"Scan-negative" cauda equina syndrome: a prospective cohort study

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Abstract

Objective: To describe clinical features relevant to diagnosis, mechanism and aetiology in patients with 'scan-negative' cauda equina syndrome (CES).

Methods: We carried out a prospective study of consecutive patients presenting with the clinical features of CES to a regional neurosurgery centre comprising semi-structured interview and questionnaires investigating presenting symptoms, neurological examination, psychiatric and functional disorder comorbidity, bladder/bowel/sexual function, distress and disability.

Results: 198 patients presented consecutively over 28 months. 47 were diagnosed with 'scan-positive' CES (mean age 48yrs, 43% female). 76 'mixed' category patients had nerve root compression/displacement without CES compression, (mean age 46yrs, 71% female) and 61 patients had 'scan-negative' CES (mean age 40yrs, 77% female). An alternative neurological cause of CES emerged in 14/198 patients during admission and 4/151 patients with mean duration 25 months follow up.

Patients with 'scan-negative' CES had more positive clinical signs of a functional neurological disorder (11%'scan positive' CES v. 34%mixed and 68%'scan-negative', $p<0.0001$), were more likely to describe their current back pain as 'worst ever' (41% vs. 46% and 70%, $p=0.005$) and have symptoms of a panic attack at onset (37% vs. 57% and 70%, $p=0.001$). Patients with 'scan positive' CES were more likely to have reduced/absent bilateral ankle jerks (78% 'vs. 30% and 12%, $p=<0.0001$). There was no significant difference between groups in the frequency of reduced anal tone and urinary retention.

Conclusions: The first well phenotyped, prospective study of 'scan-negative' CES supports a model in which acute pain, medication, and mechanisms overlapping with functional neurological disorder may be relevant.

Introduction

Cauda Equina Syndrome is a surgical emergency caused by compression of the cauda equina nerve roots. It is suspected when patients present with bladder, bowel, sexual dysfunction or saddle numbness with or without new back or leg pain. 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 [1,2]. However, a mean of 81% of patients referred to neurosurgery with cauda equina syndrome (CES) have normal or non-explanatory imaging, 'scan-negative' CES[3] despite having similar rates of pain, bladder and neurological dysfunction. These patients have not previously been prospectively studied and the mechanism underpinning symptom presentation in 'scan-negative' CES is unknown. Two previous studies suggest that at least some patients presenting with 'scan-negative' CES have symptoms partially or fully explained by functional neurological disorders [4,5]. This hypothesis has not been tested in a large prospective study

We aimed to use a cohort 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 patients 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[6];

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[7]; 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[8]. Patients were included if they had: 1) Clinically defined CES presentation 2) symptoms necessitated a scan to exclude 'scan-positive' cauda equina compression. Recruitment occurred between November 2015-December 2017. Patients were identified through daily neurosurgery handover. Patients were given an information leaflet by a member of their clinical care team and if interested in the study were consented. They were seen either during their inpatient stay, or if discharged quickly, were contacted by post and offered the opportunity to take part in the questionnaire component 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 scans 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, leg numbness and arm weakness. Back and leg pain were rated on a four-point Likert scale; 'worst ever', 'severe', 'somewhat painful', 'not very painful'. Interview questions comprised; panic attack at onset as defined by DSM-5 ($\geq$ 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?"[9]). Medications patients were taking when admitted which were likely to be associated with incontinence or retention or sexual dysfunction were recorded; opiates (classed as tramadol or stronger), benzodiazepines, codeine and tricyclics or gabapentinoids, [10–12]. 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 were included. 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. The interview was the validated structured clinical interview for DSM-IV , undertaken and scored in the usual way[13].

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 neurosurgical registrars. Functional neurological disorders were diagnosed according to DSM-5 criteria on the basis of positive evidence from the clinical presentation and examination by IH[14] (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, diagnosis of persistent postural perceptual dizziness[15]). Evidence of neurological disorders which may present as 'scan-negative' CES, such as inflammatory, infectious, vascular, neurodegenerative and neoplastic causes was sought[5]. Any patients with additional clinical features that may have suggested an alternative neurological cause for CES were discussed systematically with a Neurologist (JS) with investigations and follow up arranged as appropriate,

Questionnaires

We administered patient-reported questionnaires about bladder (Urinary Symptom Profile (USP); measuring stress incontinence, overactive bladder symptoms and low stream) [16], bowel (Neurogenic Bowel Dysfunction Score (NBDS)[17]), sexual function (Arizona Sexual Experiences Questionnaire (ASEX) [18]), quality of life (Work and Social Adjustment Scale(WSAS)), 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 (HADS)), dissociation (Peritraumatic Dissociation Questionnaire) and adverse childhood experience (Adverse Childhood Experiences (ACE) questionnaire [19]) . To understand premorbid health status patients were asked to fill out all of the scales above, bar illness perception and adverse childhood experience, based upon the month prior to symptom onset. These questionnaires were given together as a questionnaire pack.

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.

Electronic notes review in the 'scan-negative' and mixed groups in October 2018 was undertaken to determine whether patients had developed conditions which explained their initial clinical CES symptoms.

Statistical Analysis

Individual questionnaires with clinical cut-offs 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, odd ratios (OR) and Mann Whitney U tests were performed with scan-positive CES as the control group. Relative risk (RR) with 95% confidence intervals (CI) assessed probability of clinical features occurring in patients in the 'scan-negative' CES and mixed group using Statsdirect (http://www.statsdirect.com).

Standard Protocol Approvals, Registrations, and Patient Consents

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

Data Availability

Anonymised data will be shared on request from a qualified investigator.

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) (Figure one). 177 patients were seen as an inpatient, 21 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).

14 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), acute inflammatory

demyelinating polyneuropathy (n=2) and one each of; 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 14 patients was excluded from further analysis.

Figure One: Flow of patients through the study showing division of diagnostic explanations at baseline and at follow up

47 patients (24%) had 'scan-positive' CES (43% female, average age 48yrs old; discogenic n=42; fracture n=2; stenosis, spondylolisthesis, tumour each n=1). 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). 61 patients (31%) were in the 'scan-negative' CES group (77% female, average age 40yrs old).

81% of patients with 'scan-positive' CES (n=38), 80% of patients in the mixed group (n=61) and 66% of patients with 'scan-negative' CES (n=40) returned their questionnaire pack. There were no significant differences in the questionnaire pack return frequency by diagnostic group or gender. Patients who did not return questionnaire packs were significantly younger (median age 36.5 years vs. 43 years, p=0.004).
Individual questionnaire completion for the three groups studied were (n,%); USP; stress incontinence n=132, 72%, overactive bladder symptoms n=132, 72% low stream n=135,73%); NBDS n=137, 74%; ASEX n=136; 74%, WSAS n=127, 69%; SF-12 physical function scale n=130, 71%; PHQ-15 n=136; 74%, HADS n=137,74%; Peritraumatic Dissociation Questionnaire n=133, 72% and ACE questionnaire n=135, 73%. Patients with 'scan negative' CES were less likely than patients with 'scan positive' CES to complete individual questionnaires on current overactive bladder symptoms (p= 0.048, OR 2.4), SF-12 physical function (p-0.01,OR 3.1) and peritraumatic dissociation (p=0.04OR 2.5). There were no differences in completion of the eleven other questionnaires.

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, RR(95% CI) mixed 0.7 (0.5-1), ‘scan-negative’ 0.7(0.5-1)) 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, RR(95% CI) mixed 1.4(1-1.9), ‘scan-negative’ 1.8(1.3-2.8)). 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, RR(95% CI) 1.1(0.8-1.4), 1.7(1.2-2.6)) and report dissociation (32% v. 39% and 65%, p=0.03, RR(95% CI) 1.1(0.8-1.5), 1.5(1-2.1)) at onset.

Figure Two: Key clinical features and comorbidities of ‘scan-negative’ cauda equina syndrome and the ‘mixed’ group with some nerve root compression compared to ‘scan-positive’ cauda equina syndrome

Signs

Data were taken from the records in those who refused research clinical examination (‘scan-positive’(n=4), mixed (n=6) ‘scan-negative’ (n=4)), 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%, RR(95% CI) mixed 0.5(0.3-0.6), ‘scan-negative’ 0.2(0.1-0.4)) (Table One). Positive motor or sensory signs of a functional neurological disorder were more common in the mixed and ‘scan-negative’ CES group; (11% v. 34% and 68%, p=0.009, p=<0.0001, RR(95% CI) 1.5(1.1-2), 2.6(1.8-4)), especially in those with leg weakness (16% v. 42% and 71%, p=0.002, p=<0.0001, RR(95% CI) 1.5(1-2.3), 3.7(1.9-8.4)).

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

Medications on admission

The majority of patients in all groups were on ≥1 analgesic associated with bladder +/- sexual dysfunction (88% v. 81% and 82%). (Table Two).

Table One: Symptoms and Signs at Onset and on admission

Bladder, Bowel and Sexual Dysfunction from Questionnaire

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 bowel or sexual dysfunction between all three groups on admission (Table Two). 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).

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=61), 31 patients had an MRI brain and one had a CT brain. MRI brain scans were abnormal in three patients including an incidental enlarged pituitary (n=1) and an incidental temporal cavernoma (n=1). One patient had possible inflammatory 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 follow-up or present with 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

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 $p<0.0001$, RR(95% CI) mixed 3.4(2.2-5.9), 'scan-negative' 3.8(2.2-7)). Patients with 'scan-negative' CES also reported higher rates of social functional impairment in the month prior to symptom onset (WSAS >20, 9% vs. 11% and 43%, $p=0.0007$, RR(95% CI) mixed 1.1(0.6-1.6), 2(1.4-3)). 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

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 or irritable bowel syndrome. Pain was the most common functional disorder subtype particularly chronic widespread or back pain (24% v. 64% and 81%, $p=0.003$, $p=<0.0001$) (Table Four). 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 $p<0.0001$, RR(95% CI) mixed 2.2(1.4-3.8), 'scan-negative' 3(1.6-6.5); current rates 44% vs. 75% and 90%, $p=0.002$ and $p=<0.0001$, RR(95% CI) 1.8(1.2-2.7), 3.6(1.9-7.5))(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%, $p=0.0003$, RR(95% CI) 1.8(1.4-2.5)) and panic disorder (20% v. 56% and 61%, $p= 0.00002$, RR(95% CI) 2(1.4-3)). Interestingly, there was no difference on the adverse childhood events questionnaire.between mean scores, numbers of patients in all three groups with ≥1 or ≥4 adverse childhood events or reporting sexual abuse

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%, $p=0.02$, $p=0.001$, RR(95% CI) mixed 1.5(1.1-1.9), 'scan-negative' 1.7(1.3-2.3)) and patients with

'scan-negative' CES were more likely to be receiving disability-related benefits at the time of admission (7% v. 22% and 27%, p=0.01, RR(95% CI) 1.4(1-1.8), 1.5(1.1-2)).

Table Four: Predisposing factors and comorbidity

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 (spinal inflammation n=2, cervical haematoma n=1, sacral chordoma n=1) . (Figure One).

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), dissociative seizures (n=3), 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 (Table five). Only one patient was diagnosed with neuropathic voiding dysfunction, 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).

Figure One:

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 . Patients in all groups who returned their questionnaires had high rates of overactive bladder symptoms (74-86%) and similar levels of bowel (12%,, 26% and 33%)and sexual dysfunction (58%, 51% and 44%). 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, approximately half of patients in all groups were working at follow up (48%, 47% and 50%) and one fifth receiving disability related benefits (16%, 21% and 18%).

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 and records follow up, to assess the possibility of other neurological explanations for patient's clinical CES symptoms after presentation.

Symptoms and Signs

As expected, there was no one clinical symptom or sign of sufficient discriminatory value to render an MRI scan unnecessary. Chronic leg pain and especially 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 describing having their "worst ever back pain", symptoms of a panic attack or dissociation at onset and more bladder symptoms in the month prior to admission. Most strikingly, inpatients 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. Patients with 'scan negative' CES and in the mixed group had markedly higher rates of abnormal social function and pain suggesting greater disability and impairment on admission. Social impairment is commonly seen in patients with chronic back pain[20] and functional neurological disorders[21] and may be precipitating factors for 'scan negative' CES.

For many of the studied variables there was a dose-response effect with higher -relative risk in mixed, and higher values again in 'scan-negative' patients (Figure One). Figure two highlights key features which may help predict 'scan negative' CES, and tests which did not assist with diagnosis. Tests such as abnormal anal tone, have been shown to be unhelpful in predicting CES[22,23] and are unpleasant and often inaccurate[24].

Potential explanations of 'scan-negative' CES

Alternative neurological disease explanation

From this prospective study and previous retrospective work we carried out in 276 individuals from the same centre[5] 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 a mean follow

up of 23 months. This supports retrospective work which found only one similar patient out of 191 scan-negative CES with a follow up of 15 months[5].

The authors considered the differential diagnoses for clinical CES throughout the studyincluding inflammatory of infectious myelitis or radiculitis, vascular abnormalities such as spinal arteriovenous malformations and stroke, neurodegenerative conditions and neoplasia[5] (for full differential see Table 4 in [5]). Some diagnoses such as infectious lumbosacral polyradiculitis from HSV, Elsberg syndrome, can be difficult to diagnose due to 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[25]. 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[26].

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[27,28]. As this was a real-world study not all patients received imaging of the whole neuraxis where this was not clinically indicated, but there was no evidence of further clinical presentations suggesting that additional missed cases are likely to have been few.

Potential mechanisms of bladder dysfunction

There are several potential explanations of how clinically significant bladder dysfunction could arise without a clear pathophysiological cause in 'scan-negative' CES:

- *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. High numbers of patients in the mixed and 'scan-negative' CES groups had severe pain caused either by nerve root entrapment or their worst ever back pain. These patients also had higher rates of prior chronic pain which may have amplified their pain response through central sensitisation.

- *Effects of medication*. Medications such as opiates, tricyclics, benzodiazepines,or gabapentinoids can cause urinary incontinence or affect bladder and bowel function causing voiding dysfunction +/- urinary retention [29]. Over 80% 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 [30]. 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*. Paruresis, also called "shy bladder syndrome", affects 3-16% of the population, causing intermittent inability to initiate or maintain urination. It is due to failure of external urethral sphincter relaxation with inhibitory top-down brain-bladder signals. Patients are unable to void when aware of others around them. It is usually triggered by an anxiety invoking experience in a toilet, is associated with higher than population rates of psychopathology (5-70%) [31] and responds to graded exposure therapy [32]. Fowler's syndrome describes chronic urinary retention due to a primary failure of external urethral sphincter relaxation triggered by pain or surgery or medications such as opiates. Patients with Fowler's syndrome have high rates of comorbid functional neurological disorders and pain[33]. 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 similarly low rates of functional neurological disorders pre-admission (7% vs. 6% and 12%, p=0.8, p=0.5). This suggests that in some patients 'scan negative' CES is an acute functional disorder perhaps triggered by the components outlined above. 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 [14], 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 only as the result of physical conversion of traumatic emotional events, recent understanding is of Bayesian 'top-down' expectation and abnormal self-directed attention overriding normal motor and sensory pathways[34,35]. Without diagnosis and treatment 80% of patients have symptoms on 14 year follow-up[21]. Tailored physiotherapy has the potential to improve outcome[36,37].

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% [38], in another study panic preceded symptoms in 59% of patients[39]. Our study is the first to test the hypothesis that panic is more likely to occur in patients with functional neurological disorders than a control group with similar symptoms due to pathophysiological disease. 57% and 70% of patients in the mixed and 'scan-negative' groups had symptoms of a panic attack at symptom onset versus 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 muscle spasm react with panic and dissociation[40]. Abnormal

bladder function occurs 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, particularly opiates, which >40% of patients were taking, could compound voiding dysfunction and medications such as gabapentinoids, which >30% of patients were taking, could compound urinary incontinence. Improvement can occur with reassurance, analgesia and physiotherapy during admission. 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 two).

Figure Three: Proposed Mechanism of 'Scan-Negative' Cauda Equina Syndrome (CES)

Clinical Implications

Our study highlights that patients with scan negative CES are a group with high rates of chronic pain, psychiatric comorbidity, bladder dysfunction and impaired social functioning. We propose several clinical implications:

1.*Urgent neuroimaging is still required in all CES presentations.* Although we have, for the first time, demonstrated some clinical features that may help differentiate scan negative from scan positive CES at presentation, an urgent MRI scan continues to be essential, as none of them allow clinical separation with sufficient confidence.

2. *Some clinical features should no longer be considered to have any specificity* for a structural cause for CES including anal tone, saddle numbness and urinary retention. There is an argument for abandoning examination of anal tone unless otherwise indicated.

3. *Providing positive diagnosis and treatment pathways for Scan-Negative CES.* At present patients with CES are rushed into hospital but then when the scan is normal generally given no explanation for their symptoms. Clinical features we have found including pre-existing bladder dysfunction, particularly stress incontinence, chronic widespread or back pain, panic and dissociation at the onset of CES symptoms and positive signs of functional neurological disorders should raise expectations of a negative scan. More explicit discussion, both before and after imaging, about the possible mechanisms of CES symptoms (with consideration for other neurological

disease causes) can give patients and health professionals an explanatory model compatible with rehabilitation treatment. Ingredients may include: management of constipation, reduction of opiates, use of flip flow catheters with early trial of removal of catheter, physiotherapy directed towards chronic pain or FND issues and follow up within a multidisciplinary team including psychological input where appropriate.

Limitations

This was a real-world study which had limitations including case definition, single center bias, blinding, potential bias in control and cases selection, questionnaire return rate, measures used and extent of investigations. There is no internationally agreed clinical or radiological definition of CES. Our definition originated from the systematic review of CES definitions but this is a broad definition which does not have an agreed radiological component and therefore could limit the generalisability of the findings[3,6]. Characterising patients' disorders negatively, as 'scan negative' CES, is not ideal. However, this is a clinically replicable and relevant patient group. Patients who did not return any questionnaires were significantly younger and there were some questionnaires which were less likely to be filled out by patients with 'scan negative' CES. This may have resulted in bias. 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, across 18 studies of patients with suspected CES 81% had 'scan negative' CES, and it is associated with higher levels of functional disorder comorbidity than 'scan positive' CES[3,41].

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” risk factors.

Appendix One:

Name	**Location**	**Contribution**
Ingrid Hoeritzauer	Centre for Clinical Brain Sciences, University of Edinburgh, UK	Designed and conceptualized study; collected the data; analysed the data; wrote the manuscript
Alan Carson	Department of Clinical Neurosciences, Western General Hospital, UK Department of Rehabilitation Medicine, NHS Lothian, Edinburgh, UK	Designed and conceptualized the study; interpreted the data; revised the manuscript for intellectual content
Patrick Statham	Department of Neurosurgery, Western General Hospital, UK	Assisted with study design; interpreted the data; revised the manuscript for intellectual content
Jalesh N. Panicker	Department of Uro-Neurology, The National Hospital of Neurology and Neurosurgery and UCL Queen Square Institute of Neurology, London UK	Assisted with study design; interpreted the data; revised the manuscript for intellectual content
Voula Granitsiotis[6]	Department of Urology, Western General Hospital, Edinburgh UK	Assisted with study design; interpreted the data; revised the manuscript for intellectual content
Maria Eugenicos	Department of Gastroenterology, Western General Hospital, Edinburgh, UK	Assisted with study design; interpreted the data; revised the manuscript for intellectual content
David Summers	Department of Neuroradiology, Western General Hospital, Edinburgh UK	Assisted with study design; interpreted the data; revised the manuscript for intellectual content
Andreas K. Demetriades	Department of Neurosurgery, Western General Hospital, UK	Assisted with study design; interpreted the data; revised the manuscript for intellectual content
Jon Stone	Department of Clinical Neurosciences, Western General Hospital, UK	Designed and conceptualized the study; interpreted the data; revised the manuscript for intellectual content

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Tables

Table One: Symptoms and Signs at Onset and on admission

DEMOGRAPHICS	**'Scan positive' CES n=41**		**Mixed n=67**		**P value**	**Relative Risk(CI)**	**'Scan negative' CES n=57**		**P value**	**Relative Risk(CI)**
Mean age	48yrs		46yrs				40yrs			
Female %	43%		71%		0.002	1.6(1.2-2.3)	77%		0.0005	2 (1.4-3.3)
SYMPTOMS –at onset	n	**%**	n	**%**	P value	Relative Risk (CI)	n	**%**	P value	Relative Risk (CI)
Describes current back pain as 'worst ever'	17	**41%**	31	46%	0.6	1.08 (0.8-1.4)	40	70%	**0.005**	**1.7 (1.2-2.6)**
Meet DSM 5 criteria for Panic Attack	15	**37%**	38	**57%**	**0.046**	**1.4 (1-1.9)**	40	**70%**	**0.001**	1.8 (1.3-2.8)
SYMPTOMS – on admission	n	**%**	n	**%**	P value	Relative Risk (CI)	n	**%**	P value	Relative Risk (CI)
Leg weakness	25	**61%**	52	**78%**	0.07	1.4 (1-2.2)	49	**86%**	**0.006**	**2 (1.2-3.7)**
Both legs weak	7	**17%**	12	**18%**	0.9	1(0.6-1.4)	22	**39%**	**0.02**	**1.5 (1-2)**
Both legs numb	13	**32%**	14	**21%**	0.2	0.8(0.5-1.1)	20	**35%**	0.7	1.1 (0.7-1.4)
Unilateral sciatica	19	**46%**	36	**54%**	0.5	1.1(0.8-1.5)	18	**19%**	0.1	0.8 (0.5-1.1)
Bilateral sciatica	15	**37%**	14	**21%**	0.08	0.7 (0.5-1)	14	**25%**	0.2	0.8(0.5-1.1)
Non dermatomal leg pain	2	**5%**	12	**18%**	0.051	1.5(1-1.9)	19	**33%**	**0.0005**	**1.8(1.4-2.4)**
Arm weakness	3	**7%**	14	**22%**	0.06	1.4(1-1.8)	15	**27%**	**0.04**	**1.6 (1.1-2.1)**
Neurogenic Claudication	13	**27%**	15	**22%**	0.3	0.8(0.5-1.1)	11	**19%**	0.2	0.7 (0.4-1.1)

SIGNS **Exam and from notes**	**'Scan positive' CES n=41[1]**		**Mixed n=65[1]**		P value	Relative Risk (CI)	**'Scan negative' CES n=57[1]**		P value	Relative Risk (CI)
	n	**%**	n	**%**			n	**%**		
Bilateral reduced/absent ankle jerks	32	78%	20	30%	**<0.0001**	**0.5 (0.3-0.6)**	7	12%	**<0.0001**	**0.2 (0.1-0.4)**
Abnormal saddle pinprick	30	75%	35	55%	**0.04**	**0.7 (0.5-1)**	40	70%	0.6	0.9 (0.6-1.3)
Refused	1		1				0			
Reduced anal tone on digital rectum exam	20	61%	19	33%	**0.04**	**0.6 (0.4-0.9)**	28	51%	0.9	0.9(0.6-1.2)
Refused/not done pre scan	8		7				2			
Unilateral reduced/absent ankle jerks	4	10%	17	25%	**0.04**	**0.4 (0.2-1)**	14	25%	0.07	1.4(1-1.9)
Any leg weakness	19	46%	31	47%	0.9	1(0.7-1.3)	28	49%	0.8	1 (0.7-1.5)
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**	**1.5 (1.1-2)**	36	68%	**<0.0001**	**2.6 (1.8-4)**
In patients with weakness										
Hoover's *	3 of 19	16%	13 of 31	42%	0.06	1.5(1-2.3)	23 of 28	82%	**<0.0001**	**3.7 (1.9-8.4)**
Thigh abductor sign *	2 of 19	11%	6 of 31	19%	0.5	1.3(0.7-1.9)	15 of 28	54%	**0.003**	**2 (1.3-3.3)**
Functional Sensory Symptoms	1	3%	15	25%	**0.003**	**1.7 (1.2-2.1)**	27 of 55	49%	**<0.0001**	**2,2 (1.7-3)**
Functional Gait Disorder	0	0%	2	3%	0.1	1.6(0.4-1.7)	3	5%	0.1	1.7(0.6-2)

Statistically significant findings in bold. Examination findings for these patients were taken from the notes. *test results in patients with leg weakness.

Table Two: Bladder Dysfunction and Medications

Bladder symptoms in the month prior to symptom onset

Urinary symptom Profile	**'Scan positive' CES n= 38**	**Mixed n=61**		**'Scan negative' CES n=40**	
	Mean Score (CI)	Mean Score (CI)	**P value**	Mean Score (CI)	**P value**
Stress Incontinence	0.54 (-0.1-1.1)	1(0.3-1.7)	0.3	3 (2-4.1)	< **0.0001**
Overactive Bladder	1.83 (0.9-2.7)	3.62 (2.4-4.8)	0.06	5.7 (3.7-7.7)	< **0.0001**
Voiding Dysfunction	0.89 (0.3-1.5)	0.91 (0.4-1.4)	0.5	1.8 (1.2-2.4)	< **0.0001**

Bladder symptoms on admission

	'Scan positive' CES n= 38	**Mixed n=61**		**'Scan negative' CES n=40**	
	Mean Score (CI)	Mean Score (CI)	**P value**	Mean Score (CI)	**P value**
Stress Incontinence	0.92 (0.2-1.6)	3.57 (0.6-6.6)	**0.02**	3.8 (2.7-4.9)	**0.0009**
Overactive Bladder	4.43 (3-5.8)	6.43 (5-7.8)	0.07	7.6 (5.7-9.4)	**0.04**
Voiding Dysfunction	3.73(2.7-4.7)	3.81 (3-4.6)	0.8	3.8 (2.8-4.8)	0.8

Bed side Investigations of Bladder Dysfunction

Bladder Scan	**n**	**%**	**n**	**%**	P value	Relative risk (95% CI)	**n**	**%**	P value	Relative risk (95% CI)
Post void residual Total	n=28	68%	n=58	86%			n=49	86%		
>500mls	10	36%	19	33%	0.8	1 (0.7-1.3)	16	33%	0.8	0.9(0.6-1.3)
>200mls	17	61%	24	50%	0.4	0.7(0.6-1)	23	47%	0.3	0.8(0.6-1.1)

Bowel Dysfunction in the month prior to symptom onset

Neurogenic Bowel Dysfunction Score	**n**	**%**	**n**	**%**	P value	Relative risk (95% CI)	**n**	**%**	P value	Relative risk (95% CI)
Severe	0	0%	3	5%	0.2	1.7(0.6-1.9)	6	15%	**0.02**	**2.2 (1.1-2.8)**
Bowel Dysfunction on admission										
	n	**%**	**n**	**%**	P value	Relative risk (95% CI)	**n**	**%**	P value	Relative risk (95% CI)
Minor/moderate	8	21%	13	21%	0.98	1(0.6-1.4)	10	24%	0.7	1.1 (0.6-1.7)
Severe	3	8%	14	23%	0.055	1.4(1-1.9)	6	15%	0.4	1.4(0.7-2)
Arizona Sexual Experiences Questionnaire (ASEX) on admission										
	n	**%**	**n**	**%**	P value	Relative risk (95% CI)	**n**	**%**	P value	Relative risk (95% CI)
Total completed	35	92%	60	98%	0.2		41	100%	0.5	
Symptomatic	16	46%	33	55%	0.7	1.1(0.8-1.6)	19	46%	0.3	1 (0.7-1.5)
Medications taken PRIOR to admission which could impair bladder dysfunction										
Total taking ≥ 1	36	88%	54	81%	0.4	0.8(0.6-1.2)	47	82%	0.5	0.9(0.6-1.5)
Opiates	13	32%	32	42%	0.1	1.3(0.8-1.7)	28	45%	0.09	1.3(1-1.9)
Gabapentinoids	12	29%	33	43%	**0.04**	**1.4(1-1.8)**	21	34%	0.4	1.2(0.8-1.8)
Benzodiazepines	5	12%	14	18%	0.3	1.2(0.8-1.6)	20	32%	0.01	1.6(1.1-2,1)

Codeine	24	59%	30	45%	0.2	0.9(0.6-1.2)	23	37%	0.08	0.7(0.5-1)
Tricyclics	8	20%	19	25%	0.3	1.3(0.9-1.7)	13	21%	0.7	1.1(0.7-1.5)
NSAID	23	56%	25	33%	0.06	0.8(0.5-1.1)	24	42%	0.18	0.8(0.5-1.1)

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); ASEX compared number completed and number of symptomatic patients ; 95% CI= 95% confidence intervals

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	Relative risk 95% CI	N (%)	P value	Relative Risk 95% CI
Abnormal (>20)	4/34 (12%)	44/55 (80%)	**<0.0001**	**3.4 (2.2-5.9)**	29/38 (77%)	**<0.0001**	**3.8 (2.2-7)**
Median scores	21	28	0.08		31	0.1	
SF-12 Physical Function							
	Mean scores (95% CI)	Mean scores (95% CI)	P value		Mean scores (95% CI)	P value	
	5(4.22-5.78)	4(3.57-4.43)	0.1		5 (4.37-5.63)	0.5	
HADS							
Mean scores (SD)	14(13.8-14.2)	19(16.4-21.6)	**0.02**		17(13.9-20.1)	0.1	
PHQ							
Mean scores (SD)	9 (7.4-10.6)	13 (11/5-14.5)	**0.001**		15 (12.8-17.2)	**<0.0001**	
Peritraumatic Dissociation Questionnaire							
Mean scores (SD)	15 (12.8-17.2)	21 (18.4-23.6)	**0.005**		22 (17.9-26.1)	0.01	
P values compare patients in the 'scan positive' CES group with the mixed and 'scan negative' CES groups.							

Table Four: Predisposing factors and comorbidity

	'Scan positive' CES n=47	**Mixed N=76**	P value	Relative Risk (CI)	**'Scan negative' CES N=61**	P value	Relative Risk (CI)
Prior Functional Disorder comorbidity *	10 (24%)	43 (64%)	**<0.0001**	**1.7 (1.3 -2.3)**	46 (81%)	**<0.0001**	**2.8 (1.9-4.5)**
Subtypes of functional disorder:							
Chronic back pain *Chronic pain***	8 1 widespread	34 5	**0.002**	**1.6 (1.2-2)**	25 10	**0.008**	**1.6(1.1-2.1)**
Irritable Bowel *Syndrome* *Non-cardiac chest* *pain* *Other*	1 0	1 3			6 0 5 ***		
Functional neurological disorders*	3 (7%)	4 (6%)	0.8	0.9 (0.4-1.4)	7 (12%)	0.5	1.3(0.7-1.8)
Limb Weakness *Dissociative Seizures*	1 1	2 2			1 7		
Other:	1 (n=1 memory)	1 (n=1 memory)			1 (n=1 visual,/movement disorder)		
Psychiatric Diagnoses (SCID DSM-5) on admission*							
	N= 41	N= 64			N= 56		
Lifetime Total	21 (51%)	54 (84%)	**0.0004**	2.2 (1.4-3.8)	50 (90%)	**<0.0001**	3 (1.6-6.5)
Current Total	18 (44%)	48 (75%)	**0.002**	1.8 (1.2-2.7)	50 (90%)	**<0.0001**	3.6(1.9-7.5)
Current Depression	4 (10%)	26 (41%)	0.0008	1.7 (1.3-2.2)	21 (38%)	**0.002**	1.7 (1.2-2.3)
Past Depression	14 (34%)	33 (52%)	0.1	1.3 (1-1.8)	37 (66%)	**0.002**	1.8 (1.2-2.6)
Panic	8 (20%)	34 (56%)	**0.003**	1.7 (1.3-2.3)	34 (61%)	**0.00002**	2 (1.4-3)

Agoraphobia	5 (12%)	22 (36%)	**0.04**	1.5 (1.1-2)	24 (43%)	**0.003**	1.5 (1.1-2)
Health Anxiety	1 (2%)	7 (11%)	0.1	1.5(0.9-1-9)	9 (16%)	**0.03**	1.7 (1-2.1)
Generalised anxiety disorder	9 (22%)	18 (28%)	0.6	1.1 (0.8-1.5)	24 (43%)	**0.03**	1.4 (1-2)
Obsessive compulsive disorder	5 (12%)	19 (30%)	0.051	1.4 (1-1.9)	23 (41%)	**0.002**	1.7 (1.2-2.3)
Post-Traumatic Stress Disorder	4 (10%)	17 (27%)	0.92	1.4(1-1.9)	24 (43%)	**0.0003**	1.8 (1.4-2.5)
Adverse Childhood events Score (ACE) from questionnaires							
	'Scan positive' CES n=38 (81% total)	**Mixed N=61** (80% total)	**P value**	Relative risk (95% CI)	**'Scan negative' CES N=40** (66% total)		Relative risk (95% CI)
Refused	2	1			1		
Mean (95% CI)	1.5	1.7	**0.3**		2.2	**0.2**	
ACE scores ≥1	17 (45%)	37(62%)	0.1	1.1(0.8-1.6)	23 (59%)	0.3	1.2 (0.8-1.9)
ACEs core ≥4	6 (16%)	12 (20%)	0.6	1 (0.7-1.5)	12 (31%)	0.1	1.4(0.8-2)
Sexual abuse	2 (5%)	8 (13%)	0.2	1.4(0.8-1.8)	8 (20%)	0.07	1.7 (1-2.5)
Employment							
Working/on maternity leave	22 (54%)	30 (47%)	0.4	0.9 (0.6-1.2)	27 (48%)	0.6	0.9 (0.6-1.3)
Off sick on admission	3 (7%)	18 (28%)	**0.009**	**1.5 (1.1-1.9)**	20 (36%)	**0.001**	**1.7 (1.3-2.3)**
Receiving state related disability benefit	3 (7%)	14 (22%)	0.06	1.4(1-1.8)	15 (27%)	**0.01**	1.5(1.1-2)

***** 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
95% CI = 95% confidence intervals

Figure One. Flow of patients through the study showing division of diagnostic explanations at baseline and at follow up

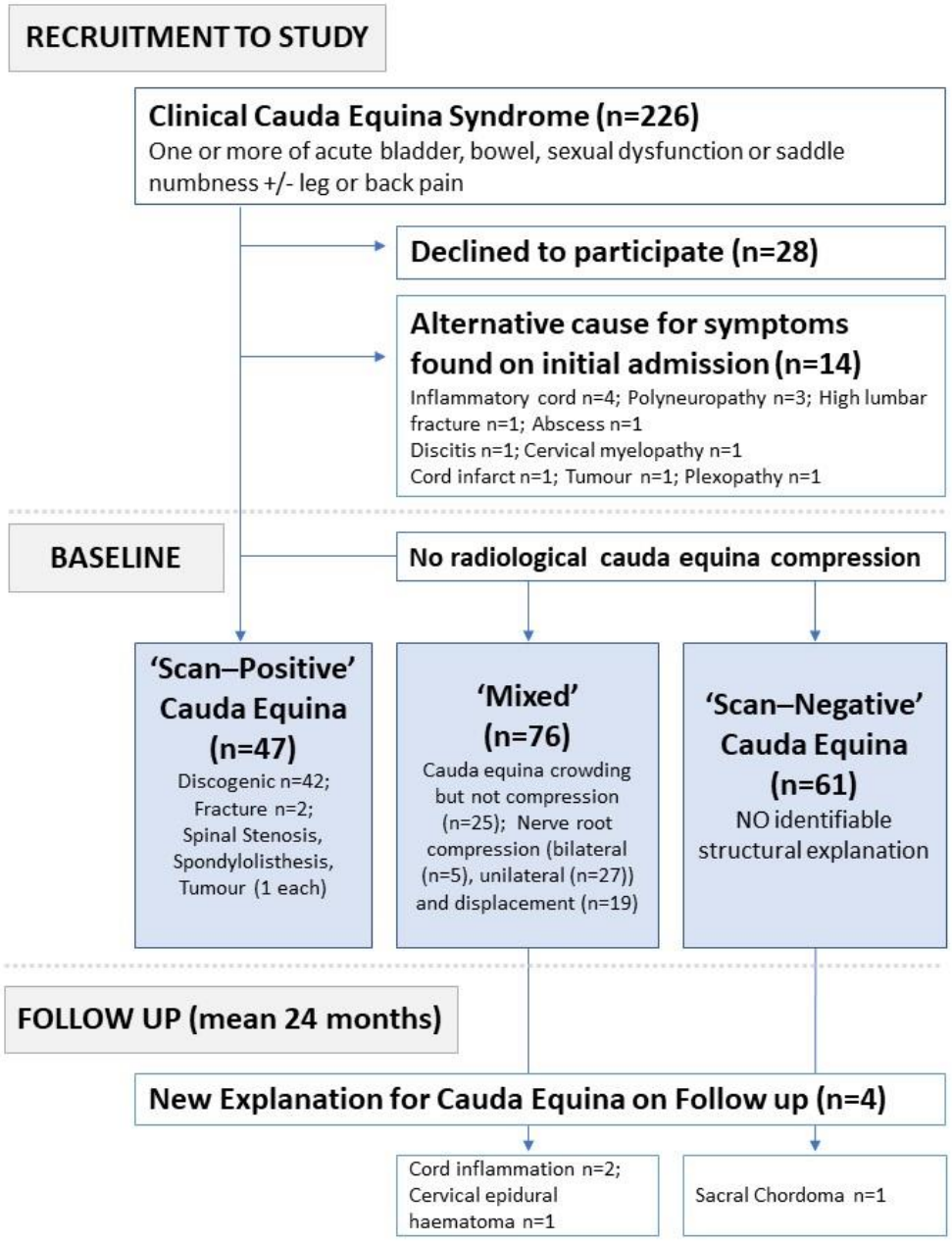

Figure TwoKey clinical features and comorbidities of 'scan-negative' cauda equina syndrome and the 'mixed' group with some nerve root compression compared to 'scan-positive' cauda equina syndrome. Note 'dose response' relationship for many variables that are known to associate with functional disorders. Relative Risk (95% confidence interval) *plot shows mean age (95% confidence intervals) relative to scan positive group as 1

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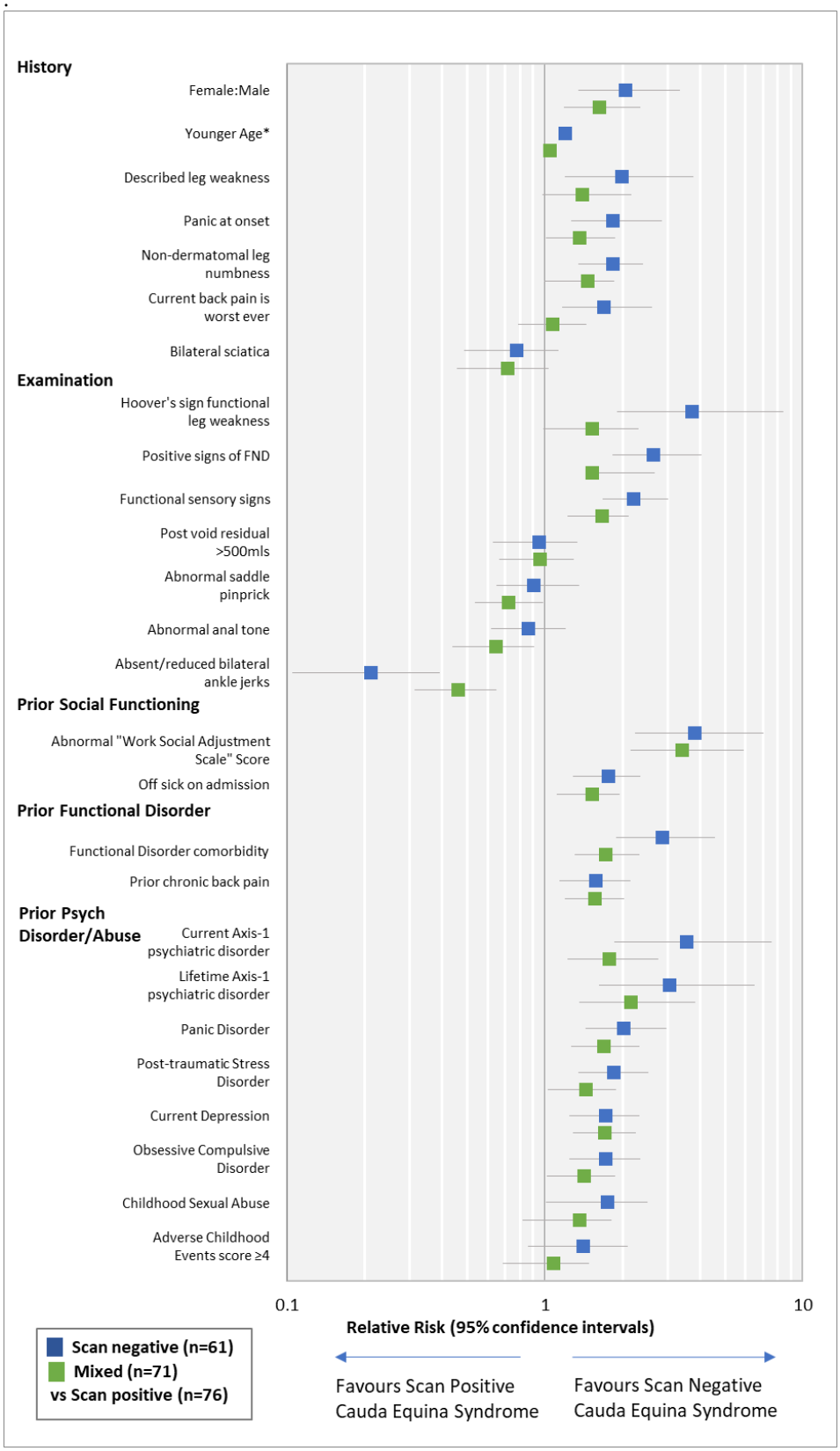

Figure Three: Proposed Mechanism of 'Scan-Negative' Cauda Equina Syndrome (CES) (adapted from Osman N and Chapple C, Nature Reviews Urology 2014 with permission)

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