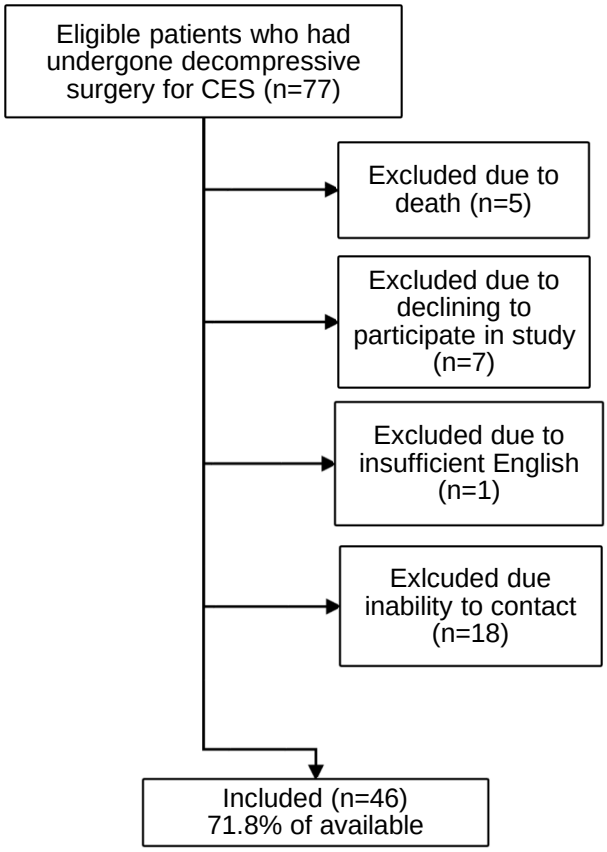

Eligible patients who had undergone decompressive surgery for CES (n=77)
Excluded due to death (n=5)
Excluded due to declining to participate in study (n=7)
Excluded due to insufficient English (n=1)
Exlcuded due inability to contact (n=18)
Included (n=46)
71.8% of available

Table 1. Patient Characteristics at follow up

Measure	n =	%	Mean Score (±SD)
Urinary Symptoms Profile			
Overall Urinary Dysfunction Score	35	76	7.15 (±7.17)
Stress incontinence	18	39	1.20 (±2.07)
Overactive Bladder	33	72	4.37 (±4.72)
Low Stream	19	41	1.59 (±2.70)
Neurogenic Bowel Dysfunction Score			
Very minor	40	87	
Minor	4	9	
Moderate	0	0	
Severe	2	4	
Arizona Sexual Experiences Questionnaire			
Sexual dysfunction	18	39	
Physical Function			
Working	29	63	
Working in a reduced capacity	6	13	
Not working	6	13	
Retired	5	11	

Fig 2 Histogram of patient SF-12 PCS distribution

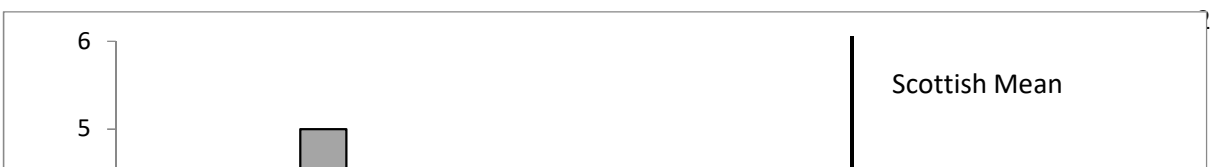


Figure 3 Patients' symptom for which they would most value treatment

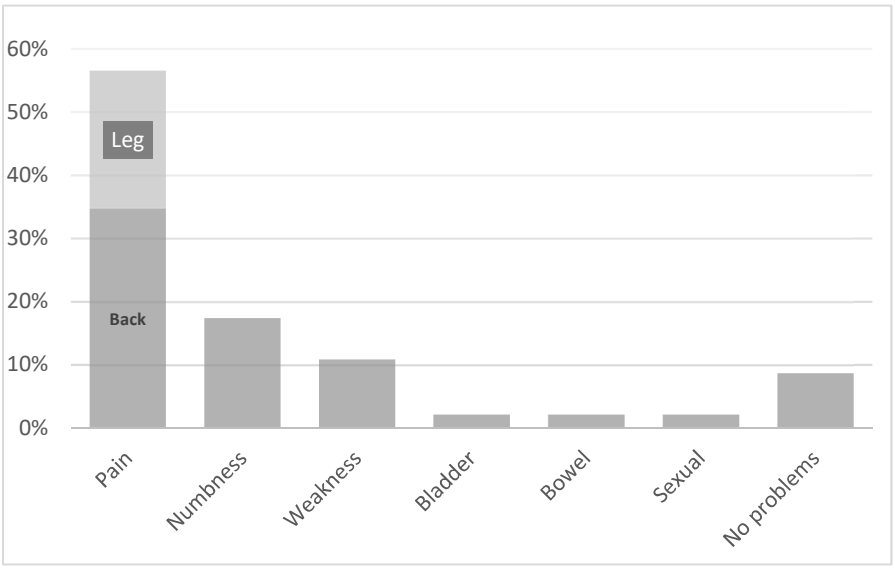
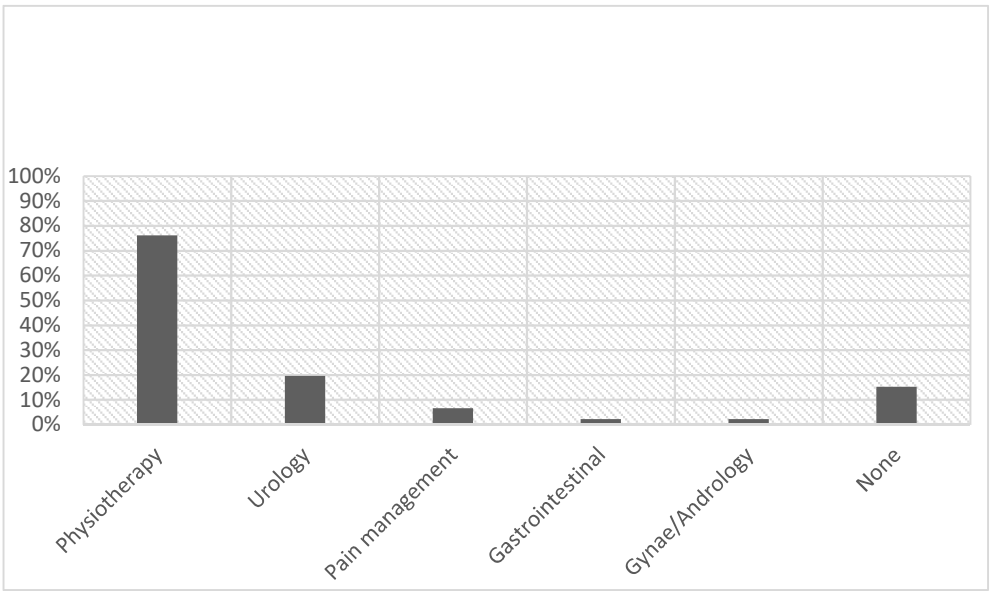


Fig 4 Patients' reported post-discharge healthcare service use


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Physiotherapy
Urology
Pain management
Gastrointestinal
Gynae/Andrology
None

Paper Four: Hoeritzauer I[1], Carson AJ[1,2,3], Stone J[1,3]. 'Cryptogenic Drop Attacks' revisited: evidence of overlap with functional neurological disorder. JNNP 2018 Jul;89(7):769-776.

"Cryptogenic Drop Attacks" revisited – evidence of overlap with Functional Neurological Disorder

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Tables: Three (two additional supplementary tables) **Figures:** One

References: 40

Key Words: 1. Drop attacks **2.** Cryptogenic **3.** Psychogenic **4.** Non-epileptic **5.** Functional Neurological Symptom Disorder

ABSTRACT

OBJECTIVE

In their 1973 BMJ paper ' Cryptogenic Drop Attacks', Stevens and Matthews described 40, mostly middle aged, female patients with drop attacks of unknown cause. Although clinically common, there has been little on this topic since. We aimed to determine clinical features, comorbidity and outcome of patients with drop attacks.

METHODS

We carried out a retrospective review of patients with cryptogenic drop attacks seen consecutively by one clinician (JS) between 2006 and 2016. Demographics, phenomenology, duration and frequency of attacks, attack description and comorbid diagnoses were recorded. Patients were followed up with a notes review.

RESULTS

83 patients with cryptogenic drop attacks were predominantly female (89%,n=79) mean age 44yrs. The majority (93%,n=77) could not remember the fall itself and almost half (43%, n=36) experienced prodromal dissociative symptoms. Mechanical trips or syncope preceded drop attacks, historically, in 24% (n=20) of cases. Persistent fatigue (73%,n=61), chronic pain (40%,n=33), functional limb weakness (31%,n=26) and dissociative (non-epileptic) attacks 28% (n=23) were common, with the latter usually preceding or emerging from drop attacks. At follow-up (88%,mean 38 months), 28% (n=23) had resolution of their drop attacks. Predisposing (but non-causative) disease comorbidity was found at baseline (n=12) and follow up (n=5).

CONCLUSIONS

Cryptogenic drop attacks are associated with high frequency of comorbid functional somatic and functional neurological disorders. Patients commonly have prodromal dissociative symptoms and in some there was a clear relationship with prior or subsequent dissociative (non-epileptic) attacks. Some cryptogenic drop attacks may be best understood as phenomena on the spectrum of dissociative attacks.

INTRODUCTION

Cryptogenic drop attacks were defined in a seminal paper by Stevens and Matthews in 1973 as falls without warning, without clear cause of loss of consciousness, 'vertigo or other cephalic sensation' and with rapid recovery, occurring predominantly in middle- aged women[1]. Drop attacks due to various disorders including cardiac, cerebrovascular causes, vestibular or, most commonly in children, seizure disorders[2–5] have been described since the early 1900s[4,6–12].

In their study of 40 patients with drop attacks Stevens and Matthews considered various mechanisms but concluded that this 'cryptogenic' presentation was the most common. Despite their prevalence, estimated at 3.5% of falls in adult women[1], and their potential to be both embarrassing and fear inducing, no consecutive series of cryptogenic drop attacks in a predominantly middle age cohort has been undertaken since 1973[6].

Several clinical observations in a series of patients with drop attacks led us to wonder whether some of them, especially in younger patients, may be considered a subtype of functional (psychogenic) neurological disorder. We hypothesize that a brief moment of dissociation, akin to that seen in dissociative (non-epileptic) attacks and/or sudden functional leg weakness, could be elicited as a conditioned response bound to the experience and subsequent fear of falling.

We studied the clinical features and outcome of a retrospective consecutive series of patients with drop attacks to investigate this idea further.

MATERIALS AND METHODS

We searched consecutive outpatient clinic letters for patients with 'drop attacks' from one neurologist (JS) with experience in the diagnosis of dissociative (non-epileptic) attacks, syncope, seizures and other causes of falls. All patients were referred to the Department of Clinical Neurosciences, Edinburgh, UK between 2007 and 2016 from one of three sources: an unselected primary care referral to a general neurology clinic which was randomly assigned to all general neurologists in the department; a clinic designed for the assessment of patients with functional disorders; or referred from colleagues due to a known research interest in patients with drop attacks.

Patients were included in the study by the authors (other than JS), if they met a modified version of Stevens and Matthews' definition of cryptogenic drop attacks: sudden fall to the ground, not caused by persistent leg weakness, change in posture or head position, nor accompanied by any vertiginous

symptoms. Our modification was to include patients with intermittent functional leg weakness. We included those who could not remember the fall itself or who described finding themselves suddenly on the ground but not those who had a witnessed or perceived loss of consciousness. We included patients who had drop attacks even if it was not their primary neurological complaint.

We excluded patients with prolonged loss of consciousness or responsiveness and cases when there was insufficient description of the attack itself. Dissociative (non-epileptic) seizures, including hypokinetic episodes (psychogenic pseudosyncope) and hyperkinetic episodes, were differentiated from drop attacks by the presence of reported or witnessed loss of consciousness or responsiveness with typical positive clinical features seen in those diagnoses[13]. We also excluded patients whose drop attacks were not cryptogenic, but included patients where comorbid medical diagnoses may have been contributing to the clinical picture but did not fully explain it. Drop attacks referred to in this study will refer to this definition unless otherwise specified.

We retrospectively recorded data on age, gender, duration and frequency of attacks, and attack description including place, contextual use of medication, alcohol and drugs which may have caused the drop attack, injury, comorbid diagnoses including structural pathophysiological, functional somatic, functional neurological and psychiatric disorders from the medical notes and from JS's review. Particular attention was paid to the presence of dissociative symptoms (such as depersonalisation and derealisation), situational triggers, the circumstances of the first attack and whether attacks changed over time. Comorbid symptoms and diagnoses were recorded as were radiological and cardiac investigations performed by the neurologists or other health professionals. We recorded the outcome of attacks and the development during follow-up of other conditions that, with the benefit of hindsight, might have explained the drop attacks. Follow up was based on electronic medical records in the host healthcare board, NHS Lothian, and five additional health boards in surrounding areas. A UK healthcare board is a connected set of hospitals and outpatient facilities where patients receive secondary level care. For patients from outside the host healthcare board and surrounding area, we attempted follow up via an additional, more limited, online health record system. Characteristics of patients referred to specialist or general clinics with drop attacks were compared using two-sided Chi-squared and t-testing.

RESULTS

Participants and Demographics

91 patients with drop attacks were diagnosed and seen by JS between January 2007-July 2016. Eight were excluded (drop attacks due to other causes (n=2), insufficient description of attacks (n=6)). For the remaining 83 patients, medical records were available for detailed review. Full electronic patient records documenting all hospital attendances were available for 67 patients who were referred from within NHS Lothian. Sixteen patients, referred from outside NHS Lothian underwent more limited notes review.

Of 83 patients, the majority (n= 74, 89%) were female and mean age was 44yrs old (range 12-78yrs). Almost half of the patients (n=37, 44 %) were unselected referrals to a general neurology clinic (i.e. not specifically to JS), with the others divided almost equally between the functional disorders clinic (n=20) and those referred by other neurologists (n=26).

Clinical features of attacks.

Some of the key clinical features and their frequency is shown in Table 1

Description of attack. Drop attacks, by definition, occurred suddenly, from standing or whilst walking. According to their records, the vast majority of patients (93%) could not remember the fall itself. Patients typically described finding themselves suddenly on the ground. All patients initially stated they had no warning. However, when asked specifically about symptoms of dissociation or panic 43% (n=36) of patients described a brief prodrome. This commonly consisted of depersonalisation and derealisation such as feeling “unplugged”, “floating” or a feeling of one of their legs not really belonging to them for only a second or two before the fall.

Twenty-four (29%) patients had soft tissue injuries documented from the falls. More than half the patients with soft tissue injury had recurrent facial injuries indicating that they did not put their arms out to protect themselves (n=17). Injuries were also common to the knees (n=12). Eight patients (9%) had fracture of either a finger (n=3), ribs (n=2), an elbow, toe or wrist (all n=1). Unless they were injured, subjects were typically able to get up quickly but often reported being very embarrassed and worrying about future attacks.

Frequency and duration. The mean duration of drop attacks when first seen at outpatient clinic was 56 months (range 2-388 months). There were three patterns of attacks: regular attacks occurring between ten times per day to once per month (n=34), clusters of attacks with freedom from attacks between clusters (n=6) and infrequent or solitary attacks (n=17).

History of onset of attacks. In almost a quarter of patients (n=20, 24%) the first fall was reported as different from the subsequent drop attacks and was more likely a simple trip (n=11), vasovagal syncope (n=4), or associated with feeling generally unwell or dissociation (n=5).

Triggers. 35% (n= 29) of patients noted drop attacks that were more likely to occur in certain situations or at certain times. These associations could be with places where they worried excessively about falling, such as on the stairs, in the bathroom or kitchen or only occurring outside, in the context of excessive noise or bright lights or when unaccompanied. In two cases the timing of the falls could be isolated to a short daily period (only occurring between 3-6pm in one patient and between 12-2am in another). Patients frequently expressed constant background concerns about falling with persistent and significant fear of injury and embarrassment. Seven patients with regular attacks described transient feelings of relief, or a feeling that, following an attack, they would be very unlikely to get another one for a few days, and indeed that prediction would usually be true.

Comorbidities

Comorbid defined pathophysiological diseases at baseline:

At baseline 12 patients (14%) had a potentially relevant comorbidity which may have increased their vulnerability to drop attacks, by either providing an initial or an ongoing physiological trigger for the attacks (epilepsy n=4, vertigo n=2, and one each of: asymptomatic pineal cyst with prior hydrocephalus and static neuroimaging >6years, Chiari malformation with foramen magnum decompression, basilar tip aneurysm coiling without evidence of clinical or radiological brainstem damage, left lacunar stroke which caused right sided weakness, type 1 diabetes but no evidence of hypoglyacemic events, hereditary hemorrhagic telangiectasia with pulmonary arteriovenous malformation).

Comorbid functional and/or psychological disorders:

Seventy-five patients (90%) had comorbid functional somatic disorder (n=68, 82%) or functional neurological symptom disorder (n=48, 51%) which typically overlapped. Somatic symptoms included: persistent fatigue (n=61, 73%), chronic pain (n= 33, 40%) and irritable bowel syndrome (n=12, 14%). 58% (n=48) of patients had a comorbid functional neurological symptom disorder: functional limb weakness (n=26, 31%), dissociative (non-epileptic) seizures (n=23, 28%), functional movement disorders (n=11, 13%) and other functional neurological symptoms affecting speech, vision or cognition (n=20, 24%). 23% (n=19) had episodes of dissociation without loss of consciousness, (i.e. episodes of gradual zoning out lasting several minutes with interruptibility). 74%

of patients with comorbid dissociative (non-epileptic) seizures had them before the drop attacks and in 26% they developed after the drop attacks.

Perhaps unsurprisingly, given the unpleasant and random nature of drop attacks, 43% (n= 36) of patients had a record of anxiety (n=23) or agoraphobia (n=13). Fifteen patients had depression (18%), three had bipolar affective disorder (one with comorbid schizoaffective disorder) and one patient had a diagnosis of post-traumatic stress disorder.

We analysed referral bias as an explanation for comorbidity. Patients with drop attacks referred to an unselected general neurology service (i.e. not referred specifically to JS) had similarly high levels of functional somatic and functional neurological symptom disorders to those referred to a functional disorders clinic run by JS (Supplementary Table 1).

Investigations

86% (n=71) of patients had cardiac investigations, 77% (n=64) of patients had CT or MRI brain imaging and 23% (n=19) of patients had an EEG (Supplementary Table 2). Three patients had left their general practitioners and their cardiac investigations were impossible to trace. Of the 71 patients who had documented cardiac investigations, 34 were referred from either cardiology (n=15) or after normal 24-hour tape (n=19). Others had a mixture of investigations for cardiac causes of loss of consciousness including ECG plus a mixture of 24-hour blood pressure monitoring, echocardiography, tilt table testing (n=3) and implantable loop recorder (n=1). Six patients had their typical drop attacks during cardiac monitoring (n=4 telemetry, n= 1 implantable loop recorder, n=1 pacemaker) without cardiac abnormality. Three patients (4%) had neuroimaging abnormalities (n=1 cerebrovascular disease and atrophy in a patient subsequently diagnosed with frontotemporal dementia (FTD), n=1 previous posterior fossa craniectomy for Chiari malformation, n=1 small vessel ischaemic changes thought to be non-specific by consultant neuroradiologist).

Prognosis and Treatment

88% (n=73) patients had documented follow up with a mean duration of 38 months (median 29 months, range 0-115months).

During follow up, until the end of July 2016, five patients developed a potentially relevant disease; dementia n=3 (FTD n=2, Alzheimer's n=1), ischemic heart disease n=2, prolonged QTc n=1.

Half of patients' reported that their drop attacks (n=42, 51%) had either resolved (n=23, no attacks for at least 6 months) or reduced in frequency by the end of follow up. Almost a quarter had a static

rate of attacks (n=18, 22%), 5% (n=4) were worse and 11% (n=9) had evolved into dissociative (non-epileptic) seizures.

Only naturalistic data was available on treatment. Ten patients appeared to be treated effectively for their drop attacks, on the basis of episodes which resolved with distraction techniques and treatment based on a formulation of their symptoms as a conditioned response (see below).

Patients without functional comorbidity

Of the eight people without any functional disorder three were male, four had defined pathophysiological comorbidity (n=1 epilepsy and n=2 FTD, n=1 Hereditary hemorrhagic telangiectasisa with pulmonary arteriovenous malformation), and one man had events in the context of alcohol and nicotine excess. Four patients had resolution of drop attacks on follow up.

DISCUSSION

There are many clearly established causes of sudden falls with preserved consciousness including simple trips, knee instability, presyncope (and brief vasovagal syncope), arrhythmia and carotid sinus hypersensitivity, vertigo, cataplexy and colloid cyst of the third ventricle. The clinical features of alternate causes of drop attacks are addressed in other articles and summarized in Table 2 [14–35].

The consideration that cryptogenic drop attacks in the majority of patients may be due to a pathophysiological disorder causing brief loss of consciousness is warranted [36,37]. Syncope can present without prodrome or with amnesia for the event. Although any type of syncope can occur without prodrome, arrhythmic cardiac syncope and cardioinhibitory reflex syncope are perhaps most likely to be associated with a rapid onset of unconsciousness and are the main pathophysiological differential diagnosis for cryptogenic drop attacks[14,38]. In patients with syncope, amnesia for the loss of consciousness can be present, occurring in 25- 28% of predominantly older patients (>60yrs) [39]. Additionally, some patients with provoked syncope may describe dissociative symptoms including an ‘out of body’ experience (9%). However, we propose that the very brief duration of cryptogenic drop attacks is the key distinguishing feature. Patients with cryptogenic drop attacks are alert until the start of the fall and immediately again on hitting the ground, meaning any loss of consciousness or awareness in drop attacks must be less only a second or two. In any cardiac induced loss of consciousness it usually takes seconds to lose consciousness and also seconds to regain it[40,41]. We suggest that the very brief loss of awareness in cryptogenic drop attacks is too short to be due to cerebral hypoperfusion, whilst accepting that it could be in the realms of a complicated pre-syncopal episode.

Functional neurological disorders are defined as those in which patients have motor or sensory symptoms which can be clearly identified as internally inconsistent or incongruous with disease on the basis of positive signs such as Hoover's sign or tremor entrainment test[42]. These highlight the fact that functional motor symptoms are normally maintained by excessive attention paid to the limb which in turn interferes with normal voluntary movement [43–45]. The symptoms are experienced as involuntary and may or may not be associated with psychological comorbidity or prior psychosocial stress.

Research on functional/psychogenic causes of brief loss of consciousness such as psychogenic pseudosyncope and dissociative (non-epileptic) seizures highlight evidence that many patients experience dissociative responses as a conditioned response to autonomic arousal that occurs suddenly and briefly prior to their events [36,37,46]. We have found some features in our case series to support a hypothesis that cryptogenic drop attacks may, in many cases, be a functional rather than defined pathophysiological disorder of the nervous system, on a spectrum of transient dissociation which includes psychogenic pseudosyncope and dissociative (non-epileptic) seizures (Table 2, Table 3, Figure 1). Features of cryptogenic drop attacks supporting this hypothesis include: 1) cryptogenic drop attacks are inconsistent with most types of falls in adults in which the fall is usually recalled [47], 2) a period of loss of awareness too short to represent syncope and only compatible with dissociation, 3) Brief dissociative symptoms just before or after the event in 43%, 4) the co-occurrence of clear dissociative (non-epileptic) seizures either before or after drop attack (28%) or functional limb weakness (31%); 5) Attack clustering and situational attacks in 35%; 6) high comorbidity of fatigue, pain and other symptoms seen in functional neurological disorders such as dissociative (non-epileptic) seizures[48], 7) Successful treatment in some patients based on distraction techniques during the prodrome (12%).

Specifically, we propose that in some individuals with cryptogenic drop attacks, the disorder is best considered a form of brief dissociative attack which then becomes established as a patterned and conditioned response generated by a fear of falling, either with or without situational triggers (Table 2 and Figure 1). We hypothesise that patients with a biological or biopsychosocial vulnerability to drop attacks typically have a triggering event such a simple fall, trip, syncope or episode of dissociation. Excessive worry about further falls, particular in inopportune settings, leads to a cognitive representation of the attacks which drives abnormal self-directed attention and rumination about the possibility of falling. The idea of a cognitive representation can be conceived both as a consciously processed illness model and in terms of Bayesian predictive coding, an idea that has been explored in depth in more recent models of dissociative (non-epileptic) attacks[45],[49],[46]. Our hypothesis is that drop attacks are at one end of a spectrum of dissociative

attacks that includes brief dissociative episodes with staring and "zoning out", more prolonged motionless unresponsiveness (psychogenic pseudosyncope) and episodes with hyperkinetic movements (dissociative seizures) (Table 3).

We propose that falls occur due to brief loss of awareness secondary to episodes of dissociation. We hypothesise that this becomes a classically conditioned response and patients' falls become associated, in some cases, with situational triggers and in some cases reinforced by a feeling of relief after the fall is over. Some patients' drop attacks may develop through operant conditioning with conscious avoidance of stimuli associated with the drop attacks. This worry about falling can generalize to anxiety or agoraphobia through the process of 'chaining' where more background stimuli are associated with the drop attack. Neurological disease in general is a significant risk factor for functional disorder, being a potent cause of distortion of sensori-motor experience, cognition and anxiety[50,51]. We propose that some of the neurological comorbidities described in our series have increased the risk of functional disorder rather than offering an alternate pathophysiological explanation in our patients.

Table Two: Features of cryptogenic drop attacks in keeping with a functional disorder

	N	%	Functional	Syncope	Vertigo	Mechanical	Cryptogenic Organic
1. Inability of patients to recall falling	77	93	✓	✓			✓
2. Brief dissociative or panic symptoms just prior to or after attack	36	43	✓✓	✓	✓	✓	✓
3. Dissociative (non-epileptic) seizures merging to drop attacks	23	28	✓✓ ✓	✓	✓	✓	✓
4. First attack recalled as mechanical or simple faint	20	24	✓			✓	
5. Long duration of intermittent falls without worsening or development of other symptoms	79	95	✓✓	✓	✓	✓	✓
6. Co-occurrence with persistent fatigue	61	73	✓✓	✓	✓	✓	✓
7. Co-occurrence with functional weakness	26	31	✓✓				

8. Attack clustering and situational attacks in some patients (in agoraphobic situations and on stairs).	29	35	✓				
9. Feelings of 'relief' once the drop attack had occurred, akin to relief seen after some patients with dissociative (non-epileptic) seizures.	7	8	✓				
10. Successful treatment of attacks using a model of distraction developed for the treatment of dissociative (non-epileptic) seizures.	10	12	✓✓	✓	✓	✓	✓
11. Resolution of attacks in patients	23	28	✓	✓	✓	✓	✓
12. Female preponderance	74	89	✓				✓✓
✓=possible ✓✓=likely ✓✓✓= very likely							

Table Three: The proposed spectrum of functional (dissociative) attacks or seizures

	Cryptogenic Drop Attacks	**Dissociative hypokinetic attacks (psychogenic pseudosyncope)**	**Dissociative (non-epileptic) hyperkinetic attacks**	**Dissociative 'absence' attack**
Gender distribution	Predominantly female			
Peak age of onset	Mid 40s	Late 20s[37,40]		
Usually presents to	Cardiology, Neurology	Cardiology	Neurology	Neurology/Psychiatry
Usual Clinical setting and Prodrome	Patients describe finding themselves *suddenly* on the ground without apparent loss of consciousness	Long duration episodes of 'fall down lie still' (i.e.> two minutes), typically with eyes closed [40]	Episodes of generalized or focal limb shaking, typically with eyes closed and other positive features[15]	Episodes of being relatively unresponsive or staring, with or without experience of unawareness or dissociation
Prodrome and proposed Mechanism	Prodromal dissociative symptoms and arousal in many patients Fearful anticipation increases likelihood of events and attacks may cluster situationally in some			
Trigger	All may apparently be triggered by initial fall, vasovagal syncope or panic attacks which are different from subsequent drop attacks[16,51]			

In our series, recurrent facial soft tissue injuries were more common than the bruised knees from which drop attacks gain their French name 'la maladie des genoux bleus'. Injuries have long been associated with dissociative seizures occurring in 30-40% of case series [52,53]. Drop attacks are not a benign condition either and many of our patients gave up work or had substantial social and occupational impairment. Comorbid functional neurological disorders have not been previously described in patients with cryptogenic drop attacks including in Steven's and Matthew's paper. Given that one third of our patients were unselected referrals to a general neurology service this suggests a genuine association. The absence of comorbid functional disorders in reported literature may be due to lack of expertise in identifying functional disorders by non-neurologists seeing these patients or lack of confidence in making a diagnosis by neurologists. Similar underreporting of psychogenic pseudosyncope is seen in large cohort studies of syncope [54]. The lack of any in-depth studies of younger patients with cryptogenic drop attacks since 1973 may also play a role.

Even if the majority of patients with cryptogenic drop attacks can be thought of as attacks within the spectrum a functional neurological disorder, there are patients in our study in whom the aetiology of their drop attacks remains cryptogenic. Men were entirely absent from the Stevens and Matthews

series. They represented 11% of our cohort and are under-represented even in older drop attack populations [5]. In our study the comorbid defined pathophysiological risk factors at baseline or follow up was over three times that in men than women (55% vs. 15%), raising the possibility that mechanisms of drop attacks in men may have some differences to women. The absence of a comorbid functional disorder should also signal a warning flag for underlying pathophysiological disorders given the high proportion (50%) in our eight patients.

We acknowledge significant limitations in this data which we present as hypothesis generating. This was a retrospective study of consecutive cases seen in routine clinical care and clinical variables were chosen from this material. There are many variables, including adverse childhood experience, that we did not collect.

. Importantly, not all patients were subject to neuroimaging or cardiac investigation such as 24 hour ECG or EEG. More detailed investigations such as tilt table testing and specific measures of balance were not applied[55]. It remains the case, that some of these patients may have alternative diagnoses, particularly syncope. A comparison group with a paroxysmal condition such as neurocardiogenic syncope would have helped to examine the specificity of some of the proposed associations. JS's clinical interest in functional disorders may have biased frequency of comorbidity, although similar frequencies were seen in unselected referrals to a general neurology clinic. Because our patients were seen clinically rather than in a research study, physiological and structural measures of falls, such as dynamic posturography, used in other studies were not routinely used in our patients. Sixteen of the 83 patients were referred from outside of the health board which may have led to an underestimate of follow up diagnoses. Data on treatment modalities and outcomes was insufficient for more in-depth analysis, so was only considered anecdotally.

Additionally, ideas solidified through the process of seeing patients and some of the questions asked of the 83rd patient were not the same as those asked of the first. We have endeavored to make the process as uniform as possible by including only those patients who were seen by the author JS and excluding patients where the description of the attack could not be judged by the rest of the research team.

We present our data to support a hypothesis weaved together from the stories of the patients seen in routine clinical practice. We suggest considering cryptogenic drop attacks in some patients as a subtype of functional neurological disorder. We propose that brief episodes of dissociation, often precipitated by a mechanical fall or faint, perpetuated by fear of falling can become habitual via a conditioned behavioral response. This could lead to specific treatment techniques involving

education, distraction techniques, overcoming avoidance and graded exposure to the conditioned stimuli.

A prospective multi-centre controlled study of drop attacks in younger individuals that avoids the limitation of this case series including tilt-table testing and, where possible, timing of loss of awareness as well as multiple psychological, physiological and structural measures is warranted to examine the question of whether cryptogenic drop attacks overlap with functional neurological symptom disorders or are better thought of, and treated as, functional drop attacks.

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Note to reviewers who may have seen the abstract for this study (not to be published)

Data on investigations have been updated since an earlier version of this study

Table One: Differential Diagnoses of Drop Attacks

	Cryptogenic Drop Attacks	Cardiac Syncope	Carotid sinus hypersensitivity	Vestibular drop attacks	Posterior circulation TIA	Chiari malformations	Colloid cyst of the third ventricle	Epileptic drop attacks (including brief focal, tonic or atonic seizures)	Structural cardiac diseases (e.g. atrial myxoma)
Usual Demographics	**Women, mid 40s**	Rare in children Often occurs >60s[38]	M:F ratio 4:1 >50yrs[17]	F:M ratio 1-3:1[18] 40-60yrs	M>F; >65yrs	F:M ratio 1.3-1.7:1 [19] 30-35yrs	M:F ratio 1.5:1,[20] 30-40yrs	M:F ratio variable Childhood onset[4,21]	F>M 60s[22,23]
Frequency	**Unclear Estimated at 3.5-9% of all falls referrals**[1,35]	15% of patients with syncope[24]	10% of population >65yrs old 22-68% of older patients with syncope and falls[17],[5]	190 per 100,000 of the population)[25]	20% of ischemic events[26]	Radiological prevalence 0.77% 3% of patients present with drop attacks[3]	0.5-2% of intracerebral tumours[20,27]	2% of patients admitted to national VEEG unit[4]	Estimated at between 0.001-0.28% of the population from autopsy studies[32]
Usual Clinical setting and Prodrome	**Patients describe finding themselves suddenly on the ground** **Dissociative symptoms pre or post attack**	Can occur in any posture no prodrome or brief prodrome without autonomic symptoms (no nausea or sweating)	Occurs on head turning, shaving, or when wearing a tight collar[38] Syncope occurs but	Patients describe a feeling of being pushed to the ground OR A feeling of the surroundings suddenly moving or	Associated with limb weakness, ataxia and oculomotor palsy[33],[26] Usually lasts >5minutes[35]	Suboccipital headache, numbness exacerbated by Valsalva maneuvers Weakness, numbness, loss of temperature sensation	Symptoms of raised intracranial pressure[27] e.g. headache with nausea and vomiting[20] Altered GCS	Occur almost exclusively in patients with other neurological abnormalities Often linked to severe epilepsies in childhood	Most commonly presents with cardioembolic stroke or symptoms of congestive heart failure[23] Angina, pyrexia and palpitations may co-occur[32]

	Overlap with dissociative (non-epileptic) attacks **Fearful anticipation increases likelihood of events and attacks cluster situationally**	Pallor Rapid recovery after loss of consciousness	many patients (20-70%) have amnesia for the syncope and present with falls only [17]	tilting causing the fall[34] Patients often fall in the same direction during each fall		90% have abnormal signs on examination including hyperreflexia and 'cape' sensory loss[3,19]	Can be found incidentally	In parasagittal seizure foci somatosensory auras and generalized seizures usually occur[28].	
Trigger	**Often triggered by fall or faint which is different from ongoing drop attacks**	More common during exercise	Occurs on head turning, shaving, or when wearing a tight collar	None	None	Unclear, controversy about link with orthostatic intolerance[29]	None stated	Usual triggers for seizures e.g. withdrawal of anticonvulsants	None
Long term outcome	**Can resolve spontaneously or be present for years without escalation.** **Patients may develop dissociative attacks.**	Depends on aetiology. Causes are: Structural heart disease, Brady/tachy-arrhytmias or inherited channelopathies	Over 50% of patients suffer serious injury due to fall High rate of recurrence	Occurs frequently during the first year of symptoms then spontaneously remits[2]	At increased risk of MI, IHD and stroke	Will usually develop other neurological symptoms	Symptomatic cysts can lead to raised ICP and death if untreated. >80% of patients treated with	Falls can lead to injury Seizure frequency often high	Life-threatening complications can occur if symptomatic tumors are left untreated Asymptomatic tumors often have good long term prognosis

							microsurgery have a good long term outcome[30],[20]		
Treatment	**No good evidence** **We suggest trials of: Distraction techniques, CBT, physiotherapy**	Structural disease and inherited channelopathies: implantable defibrillator Brady/tachy-arrhytmias: Pacemaker	Pacemaker	Conservative management, Intratympanic gentamycin injection[18]	Thrombolysis, antiplatelet agents and management of cardiovascular risk factors.	May require operative management if clinically deteriorating	Symptomatic or large cysts require operation.	Anticonvulsants[21],[31]	Complete surgical excision can be carried out in most cases[22]

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Paper Five: Stone J[1], **Hoeritzauer I[1]**, Tesolin L[2], Carson A[1,3] Functional Movement Disorders of the Face: A Historical Review and Case Series. J Neurol Sci. 2018 Sep 26;395:35-40.

Functional Movement Disorders of the Face: A Historical Review and Case Series

Abstract

Functional facial dystonia or spasm has, in recent years, been recognised as a relatively common form of functional movement disorder. We describe historical 'forgotten' neurological literature indicating that this was a well described phenomenon by the early part of the 20th century but subsequently faded from awareness. We add data from our own series of 41 patients with functional facial dystonia to explore the clinical features and associated comorbidities of patients with this movement disorder.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

INTRODUCTION

The last decade has seen increasing awareness of the fact that functional movement disorder may affect the muscles of the face. An initial report on four patients by Tan and Jankovic in 2001[1], was followed by scattered reports[2][3] prior to a seminal case series of 63 patients by Fasano *et al* in 2012[4][5]. Subsequent small series[6] have all added to the characterisation of functional facial movement disorders which were defined by Fasano and Tinazzi as a dystonia with fixed unilateral facial contraction, usually involving the lower lip and often with ipsilateral orbicularis oculis and jaw involvement. They are often of maximal severity at onset and display inconsistencies on clinical examination, such as resolution with distraction and changes in side and pattern during or between examination or spontaneous remissions[5].

The history of the field has not been one of linear accumulating knowledge. 'Hysteria' was a core part of neurological textbooks in the 19th century but it gradually lost its popularity as a subject of neurological study over the course of the 20th century [7][8]. Consequently, a considerable number of useful but older clinical descriptions have been forgotten. Much of our apparently new knowledge in this field revisits clinical experience that had been documented in the past.

Fasano *et al* noted that patients diagnosed with atypical facial movement disorders in studies going back to 1986 also probably fulfilled the diagnostic criteria for functional movement disorders[4]. From our own reading of the older literature, however, it was clear that this clinical entity had already been recognised much further back in the 19th century.

In this article, we re-examine the historical literature on functional facial movement disorders and compare it, and recent work, with a new case series of 41 patients with functional facial movement disorders to extend the historical and clinical perspective of this clinical presentation.

METHODS

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

For the historical review, we carried out a systematic search of a collection of neurological textbooks and books on hysteria and allied conditions published prior to 1920. All book titles are available for public download from www.archive.org. Each book was searched for the terms 'facial', 'blepharospasm' and 'ocular'. In this section, we sometimes use the term hysterical since it was the term used in these publications. In addition, we searched for descriptions of patients with atypical facial dystonia or movement disorder from 1960 until 2017 who had features in keeping a functional facial movement disorder. For both the historical literature and recent search we explored references when relevant. Our case series is derived from 41 patients with functional facial movement disorders seen consecutively in general neurology and specialist 'functional' clinics in the Department of Clinical Neurosciences, Edinburgh by one of the authors (JS) over a period of from 2008-2013.

REVIEW OF LITERATURE 1880s to 1960s

We cannot find an earlier reference than 1887 when Charcot described unilateral hysterical facial spasm in the well-known patient 'Le Log' as follows[9]: *"...left labial commissure is raised and mouth is partly open. At first thought to be paralysis of right inferior facial...on further examination it is due to spasm of the muscles on the left side of the face*".

Gowers at around the same time[10] also described hysteria affecting the face:

"*In hysteria there is either tonic contracture, especially in the orbicularis, or attacks of quivering movement, which do not resemble true facial spasm.... The effect of the preponderant contraction in the orbicularis and zygomatic muscles is a curiously mixed emotional aspect, a sort of whimpering smile* ". Gowers, whose chapter on hysteria in that book has rarely been surpassed, also commented that these spasms were " *usually lessened by rest, physical and mental... always increased by emotion, and by movement of the face, whether in speaking or chewing and ...by light and by cold."* He noted that *"The influence of light is intelligible, since the orbicularis palpebrarum is almost always involved, and a strong light produces reflex contraction in this muscle under normal circumstances".* Gowers also refer to the presence of 'wrong way' tongue deviation, in which the

tongue deviates to the side of facial spasm/apparent weakness, and is the opposite of what would be expected were the patient to have a pontomedullary lesion.

Babinski and Froment summarise earlier descriptions under the term 'glosso-labial hemispasm', under which it can often be found in subsequent textbooks[11]: *"In glosso-labial hemispasm, described by Charcot, Brissaud and P. Marie, the spasm, as its name indicates, may be limited to the tongue and lips but sometimes affects simultaneously the orbicularis palpebrarum, platysma and neck muscles. The hook-like appearance of the tongue and the intermittent spasms of the contracted muscles give it an almost pathognomonic appearance*." They also reinforce the potential for confusion that could arise regarding whether there was paralysis or not "*when there is facial asymmetry it will be found to be due not to muscular hypotonus but to spasm.*"

Dejerine commented *'as far as the face is concerned one much more frequently observes a glossolabial spasm than a facial paralysis properly so called*[12]*'*. Charcot and Dercum were not convinced that facial muscular paralysis could occur as a hysterical symptom stating *'in the hysteric the deviation of the mouth and tongue, and facial paralysis, are wanting.'*[13] Preston in 1897,considered facial spasm to be 'not rare' but hysterical facial weakness *'very infrequent'*[14].

Wood, in JAMA in 1898 [15]writing about neuro-ophthalmological aspects of hysteria commented, "*a very common and in my opinion characteristic eye-sign in hysteria is spasm of orbicularis, the so-called blepharospasm…When this is unilateral it is almost invariably hysteric.*" Pershing discusses this diagnosis in 1901[16] and Oppenheim in 1900[17]. Janet, wrote that he had seen 'many cases of hysterical facial paralysis' that were 'typical' [18] but he may have been describing spasm since he doesn't refer specifically to weakness. In the 1920 edition of *Diagnosis of Nervous Diseases* by Purves-Stewart there are three photographs of patients displaying functional unilateral blepharospasm (Fig.1)[19].

Figure 1: Functional facial movement disorder – historical cases. A-D[22]: (A) Bilateral ptosis with frontalis overactivity, cured within several weeks. (B) Right ptosis requiring frontalis overactivity to see. Left orbicularis overactivity with amblyopia, resolved with a one-hour treatment (right hand image). (C) Right orbicularis overactivity and left frontalis overactivity with ptosis and amblyopia of five months duration, and after a half-hour treatment (left hand image). (D) Bilateral ptosis at rest with right facial spasm and apparent left facial weakness; left eyelid raised to see; attempt to open eyes resulting in overactivity of left frontalis and spasm of the right side of the face. (E) Functional facial spasm and torticollis[48]. (F & G): Left 'hemiglossolabial spasm' associated with ipsilateral functional limb weakness and contracture[19].

Also at that time Arthur Hurst, a British physician known best for his films of patients with shell shock[20][21], described facial weakness and ptosis which resolved rapidly with suggestion and persuasion[22]. Hurst also provides some of the best images of patients with 'hysterical' facial spasm (Fig. 1).

There were sporadic mentions of 'hysterical' facial spasm in the 1950s[23] and 1960s[24] but then the problem largely disappeared from view.

From the historical review, functional facial movement disorders were positively described as unilateral facial spasm, most commonly presenting with unilateral orbicularis, lower face or platysma contraction. They differed from other types of dystonia by the sustained nature of their contraction. There was general agreement that functional facial weakness, as opposed to muscle overactivity giving the appearance of overactivity, was very rare.

PREVIOUS PUBLISHED REPORTS OF ATYPICAL FACIAL MOVEMENT LIKELY TO REPRESENT FUNCTIONAL FACIAL MOVEMENT DISORDERS

With hindsight, and as previously described by Fasano *et al*.[4], some case reports and series of patients with facial dystonia from the 1980s to the early 2000s may be better classified as a functional movement disorder in terms of variability, associated features and response to treatment[25–27][28][29][30]. Four such cases from the paper by Thompson *et al*. [25] are shown in Fig.2 along with two other subsequent reported cases mentioned by Fasano *et al*. Schrag[31] *et al* reported eight cases who developed cranial dystonia within hours to months following a dental procedure. Two of these eight cases had fixed jaw deviating dystonia, and four had painful dysaesthesia which the authors suggested was similar to the limb causalgia–dystonia syndrome, now described as complex regional pain syndrome. The authors discussed how the fixed nature of the jaw deviation, lack of sensory *geste antagoniste*, presence of pain and long duration of symptoms without progression to a segmental or *Meige* syndrome supported the unusual nature of the movement disorder and left open the possibility of a functional/psychogenic movement disorder in these four cases.

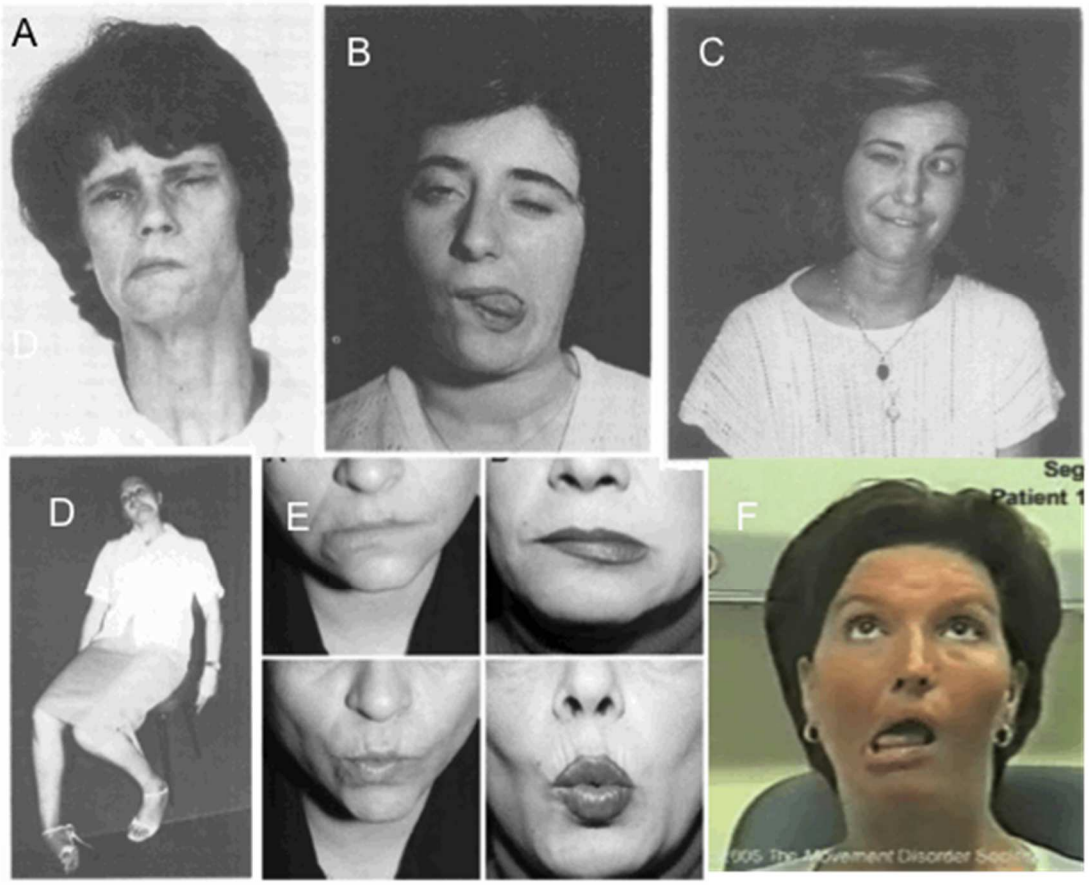

Figure 2: Published cases of facial dystonia that in hindsight fit better with a diagnosis of functional movement disorder. Cases A-D[25] reproduced by permission of BMJ publishing group Ltd. (A) Painful jaw deviation following dental extraction with normal R2 blink response latency. (B) Intermittent left face/tongue/jaw spasm. (C) Episodes of complex face and eye spasm with convergence spams of the left eye. An original diagnosis of multiple sclerosis was made, but MRI brain scan and CSF parameters were normal. (D) Episodes lasting 2-5 minutes as shown associated with hyperventilation and relieved by intravenous calcium gluconate despite normal calcium levels during the attacks. (E) Two of the four cases of acute lip deviation reported by Kleopa et al.[26] associated with ipsilateral limb weakness. Reproduced by permission of John Wiley and Sons. (F): One of two similar cases to Kleopa reported by Wohlgemuth et al.[27]. Reproduced by permission of John Wiley and Sons.

At the time of Thompson *et al*.'s paper there remained a common view that 'psychogenic' movement disorder could only be diagnosed in patients with recent life events or with concurrent psychiatric abnormalities. In addition, a diagnosis of hysteria was still seen as pejorative and therefore often avoided in cases where the doctor believed the patient had a genuine problem. In a climate in which some focal dystonias had only recently been 'rescued' from psychodynamic interpretations such as torticollis being a 'turning away from responsibility' it is understandable that

there was a desire to avoid the diagnosis of "hysteria", although David Marsden, who led the work on focal dystonia was perspicacious on hysteria and made the diagnosis often[8,32]. The problems with diagnosis at that time can be seen, for example, in the four patients said to have psychogenic blepharospasm in the paper by Cavenar *et al* in 1978[33]. based on profound psychopathology. All of these patients had features in keeping with organic blepharospasm with bilateral involvement and psychiatric comorbidity. The changing view of functional movement disorders now encompasses movement disorders that are genuine, variable, utilise voluntary muscle pathways and have diagnostic features that indicate the role that attentional focus plays in the movements. A diagnosis of functional movement disorder no longer requires psychological causation in the latest revision of DSM-5, the American Psychiatric Association's psychiatric classification[34].

EMERGENCE OF REPORTS OF FUNCTIONAL (PSYCHOGENIC) FACIAL MOVEMENT DISORDERS

Keane, in 1986, noted the presence of 'wrong way tongue deviation' as a sign of functional disorder and commented on the presence of ptosis in some patients[35]. Case reports of functional or psychogenic pseudoptosis (in fact related to orbicularis oculi contraction rather than eyelid drooping) appeared from 1997 onwards [36–39]. Psychogenic hemifacial spasm, involving the lower face, was reported by Tan & Jankovic in 2001 [n=4][1], with subsequent case series by Tarsy *et* al. [n=5][2], and a report by Stone [n=1[3]] between 2001-2010. Patients with psychogenic blepharospasm were also reported in case series of other psychogenic movement disorders without detailed description of how the positive diagnosis had been made[40,41]. In 2011 Schwingenschuh and colleagues reported that the blink recovery cycle reflex was normal in patients with "presumed psychogenic" blepharospasm (n=9) but abnormal in essential blepharospasm [42]. More recently Ganos *et al* describe psychogenic paroxysmal movement disorders affecting the face and head in six and seven patients respectively[43]. The case reports of Gozke *et al* [44] and illustrated case series of four patients with tonic lip deviation by Colosimo *et al* highlight the growing awareness of functional facial movement disorders [45].

NEW CASE SERIES IN CONTEXT

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Data from our new case series, the second largest, are described in table one and compared to the other large series of patients with functional facial movement disorder described by Fasano *et al*[4].

The presence of 41 cases collected over a 5-year period indicates a movement disorder that must be relatively common relative to many other disorders. The neurologist seeing these patients (JS) does have an interest in functional disorders but nevertheless many of these patients were seen in a general neurological setting and the population catchment of the centre is only 1 million persons.

Patients in our case series were predominantly female (81%) and middle aged (mean age 44yrs). The most common signs were downward lip pulling and orbicularis oculis spasm (both 90%). Platysmal overactivity frequently accompanied this (85%). It was usually unilateral (90%), without right or left preponderance, and 71% episodic. Tongue deviation, exclusively *towards* the side of facial spasm, was not seen commonly (12%) and jaw deviation was much less frequently seen than was described by Fasano *et al* (22% vs. 84%).

Not recorded by Fasano *et al*[4] but seen in our series, were facial spasms triggered by examination of eye movements or by asking the patients to sustain muscular contraction of the face (51%). This is a similar mechanism to the triggering of functional convergence spasm by sustained gaze in Kaski et al's study of patients with functional eye movement disorders and likely relates to the effect of sustained attention in functional facial movement disorders[6]. From a clinical perspective we found this a good way of inducing the symptom in those patients who attended clinic with a history of episodic spasm but without the movement disorder at the time of assessment.

In 78% patients, there was evidence of functional limb weakness. This was mostly in the ipsilateral limb (91% of the time when present. Our series is also notable for a high frequency of other comorbid functional neurological disorders not reported by Fasano *et al* including convergence spasm of eye abduction (22%), dissociative (non-epileptic seizures) (32%) and functional dysphonia (12%). Other physical comorbidities including persistent fatigue (83%) and migraine (51%) were also common, in keeping with findings of multiple comorbidity in other functional movement disorder.

Migraine triggered functional facial movement disorders in 17% and 7% of patients reported premonitory symptoms that were abolished by paroxysmal movements. Such premonitory symptoms also occur in 'organic' forms of oromandibular dystonia and are certainly not diagnostic[46]. The phenomenology here was similar to patients with non-epileptic attacks who commonly experience an unpleasant aura that is relieved by the attack (even though the attack itself is also unwelcome) [47]. In the context of a functional facial movement disorder this finding could be used in treatment strategies during cognitive behavioural therapy.

Conclusion

Functional facial dystonia or spasm has recently been recognised as a relatively common form of functional (psychogenic) movement disorder with clearly identifiable clinical features. We have highlighted historical and 'forgotten' neurological literature dating back to 1887 indicating that it was a well described phenomenon at that time, although awareness of it slipped from general neurological awareness in the middle of the 20th century. With hindsight, many published cases of facial dystonia from the 1980s onwards fit best with this entity. Our own case series of 41 patients from one regional centre highlights that this must be a relatively common clinical problem and highlights some new data, especially in relation to triggering manoeuvres during examination and comorbidities with other functional disorders.

Documentation of author roles

J Stone conceived of the project, collected the patient data, started and edited the manuscript. I Hoeritzauer and L Tesolin wrote and edited the manuscript. A Carson organised, critiqued and reviewed the manuscript.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Table 1 Clinical features in a new series of 41 patients with functional facial movement disorder. Compared to other large series of Fasano *et al.* [4]

	This Series (n=41)	Fasano *et al.* (n=61)
Mean Age (range) / Sex	44(19-75), 81% F	44 (19-66), 92% F
Median Duration (range)	12 months (0-30)	6.7 years (0-30)
Side (R:L:Both)	40% R; 50% L; 10% B	31% R; 39% L; 29% B*
Episodic vs Fixed	93% vs 7%	73% vs 27%*
Location		
Eye	90%	51%
Mouth	90%	84%
(Down vs up)	(90% vs 10%)	(63% vs 26%)
Unilateral Platysma Contraction/ Jaw Deviation	85%	61%
Tongue deviation	12%	Not recorded
	17%	84%
Functional Movement Disorder		
Weakness	78%	18%
Ipsilateral limb	71%	Not recorded
Contralateral limb	7%	Not recorded
Limb Dystonia	22%	Arm (29%), Leg (16%), Neck (16%)
Movement triggered by eye movement or sustained facial muscle contraction	51%	Not recorded
Other Functional Symptoms		
Migraine	22%	26%
Fatigue	12%	18%
Convergence Spasm	22%	Not recorded
Dysphonia	12%	Not recorded
Non-epileptic attacks	32%	Not recorded

Triggering and premonitory symptoms	17% Headache, 7% premonitory dissociation	Not recorded

* subset of 51 patients with lip involvement

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Title

Complex, but not regional: what can CRPS and functional neurological disorders learn from each other?

Summary

There have been many articles highlighting differences and similarities between complex regional pain syndrome and functional neurological disorders but until now the discussions have often been adversarial with an unhelpful focus on malingering and a view of FND as "all in the mind". However, understanding of the nature, frequency and treatment of FND has changed dramatically in the last 10-15 years. They are no longer assumed just to be a physical "conversion" of a psychological conflict or trauma but are understood as a complex interplay between peripheral stimulus, expectation, learning and attention mediated through a Bayesian framework, with predisposing, triggering and perpetuation inputs which may be biological, psychological or social. Building on this new 'whole brain' perspective of FND we seek to reframe the debate about psychological versus physical triggers or sequalae in complex regional pain syndrome (CRPS), and to recognise how research into peripheral and central nervous system abnormalities and treatment in patients with CRPS may inform future mechanistic understanding of FND. Conversely, we review advances in FND, especially treatment, which could have implications for improving understanding and management of CRPS.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Introduction

Complex regional pain syndrome (CRPS) is a disabling chronic condition following physical injury to a limb, that is characterized by local inflammatory and autonomic dysregulation combined with trophic and motor dysfunction of the affected body part[1]. Although its defining features (sensory, autonomic, motor and trophic) have been extensively studied and incorporated into validated diagnostic criteria ("Budapest Criteria"[2,3]), their pathophysiological nature and the role of the incipient event remain a matter of debate and research[1].

In the debate surrounding CRPS one conceptual schism stands out as particularly polarizing and counterproductive: the role of psychological processes[4,5]. This debate has typically been characterised over the years as a battle between those who see CRPS as a genuine medical disorder, and those who seek to define it as a 'non-organic' or 'psychogenic' disorder. Within the umbrella of 'non-organic' there has often been little distinction between patients with a genuinely experienced functional neurological disorder (FND; also called psychogenic or conversion disorder) and those patients wilfully exaggerating symptoms for medical care or financial gain[6,7]. Voluntary feigning of CRPS signs and symptoms is sometimes found in rare cases of malingering or factitious disorder[8–10] and must not be equated with "functional" or "psychogenic" disorders.

FND describes the presence of disabling and/or distressing motor and sensory symptoms which can be identified by the presence of positive evidence of internal inconsistency such as Hoover's sign or tremor entrainment sign, or other evidence of incompatibility with a structural disease process (i.e. incongruence). Such positive motor and sensory signs have been consistently identified as also characterising the motor and sensory features of CRPS. For example, there is no clinical difference between the fixed dystonia leading to clenched fist or plantarflexed/inverted ankle seen in CRPS and that seen in FND without pain[11]. Tremor[12], limb weakness[13] and sensory disturbance[14] has also been identified as having the same features in CRPS as in FND (Table One, Figure One). Importantly, the need for antecedent psychological stressors has been removed from the diagnostic criteria in DSM-IV for FND in recognition that, like CRPS, many patients don't have identifiable stressors or psychiatric comorbidity. Concurrently, there is now a large literature on changes in brain function in patients with FND, including differences to feigning, which is changing previous narrow purely 'psychogenic' thinking about the disorder [15](Hallet et al., 2016).

However, in the face of multiple indicators of central and peripheral changes in CRPS in contrast to a dualistic, anachronistic and traditionally poorly articulated idea of functional disorders as exclusively the domain of psychological disturbance, or worse still, malingering, it is perhaps not surprising that polarisation has persisted[5,16]. In much of the literature it is easy to detect, and understand, a defensive tone in which advocates for patients with CRPS defend the integrity of their patients against those who would 'doubt' them or accuse them of having a stigmatised psychiatric disorder.

In a review from 2000, Ronald P. Pawl concludes that "[t]here is no convincing evidence that a primary organic dysfunction of the nervous system, in particular the autonomic nervous system, exists in [CRPS]" [17]. Diametrically opposed, Hill and colleagues recently summarized that "there is no indication that psychological factors cause the onset of pain, autonomic dysfunction, and movement disorders

in CRPS patients"[16]. The dualistic nosological line of separation between CRPS and functional neurologic disorders (FND) is drawn with such unanimous certainty that it extends well into the newest international diagnostic criteria, that see FND as a differential diagnosis which strictly precludes CRPS[2,18]. Lastly, this polarized view is perhaps best exemplified in the recent UK guidelines which was authored without input from either neurologists or psychiatrists: "a combination of elements including inflammation, dysfunction within sympathetic and somatosensory nervous system, and *cortical (not psychological)* factors are thought to contribute to the generation and perpetuation of symptoms"[19](emphasis added). With a recently reinvigorated interest in functional disorders of the nervous system, neurologists have been reasserting the conceptual proximity and physiological overlap of FND and CRPS[20,21] but these have stopped short of challenging the dualistic thinking that has dogged both disorders.

Most current authors on CRPS tend to acknowledge a limited (secondary) role of psychological factors, without considering an alternative possibility – that the conventional divide between 'organic' and 'non-organic' disorders is no longer tenable in the face of what we know about the brain and body. Discarding this division allows for a new possibility. That it is possible to have a disorder of nervous system functioning which presents with physical symptoms and which can exist independently of psychiatric comorbidity but in which cognitive and behavioural factors are still relevant.

This review will re-examine the clinical overlap and common pathology of CRPS and FND and will propose that the debate moves in this more productive middle ground. Providing first a brief overview of the pathophysiology of CRPS and FND (see Figure Two) we will then go on to present a unifying framework for understanding these disorders and will review the implications for treatment. In doing so we believe that patients, clinicians and researchers in both CRPS and FND could benefit.

The overlaps between CRPS and sensorimotor FND

CRPS is a chronic pain disorder with a combination of sensory, motor, autonomic and dystrophic changes[22]. These changes are usually triggered by an incipient event such as injury or surgery, but can occur spontaneously in a minority of cases[23]. Although traditionally FNDs have been associated with psychological trauma, systematic studies have revealed that they very often arise from physical injury[24,25]. In a systematic review of 869 cases, 37% of functional motor and sensory disorders had a history of physical injury, and In surgical settings similar to CRPS, 79% of sensorimotor FND are preceded by a physical precipitant[25]. In a prospective cohort of 50 patients with FMD (dystonia in 36%), as many as 80% reported a precipitating "physical" noxious event within the preceding three months, with 38% fulfilling the criteria for panic attack in association with said event[24]. The combination of immobilisation (reflexive due to acute pain or iatrogenic through plaster cast bandaging) and excessive anxiety is considered a potential precipitant for FMD development[24,26]. Stressful life events precede FND only in about a half of cases[27], similar to CRPS[28], and their importance has been downgraded from a diagnostic criterion to an optional risk factor in the revision of DSM-5[29].

Central to our argument is the nature of motor and sensory signs seen in both CRPS and FND (Table One, Figure One). In contrast to classic (idiopathic/primary) dystonia, functional dystonia is usually

immobile ("fixed"); develops acutely, often following minor injury; cannot be alleviated by sensory tricks (so-called *geste antagoniste*) but is instead intensified by any manipulation; is accompanied by other functional motor and sensory symptoms; and is usually associated with regional pain[30]. Even in functional paralysis without dystonic posturing, pain in the affected limb is reported in a third of cases[31]. In their large series of "fixed dystonia", Schrag and colleagues reported a 20% overlap of CRPS[11]. Meanwhile, Mailis-Gagnon and colleagues found that among 54 presumed CRPS cases, experts determined 18% to be suffering from "psychogenic" disorders[32]. Limb weakness and bradykinesia are almost universally present in CRPS, with most having 'give-way' weakness[13,28] and around 70% of patients develop movement disorders such as dystonic posturing, tremor and/or myoclonic jerks[12,28,33,34]. Patients show reduced voluntary control[35,36], and have problems initiating movement[28] or assessing limb position[37]. Sensory symptoms are often in a non-dermatomal distribution[38] and resolution of hypoesthesia followed placebo injection occurred in 50% of 27 patients with CRPS and 0% in patients with a nerve lesion (n=13)[7]. Other positive diagnostic features used in the diagnosis of FND, such as distractibility, suggestibility, clinical inconsistency and physiological incongruity [39,40] can be found in CRPS patients.

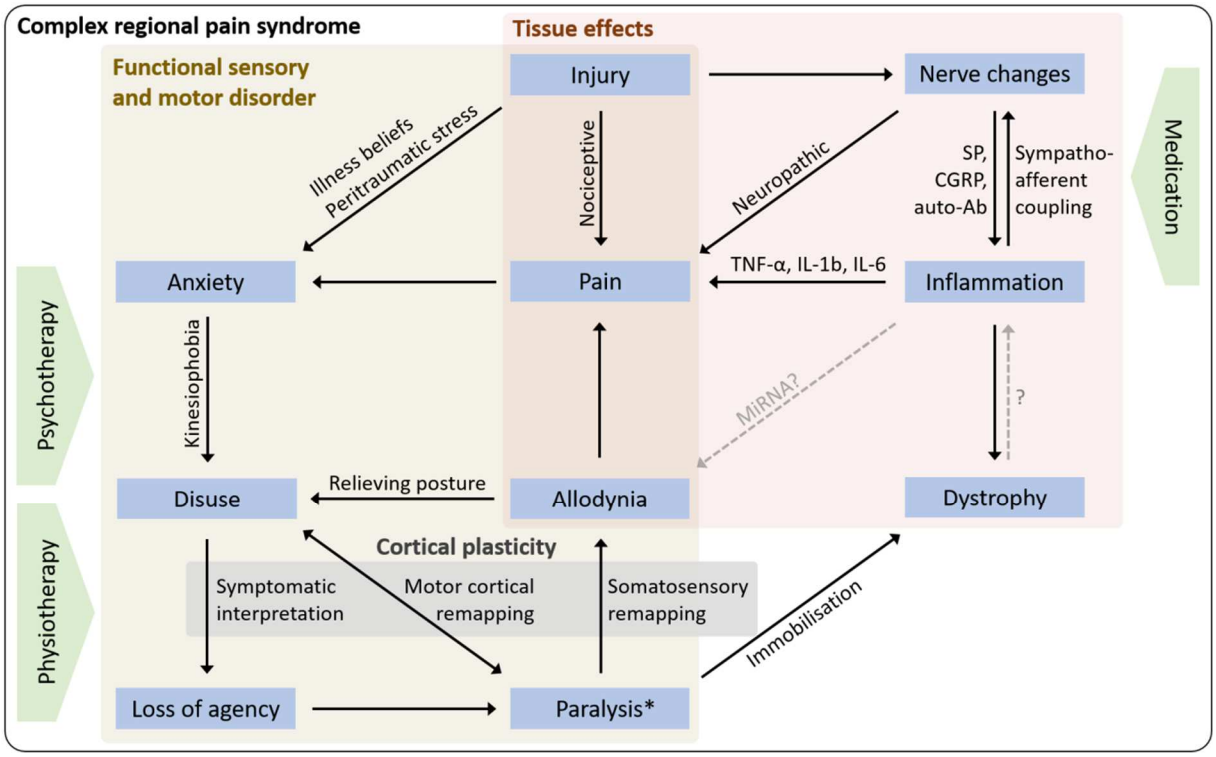

Figure Two. An illustration of the overlap between Complex Regional Pain Syndrome and Functional Neurological Disorder indicating ways in which understanding of one may benefit the other.

The early alterations seen in CRPS are dominated by peripheral inflammatory changes and autonomic response[18]. Local nerve injury is thought to underlie early neuropathic pain[41] and can trigger neurogenic tissue inflammation mediated by neuropeptides such as substance P and calcitonin gene related peptide (CGRP) [42]. Driven also by pro-inflammatory cytokines such as TNF-a, IL-1b, IL-2 and IL-

6, this inflammatory state is thought to underlie hyperalgesia[43] (Wegner et al., 2014), early allodynia[44], and autonomic and dystrophic changes[18,45]. Autonomic changes can include so-called sympatho-afferent coupling, whereby nociceptive fibres are thought to be activated by sympathetic nervous system activity[1]. The neuroimmunological interplay is further complicated by the potential contributions of neural autoantibodies[4,46] and small noncoding RNA molecules called microRNA[47]. Importantly, such pro-inflammatory, autonomic and hyperalgesic regional tissue reactions can be observed reliably in (experimental models of) acute injury, transient immobilization and chronic pain in general[48–53].

So what keeps these pro-inflammatory processes in CRPS from abating normally over time, as they usually would after injury and temporary immobilisation? In CRPS, we hypothesise that the peripheral inflammation becomes interlocked with much wider-reaching nervous system maladaptations that are identical to those seen in FND.

A temporary adaptation of movement to acute pain (or to the expectation of pain) is a physiological reaction, and involves a redistribution of muscle activity that leads to stiffening, restriction and slowing of movement, and favours relieving postures (Hodges & Tucker, 2011). Such adaptations, while normally only transient and largely under volitional control, can become entrenched in robust pathways through cycles of negative reinforcement until they are no longer within the reach of conscious control. Hypervigilance and avoidance based on anxious illness beliefs, catastrophizing tendencies, or excessive self-monitoring can imprint expectations of pain and immobility that can distort and even override incoming sensory information[26,54]. Such failure to re-adapt has been proposed to underlying chronic dysfunction in FND, and can just as well explain sensory and motor symptoms in chronic CRPS.

Studies of central nervous function using functional MRI and transcranial magnetic stimulation in both disorders have revealed subtle but comparable abnormalities of brain activations (see Aybek & Vuilleumier, 2016[55], and Di Pietro et al., 2013a[56], 2013b[57], for review). Most studies examining central function in CRPS and FND are too heterogenous to allow direct comparisons, but there is one group that has tested motor execution and imagery using the same paradigm in both CRPS[58] and functional limb weakness ("conversion paralysis")[59]. Compared to healthy controls, CRPS patients showed hypoactivation of the postcentral gyrus and inferior parietal cortex contralaterally during imagined movement of the affected hand[58]. Similarly, patients with functional limb weakness ("conversion paralysis") showed decreased activity of the contralateral supramarginal cortex (part of the inferior parietal cortex) compared to controls on imagined movement in the affected hand[59]. In van Velzen's study of patients with CRPS, healthy controls and immobilised patients showed normal corticospinal activity during motor imagery and motor observation. The authors postulated that motor symptoms of weakness, slowness and dystonia in CRPS are due to abnormal afferent (peripheral) information processing and therefore treatment should be focused on normalising this by touch and use of the affected limb[60]. However other neurophysiological investigation of peripheral mechanisms of CRPS and FMDs have demonstrated inhibition of sensorimotor integration and reduced corticospinal activity in motor imagery but not observation, suggesting a central mechanism of movement

inhibition[61–63]. In all likelihood both peripheral and central mechanisms are involved at different stages.

Central sensory disturbances go hand-in-hand with functional motor symptoms[54]. Central pain hypersensitisation has been demonstrated in experimental immobilisation[64,65]and is reflected in the non-dermatomal distribution of sensory symptoms in CRPS[66]. While sensory symptoms in motor FNDs have received woefully little attention in research so far, clinical experience shows that if inquired about, they will be reported by nearly every person with functional weakness or functional movement disorder. In a cohort study of sensorimotor FND, many patients showed a fluid shift of symptoms over time between sensory and movement domains (Stone et al., 2003). Interestingly, even characteristic autonomic changes such as regional limb temperature changes can be induced experimentally using protocols for disrupted sense of limb ownership (rubber hand illusion), emphasizing the influence of top-down processes[67].

Given the well-documented overlap in clinical presentation and the common pathophysiological pathways described above, why is CRPS not considered a form of FND, and why have FND researchers devoted so little attention to sensory symptoms and inflammatory processes? The reason, we would argue, is in the historical framing and re-framing of these disorders addressed in the introduction. Pain specialists, decidedly impressed by the evidence of tissue changes that immunologists and molecular biologists have provided, have come to see top-down cognitive and behavioural processes as secondary effects of CRPS pathology. Of course, phobic avoidance and anxiety are being recognized and treated, but they are not seen as driving factors of the disorder per se. Similarly, neurologists, often troubled with the differentiation of organic vs. "non-organic", tend to see FNDs, once identified, as strictly psychogenic disorders. Sensory alterations and trophic changes are discarded as by-products of a unidirectional top-down disorder and receive little attention both clinically and in research. Thus, CRPS and FND seem to occupy opposing lanes of the highway, with all the same landmarks of pathology clearly visible, but, alas, never the twain shall meet.

However, this is not how organic systems works, especially recursive neuronal networks and their neurohumoural and neuroimmunological continuations. Bidirectional hierarchical models based on Bayesian inference have recently been formulated for both FND[54] and CRPS[68]. They necessitate an urgent re-thinking for both disorders in which outdated ideas of "psychogenic vs. neurogenic" have to be shaken off permanently. "Top-down processes" do not refer to mysterious forms of subconscious symptom conversion. Rather, the expectation of pain will influence not just movement (kinesiophobia, avoidant disuse) but also pain perception itself, as any nocebo researcher will confirm[69]. Furthermore, these reiterative cognitive-behavioural patterns of pain expectation and pain perception, kinesiophobia and disuse, will imprint themselves into the neural systems that underly nociception and movement through synaptic and cortical plasticity, giving rise to central allodynia and functional limb weakness. Crucially, normalisation cannot be forced purely bottom-up through analgesic drugs, but has to be achieved through some form of modulation of top down influence.

Treatment

Understanding CRPS and FND in this way has potential benefit for understanding and treatment of both disorders. In FND, there have been recent promising randomised controlled trials of physiotherapy that emphasise the importance of establishing the *potential* for reversibility in FMDs, often through scrutiny of the motor signs themselves. Conversely, FMD researchers have much to learn from mechanistic and treatment studies in CRPS

In recent years there has been an evolution in how clinicians approach the explanation of FND. Previously patients may have been told they had a psychological problem and needed referral to a psychiatrist. Now many clinicians have advocated an emphasis on understanding the mechanism of the motor symptom itself and considering psychological comorbidities separately. Of central importance to this approach, and to the new DSM-5 diagnosis of FND, is to demonstrate to the patient the positive clinical signs, such as Hoover's sign of functional leg weakness, when weakness of hip extension normalises with contralateral hip flexion or tremor transiently abates with distraction. The positive signs of FND emphasize profoundly therapeutic feature of the diagnosis, that the symptoms are due to a functional rather than structural problem, arise from the brain (and not the limb), and have the potential for reversibility. This 'software rather than hardware' framework for the patient to understand how and why the disorder has occurred, with a focus on correcting abnormal self-directed attention and movement expectation, appears in many cases to be key to successful treatment. [70,71].

Two randomised controlled trials of physiotherapy [72,73] have shown the potential success of this approach in FND. A recent trial of 60 patients randomised either to specific FMD therapy or a similar number of community physio sessions showed significant improvement in in functional independence and mobility scores in the treatment versus control arms (72% vs. 18%) even in patients with long duration symptoms (5.8 years). Patients in the control arm only improved in only 18% of cases and on six month follow up 32% had developed worsening symptoms (3% in the treatment arm). Another RCT, also of 60 patients with functional gait disorder demonstrated the normalisation of gait in most patients despite a 9 month duration of symptoms. More than half of the patients in Nielsen et al's 2016 study had pain or fatigue described as severe or extreme [72]. Part of the treatment was education that the mechanisms for chronic pain and fatigue are similar to those for pain, are not correlated with worsening structural damage, potentially reversible by re-training [71].

An updated Cochrane review of physiotherapy for patients with CRPS found some evidence of improvement in pain and functional disability with graded motor therapy and improvement in impairment one year after multimodal physiotherapy; however, evidence for both was classed as very low quality [74]. Perceived harmfulness of activities and pain-related fear predicts functional limitations in CRPS [75] and patients with CRPS have increased phobic anxiety compared with patients with other types of chronic pain [76]. Based on these principles, an RCT (n=46) of exposure versus pain-contingent treatments has demonstrating significant benefit ($p<0.05$) in disability, reduced pain catatrophisation, pain intensity and increased physical and mental health-related quality of life at six months follow up (den Hollander et al., 2016). Treatment for patients with chronic CRPS (average 5.1 years) involved reducing pain related fear using exposure treatment with a similar paradiagm as used in the treatement of anxiety disorders. Another treatment series of 106 patients with 'end stage CRPS' who

had failed other CRPS treaments, described outpatient phsyiotherapy focused on achieving movement after an extensive explanation of CRPS as a 'reversible degregulation of the nervous system' and pain as a 'false warning sign' rather than something suggesting onoging tissue injury[77]. In these 106 patients function improved in 95 patients and a full functional recovery occurred in 49 (46%) despite medications being stopped and some increase in pain during treatment. There is a clear overlap between these treatment approaches for CRPS and FND which mirrors the overlap in the disorders themselves.

Psychological therapy is a first line therapy for patients with dissociative seizures and has some evidence for functional neurological disorders in general[78,79]. Psychologists and psychiatrists play an important role in successful multi-disciplinary for patients with FMDs[80]. From our experience, the best outcomes in patients with FMDs occur when patients have treatment which challenges their top down expectations and kinesiophobia and behavioural habits such as avoidance as well as physical therapy improving peripheral input. The technique of formulation of the mechanism of FMDs, taken from cognitive behavioural therapy, along with self-reflection and a personalised physical and mental management plan for dealing with exacerbations may be the key differences between very successful and largely unsuccessful physical therapy in FMDs[72].

In summary, a case series and randomised controlled trials of educational based upon understanding both FMD and CRPS as due to an abnormal potentially reversible malfunctioning nervous system, followed by physiotherapy focused on regaining function even if pain is transiently increased, have demonstrated positive outcomes. This suggest that patients understanding is key and demonstrates that improvement is possible even in those patients who have had CRPS or FMD for many years. In our view education based physiotherapy which targets both top-down processes and expectations as well as bottom up sensorimotor inputs +/- peripherally acting medication adjuncts, should be the mainstay of treatment for both disorders.

Conclusion

Discussions involving CRPS and functional disorders have been adversarial in the past. New understanding of what functional disorders are; centrally mediated processes of abnormal self-directed attention, often triggered by peripheral stimuli with complex neural and social and emotional risk factors and perpetuation, and a removal of the suspicion of feigned symptoms from the conversation of what CRPS and FMDs are, leads us to a new path of learning from each disorder. There is significant overlap between both CRPS and FMD in new mechanistic understanding, motor symptoms, imaging and neurophysiology studies (Figure Two) as well as uncertainty about the best treatment. In both CRPS and FMDs explanation-based physical treatment, which encompasses understanding of the disorders as reversible seems most positive. During this review, we were surprised by the lack of interest in peripheral processes in the FMD literature. There is much for FMD researchers to learn from the work already done into peripheral and central mechanism of CRPS and more attention is required for investigating "bottom up" input into the mechanistic model of functional disorders. Similarly, recognising shared social, emotional and cognitive risk factors and bidirectional input as the method of CRPS symptom production will allow for more encompassing explanation and treatment strategies. We hope that presenting the similarities and learning from

both disorders, with open acknowledgment of the antagonistic history, will encourage researchers in CRPS and FMD to collaborate and open useful discussions on how to understand and treat these complex and important disorders.

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Table One: Clinical overlap of Complex Regional Pain Syndrome (CRPS) and Functional Neurological Disorder(FND)

	Complex Regional Pain Syndrome	Functional Neurological Disorder	Pathophysical /structural disease
Trigger	Physical injury or surgery	Physical injury or surgery in 37-80%[25]	Dependent on disorder
Sensory	Loss or hyperalgesia[81] Non-dermatomal, dense[28], may be whole limb[38] or hemisensory[38] Common response to placebo[7]	Loss or hyperalgesia[82] Non-dermatomal, dense, may be whole limb or hemisensory[82,83] Common response to placebol[83]	In keeping with expected lesion location No response to placebo[7]
Movement Disorders	Combination of movement disorders common(dystonia, tremor, myoclonus)[84]	Combination of movement disorders or other FNDs common[88]	Unusual to have several different movement disorders
Dystonia	Rapid onset, often fixed, dystonia of hand or foot[34,85] Can spread to other limbs[12] May seek limb amputation[86]	Rapid onset, often fixed, dystonia of hand or foot[89,88] Can spread to other limbs[89] May seek limb amputation[86,88]	Gradual onset over months/years of mobile dystonia[14] Unlikely to seek amputation[86]
Tremor	Entrainment of tremor possible and diminished by distraction[85,84,87]	Entrainment of tremor possible and diminished or stopped by distraction[90]	Entrainment rare in patients with pathophysical tremor[91]
Weakness	Give-way[13,28]. Distribution and Hoovers sign not studied.	Give-way[92] Global pattern of weakness with signs of internal inconsistency (e.g. Hoovers sign)	Follows expected patterns based on lesion location.
Description from patient	"My mind tells my hand/foot to move, but it won't work",[93,12] "My painful limb feels as though it is not part of my body"[35] (described as neglect-like but actually involving *increased* attention and dissociation)	"He found that when he walked, his left leg would sometimes drag behind him, accompanied by an odd sense that it did not belong to him."[94] Common for patients to describe feelings of disconnection or lack of ownership of limbs. Usually interpreted as dissociative.	Feeling of limb dissociation can be seen in some conditions such as parietal dysfunction. Neglect of limb involves absence of interest/awareness of limb[95].
Comorbid Functional Disorders	Some evidence of excess comorbidity of functional disorders such a fibromyalgia although poorly studied[9697]	Comorbid functional disorders including FND greatly in excess of population[98], [99]	Functional disorders common in population, including those with disease [100,101]

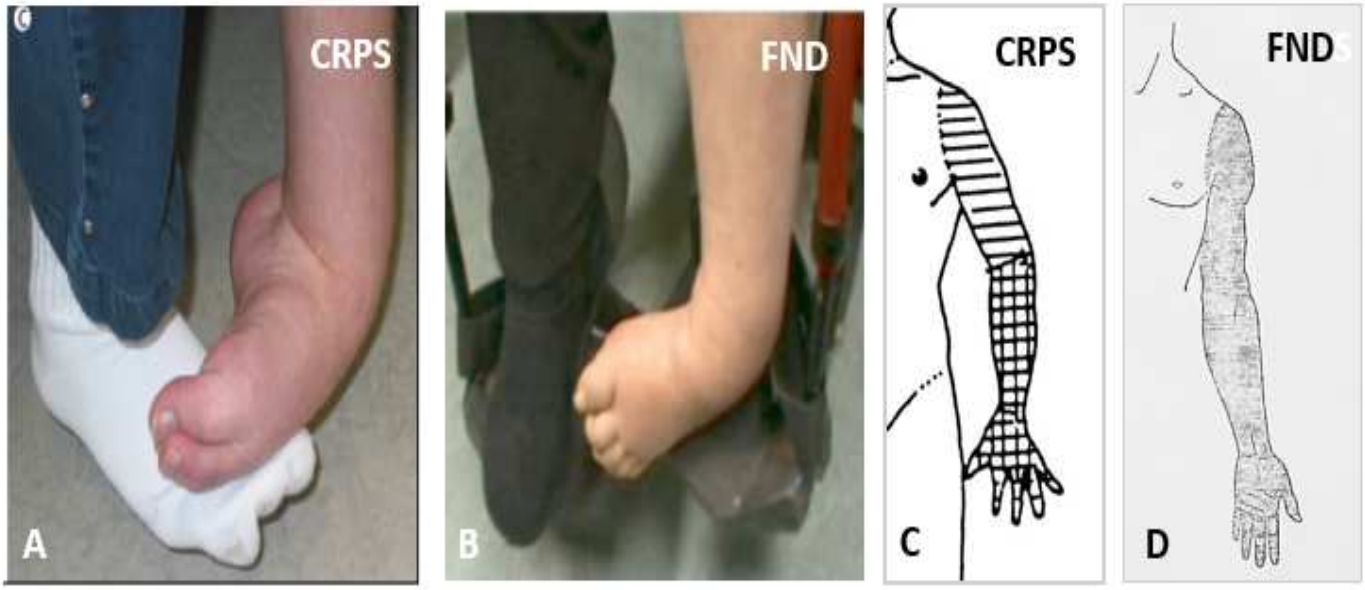

Fig 1 Similarities between Dystonia in CRPS (A) (ref) and FND (B)_and circumferential sensory loss from the shoulder in CRPS (Rommel) and FND (Charcot)

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The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Bradford Hill Criteria for Assessing Causality in Cohort Studies

Criteria for establishing causation
Strength
Consistency
Specificity
Temporality
Biologic gradient (dose-response)
Biologic plausibility
Coherence
Experiment (reversibility)
Analogy

The Clinical Features and Prognosis of 'Scan Negative' Uro-Neurological Disorders: Appendix

Thank you for reading my PhD
It's been an incredible journey