The Psychiatry of Paediatric Movement Disorders

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Michelle Sarah Lorentzos

Authorship attribution statement

The literature review in this thesis contains material published in *Peall KJ, **Lorentzos MS**, Heyman I, Tijssen MAJ, Owen MJ, Dale RC, Kurian MA (2017.) A review of psychiatric co-morbidity described in genetic and immune mediated movement disorders. Neurosci Biobehav Rev. 80:23-25*

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I was the second author of this publication as I drafted sections of the paper and it is my original work. Aspects of the above publication, that were my original work, occur verbatim within this thesis.

Michelle Sarah Lorentzos   Date   28.2.19

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Russell Dale   Date   28.2.19

Acknowledgements

Abstract

I compared the rate of psychiatric comorbidity in children with Non-tic movement disorders to children with tics and TS. In addition, this PhD explores whether children with Non-tic movement disorders have elevated rates of psychiatry compared to other hospital populations, including Emergency patients and other Neurology patients, as well as a healthy community control group.

My hypothesis was that children with Non-tic movement disorders would have rates of psychiatric comorbidities that are similar to children with tics and TS.

To examine this hypothesis, I recruited children between the ages of 5 and 16 years from Neurology clinics at The Children's Hospital at Westmead, Australia , and Great Ormond Street Hospital, United Kingdom, for the following two movement disorder groups: tic movement disorder cohort (consisting of patients with tics and Tourette Syndrome, n=158) and Non-tic movement disorder cohort, (consisting of patients with all other movement disorders, n=102). An additional 137 patients were recruited for two clinical control groups: the Emergency department control cohort (n=100) and the Neurology control cohort including children with peripheral neuropathy or epilepsy (n=37). In addition, data from 10,438 British children were included as a retrospective community control. All patients were screened for psychiatric comorbidities using the Development and Wellbeing Assessment Tool (DAWBA).

My primary outcome was that the difference in the rate of psychiatric comorbidity in the Non-tic cohort (39.2%) and the Tic cohort (41.8%) was not statically significant. Importantly, the rate of psychiatric comorbidity in the Non-tic cohort was more than four times the rate of psychiatric diagnosis observed in the large retrospective community cohort (9.5%) (p<0.00001). This is the largest study to date exploring psychiatry in children with paediatric dystonia (n=66) and psychiatric comorbidities occurred in 33.3% of these patients.

In conclusion, this study recognises that children with non-tic movement disorders are just as vulnerable to psychiatric comorbidities as children with tics and TS. This new evidence may encourage

clinicians to consider screening for psychiatric comorbidities in their movement disorder patients, therefore allowing for earlier diagnosis and treatment.

Table of contents

List of tables

List of figures

List of publications

Publications

Peall KJ, Lorentzos MS, Heyman I, Tijssen MAJ, Owen MJ, Dale RC, Kurian MA (2017.) A review of psychiatric co-morbidity described in genetic and immune mediated movement disorders. Neurosci Biobehav Rev. 80:23-25

Presentations and posters

Lorentzos, M.S., Mohammad S.S., Heyman I., Baig B., Dossetor D., Marecos C., Waugh M.C,. Evans R., Burns J., Menezes M., Grattan-Smith P., Kurian M.A., Dale R.C. Psychiatric Comorbidities in Children with Dystonia. Platform presentation at the International Child Neurology Conference, Amsterdam, May 2016

Lorentzos, M.S, Heyman, I., Baig, B., Dossetor, D., Kurian, M., Marecos, C., Waugh, M.C., Evans, R., Burns, J., Menezes, M., Dale, R.C. The Psychiatry of Paediatric Movement Disorders. Presented at the International Movement Disorder Congress, Stockholm, June 2014

Lorentzos, M.S, Heyman, I., Baig, B., Dossetor, D., Kurian, M., Marecos, C., Waugh, M.C., Evans, R., Burns, J., Menezes, M., Dale, R.C. The Psychiatric Comorbidities of Australian Children with Movement Disorders. Presented at the Royal Australasian College of Physicians Annual Conference, Auckland, May 2014

Abbreviations

5HIAA	5-hydroxyindoleacetic acid
6 PTPS	6-pyruvoyltetrahydropterin synthase
ACTH	adrenocorticotropic hormone
ADCY-5	adenylate cyclase 5
ADHD	attention deficit hyperactive disorder
ARF	acute rheumatic fever
ASD	autistic spectrum disorder
ATP	adrenocorticotropic hormone
BH-4	tetrahydrobiopterin
BHC	benign hereditary chorea
CANS	childhood acute neuropsychiatric syndromes
CAPA	Child and Adolescent Psychiatric Assessment
ChIPS	Children's Interview for Psychiatric Symptoms
CHW	The Children's Hospital at Westmead
CMT	charcot marie tooth
CNS	central nervous system
CP	cerebral palsy
CSF	cerebrospinal fluid
D2R	dopamine 2 receptor
DAWBA	Development and Wellbeing Assessment
DCI	decarboxylase inhibitor
DISC IV	Diagnostic Interview Schedule for Children IV
DRD	dopa responsive dystonia
DSM	Diagnostic and Statistical Manual of Mental Disorders

DYT-5	dopa-responsive dystonia; Segawa syndrome
DYT1	early-onset generalized dystonia
DYT11	myoclonus-dystonia
EEG	electroencephalopgragh
ET	essential tremor
GA	glutaric acidura
GAS	group A streptococcus
GCH1	GTP-cyclohydrolase
GNB1	guanine nucleotide-binding proteins
GTP	guanosine triphosphate
HD	Huntington's disease
HREC	Human Research Ethics Committee
HVA	homovanillic acid
ICD	International Statistical Classification of Diseases and Related Health Problems
JH	juvenile Huntington's
JHD	juvenile Huntington's disease
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
KMT2B	lysine (K)-specific methyltransferase 2B
MAO-B	monoamine oxidase B
MHPG	3-methoxy-4-hydroxyphenylglycol
MRI	magnetic resonance imaging
NKX-2	NK2 homeobox 1
NMDAR	N-methyl-D-aspartate receptor
OCB	obsessive compulsive behaviour
OCD	obsessive compulsive disorder

OCS	obsessive compulsive symptoms
ODD	oppositional defiant disorder
OMAS	opsoclonus myoclonus ataxia syndrome
PANDAS	paediatric acute-onset neuropsychiatric disorder associated with streptococcal infection
PANS	paediatric acute-onset neuropsychiatric syndrome
PKD	paroxysmal kinesiogenic dyskinesia
PNKD	paroxysmal nonkinesiogenic dyskinesia
PRRT2	Proline-rich transmembrane protein 2
PTS	6-pyruvoyl-tetrahydropterin synthase
PTSD	post traumatic stress disorder
SC	Sydenham's chorea
SCGE	sarcoglycan epsilon
SLC2A1	solute carrier family 2, facilitated glucose transporter member 1
SLE	systemic lupus erythematous
SSA	Site Specific Approval
TBC1D24	Tre2-Bub2-Cdc16 gene
THD	tyrosine hydroxylase deficiency
TITF	thyroid transcription factor 1
TOR1A	torsin-1A
TS	Tourette syndrome
UK	United Kingdom
WD	Wilson's disease

1 Introduction

1.1 Researcher background

I am an Advanced Trainee in Paediatric Neurology with an interest in the psychiatric and psychosocial experiences of patients with neurological disorders. Prior to undertaking my medical degree at the University of Sydney, I held a public communications background and worked in health promotion with a focus on mental health and adolescents. In 2003 I managed the State-wide implementation of a youth mental health promotion program, MindMatters, as part of the Commonwealth mental health strategy and this role acquainted me with the impact of psychiatric disease in children, families and communities across New South Wales. With this perspective, I commenced clinical medicine with an interest in addressing the psychiatric vulnerabilities of children as part of their medical management.

1.2 Origin of this research project

During my neurology training I had the privilege of learning from Professor Russell Dale, who is regarded an international leader in paediatric movement disorders, neuro-immunology and the neuropsychiatry of Tourette Syndrome. This thesis emerged from our shared appreciation of the significance of psychiatry in the lives of our patients, and enthusiasm for the emerging advances in the area of neuropsychiatry.

Having undertaken my paediatric neurology training at The Children's Hospital at Westmead, a quaternary referral service for acute and chronic neurologic disease, I have met many families affected by paediatric movement disorders. Conversations with these patients, their parents and their physicians, have revealed frequent concerns regarding emotional and behavioural comorbidities, to the extent that the impact of psychiatry often outweighs the burden of the movement disorder itself. Similar observations have been tested and confirmed in the paediatric literature with respect to Tourette Syndrome, and psychiatry is well recognised in the adult diseases of Huntington's and Parkinson's. However, for paediatric movement disorders in general, the literature is sparse to non-

existent. When I met Professor Dale early in my paediatric neurology training, he identified this area as a deficiency in the medical literature. We subsequently designed a research question, and this evolved to form the basis of my higher degree.

1.3 Ethics approval

Ethics approval was obtained for the study. A National Ethics Application Form and site-specific application was completed in accordance with the National Health and Medical Research Council. Applications were also made to the Sydney Children's Hospital Human Research Ethics Committee (HREC/11/CHW/14) and Governance office (SSA/11/CHW/62) to ensure protocols were followed with the Hospital. Separate and parallel applications were submitted to the UK Health Research Authority (15/LO/0239) for the Great Ormond Street component of recruitment.

1.4 Context: Movement disorders in children

Children with movement disorders present a challenging subset of patients in paediatric neurology. These can be caused by diverse aetiologies which are divided into two main categories:

- Primary genetic disorders due to important mutations or deletions of essential brain proteins

- Secondary disorders, due to a brain insult such as encephalitis, stroke or metabolic disorders

From a physiological process, the understanding of both primary and secondary movement disorders requires appreciation of the role of the basal ganglia. The basal ganglia comprise of sub cortical nuclear masses that include the caudate nucleus, the nucleus accumbens, the putamen and the globus pallidus. These structures have long been understood as integral to the organization of movement and as such, basal ganglia disorders have traditionally been described as conditions of abnormal movements.

There are several reasons that make the question of psychiatry in movement disorders a timely and important area of research. Increasingly, the basal ganglia have become appreciated as important in

the development and integration of psychomotor processes, as well as cognition and behaviour. We have learned that rather than operating as an isolated structure, the basal ganglia and cortex interact as part of a complex cortico-striatal network to affect movement, cognition and emotion; more recent descriptions of basal ganglia disorders include dysautonomia and psychiatric disturbance. From a biochemical perspective, we have developed an understanding of the complex role of neurotransmitters and their receptors, with an awareness that neurotransmitter disruption, either metabolic or immune, may produce psychiatric symptoms in addition to movement disorders. Finally, from a molecular level, emerging genotypes have provided the basis for improved diagnosis of rare movement disorders and therefore present an opportunity to develop a growing knowledge base of psychiatric and cognitive aspects to these diseases.

1.5   Illustrative cases

The significance of this research is given relevance and applicability by considering the patients affected.

The following four de-identified cases relay the lived experiences of patients in this study to provide context for the reader.

1.5.1   Case A: Dyskinetic cerebral palsy with generalised anxiety disorder

Patient A was a 7 yo boy with dyskinetic cerebral palsy following kernicterus. He was impaired by severe chorea and has a mild intellectual disability. His mother described a boy who *"falls to the floor screaming every morning because he is so afraid to go to school. I literally have to pick up him from the floor screaming and put him on the bus, every day. It is intolerable."*

Patient A's already severe anxiety was exacerbated when the family cat died.   This has resulted in a fear of dying that is pervasive and profound. *"We have to continually reassure him that we are not dying if we get the slightest cold."*

1.5.2 Case B: tyrosine hydroxylase deficiency with comorbid separation anxiety and obsessive compulsive disorder

Case B was a 12 yo girl with genetically confirmed tyrosine hydroxylase deficiency. She experienced dystonia and bradykinesia requiring dopamine replacement multiple times daily to manage her symptoms. Patient B also had comorbid epilepsy and a mild intellectual disability for which she received support via a teacher's aide in a mainstream class. She had been diagnosed with ADHD previously and trialled on Ritalin which was found to be ineffective at regulating her attention.

Her psychiatric problems developed around the time of commencing secondary school. She became very rigid in terms of her daily routine and needed to have items 'just so' at home. She had developed intrusive thoughts concerned with 'bad things' happening to people she cared about and was particularly reliant on being with her mother. Her mother reported *"She gets up in the morning and she wants to know what I am doing. She can't enjoy her day because she is always wondering where I am. She will even deliberately not take her medicine in the morning knowing this will cause bad dystonia, so that school will call and ask me to pick her up."*

1.5.3 Case C: Glutaric aciduria type 1 with comorbid generalised anxiety

Patient C was a 5 yo girl who was diagnosed with glutaric aciduria type 1 in early infancy following neonatal seizures and encephalopathy. Her seizures were later well controlled however dystonia became her primary neurological symptom. Her intellect was within the normal range. Patient C experienced panic attacks when taken to school in the morning. *"She finds it difficult to separate. She is afraid that she or someone else will die or that she will get her limbs cut off."* Her mother describes that she becomes extremely distressed by these thoughts and "*she holds back a lot from doing and enjoying things.*" She also has specific fears about birds which became difficult to manage. *"We can't go to parks or even the beach, in case there are seagulls. The older she gets, the harder it is. People tolerate a 3yo panicking and having a melt down because of a bird, but it is harder at 5."*

1.5.4 Patient D: Paediatric acute-onset neuropsychiatric syndrome (PANS) with comorbid separation anxiety

Patient D was a 5yo boy who experienced an explosive onset of tics and anxiety following a mycoplasma infection at 4yo. He was diagnosed with PANS *"He is wanting me to be around him all the time; he will change position on the couch to be against me. He gets upset when I leave the room. He became very upset at orientation for kindergarten… he said he has worried about being kidnapped."* He could no longer participate in activities such as swimming, as simply letting go of his mother to get in to the pool had become too traumatic.

These patient descriptions demonstrate the impact of psychiatry to individual patients recruited for the study and suggest the need for efficient diagnosis and management.

2 Literature Review

2.1 Introduction

Psychiatric co morbidities have been well described in adults with movement disorders such as Huntington's disease and Wilson's disease. Attention has also been directed to behavioural disorders and psychiatric symptoms in children with tics and Tourette Syndrome. There is, however, little known about the psychiatric and behavioural problems that affect children with a broader range of movement disorders including genetic and acquired dystonias, myoclonus, chorea, stereotypies and essential tremor.

I have reviewed the literature pertaining to psychiatric comorbidities in children with movement disorders. For the very rare movement disorders consideration has been expanded to include publications evaluating adults with these conditions. I have presented these disorders by way of aetiological process, including the developmental movement disorders such as tics and stereotypies, neurotransmitter disorders, genetic movement disorders, immune mediated disorders and other.

Each diagnosis is explained and investigated for psychiatric comorbidities within this chapter. A table summarising pertinent findings is also following. (Table 2.1)

Table 2.1 Psychiatric comorbidities in movements disorders as found in the literature

Diagnosis	Movement disorder phenotype	Established psychiatric symptoms	Occasionally reported psychiatric symptoms
Developmental			
Tourette and tic disorders	Child onset, abrupt, repetitive semi-purposeful movements that typically follow a waxing and waning course	OCD, ADHD, other anxieties, rage attacks, depression	Psychosis
Stereotypy	Repetitive, rhythmic movements (such as hand flapping) that tend to occur during excitement of stress	ADHD, OCD, anxiety, behavioural disorders	
Neurotransmitter disorders			
Dopa responsive dystonia (DYT 5)	Child onset progressive dystonia responsive to dopamine	Not established	Depression, anxiety, OCD, ADHD
Tyrosine hydroxylase deficiency	Type A: Dystonia and hypokinetic rigidity Type B: Neonatal encephalopathy	Not established	
6 PTPS deficiency	Child onset dystonia and parkinsonism if untreated	Not established	OCD, depression, panic attacks
Genetic disorders			
DYT1 (TOR1A)	Child onset focal dystonia	Not established	Depression
KMT2B dystonia	Child onset progressive dystonia	Not established	ADHD, anxiety
TBC1D24 dystonia	Dystonia and myoclonus	Not established	Not reported
Myoclonus dystonia (SCGE)	Child onset myoclonus and focal dystonia	OCD	Anxiety, depression
GNB1 dystonia	Child onset dystonia	Not established	Not reported
Glutaric aciduria type 1	Dystonia and choreoathetosis following encephalopathy	Nil specific to Glutaric aciduria (emotional/behavioural issues increased in organic acidaemias generally	Not reported
Paroxysmal kinesiogenic dystonia (PRRT2)	Paroxysmal dyskinesia precipitated by movement	Not established	1 case of anxiety reported
Benign hereditary chorea	Early onset hypotonia and motor delay followed by chorea	Not established	ADHD, OCD
Wilson's disease	Parkinsonian symptoms with dystonia, tremor and bradykinesia	Personality change, mood disorders, psychosis	
Juvenile Huntington's disease	Bradykinesia, tremor rigidity	Mood disorders, anxiety and psychosis	

Immune			
PANDAS/PANS	Acute onset tics following infection (with streptococcal for PANDAS, less specific for PANS)	Anxiety, OCD, emotional lability, rage attacks	Eating disorders, psychosis
Sydenham's chorea	Acute onset chorea	OCD, anxiety, depression, ADHD	
Antiphospholipid chorea	Acute or gradual onset chorea that may be associated with other signs of systemic autoimmune disease	Not established Psychiatry observed with APL antibodies but not studied in chorea patients	
Basal ganglia encephalitis (Dopamine 2 Receptor Antibody positive)	Acute neuropsychiatric syndrome with dystonia or chorea and encephalopathy	Not established	Agitation, emotional lability and anxiety described
Rasmussen encephalitis	Usually associated with epilepsia partialis continua however hemidystonia or hemiathetosis has been described	Not established	Not reported
Opsoclonus myoclonus syndrome	Classical triad of myoclonus, opsoclonus and ataxia (or parts of this) with severe neurodegeneration if untreated	Rage attacks, ODD, OCB, ADHD, depression	
Multifactorial			
Dystonic cerebral palsy	Non-progressive dystonia with distribution depending on the region of cerebral injury	Not established Studies of CP in general (not dystonic) show increased rates of emotional and behavioural issues	Emotional and attention difficulties

ADHD; attention deficit hyperactivity disorder, OCD; obsessive compulsive disorder, OCB; obsessive compulsive behaviours, PANDAS; Paediatric acute neuropsychiatric disorder associated with streptococcal, PANS; Paediatric acute neuropsychiatric syndrome

2.2   Developmental movement disorders

2.2.1   Tourette Syndrome

2.2.1.1   Disease overview

Tics are sudden, rapid, abrupt, stereotyped movements that occur mostly in a paediatric population. Tourette syndrome (TS), also known as Tourette's disorder or Gilles de la Tourette syndrome, is a chronic tic disorder in which patients exhibit both verbal and motor tics for at least 12 months.

Simple tics and transient tic disorders are far more prevalent than TS. (Cavanna and Termine, 2012)

TS is one of the most studied movement disorders in terms of psychiatric comorbidities, and presents an interesting prototype for analyzing the emotional components of movement pathways. Tics merge the traditional paradigms that occupy the movement disorder discourse, because the phenomenon blurs the distinction between voluntary and involuntary; tics are generally suppressible for a period of time at the cost of some discomfort to the patient, similar to trying to overcome an urge to scratch an itch (Cavanna and Rickards, 2013). The 'urge' sensation is an important part of the 'tic' and tics are increasingly considered a 'sensori-motor' phenomenon.

The prevalence of tics in childhood is estimated to be between 6 and 21% (Kurlan et al., 2002). A small percentage of children with tics fulfil criteria for TS. The incidence of TS in the general population is estimated to be between 0.5 and 2.3% (Cavanna and Rickards, 2013, Schlander et al., 2011) with most experts considering 0.5% being the most accurate incidence.

Tics primarily occur in males at a rate of four to seven times the rate of females (Comings and Comings, 1985, Ghanizadeh and Mosallaei, 2009). There is literature to suggest that this trend decreases with age, and may even reverse, with TS occurring more frequently in females, in the adults who continue to have tics above the age of 30 years (Schlander et al., 2011).

2.2.1.2   Pathogenesis in brief

The cause of TS is not entirely understood and is thought to be multifactorial with hereditary and

environmental components (State, 2010). Family studies have shown that parents of children with TS are more likely to have tics or related comorbidities than adults in the general population (Matthews, 1988). Twin studies have shown concordance rates of 50-77% in monozygotic twins as compared with only 10-23% of dizygotic twins (Price et al., 1985)

The pathophysiology implicated in tics relates to disorders of neurotransmitters, particularly dopamine, involve disruption of pathways between the basal ganglia and the frontal cortical circuits (Rizzo et al., 2013, Tamara, 2013, Eddy et al., 2012, Mol Debes, 2013). There is also evidence of other neurotransmitter dysfunction including histamine and glutamate.

2.2.1.3 Clinical course and diagnosis

Tics are diagnosed on the basis of history and clinical review. Tourette syndrome can be diagnosed when a patient fulfils the following criteria as set out in DSM IV (Betancourt et al., 2003).

1. the patient has both multiple motor tics (ie rapid eye blinking) *and* one or more vocal tics (ie throat clearing),

2. the tics have been present for at least one year

3. the tics began before he or she was 18 years of age.

4. the symptoms are not due to another pathology or medication (ie viral encephalitis or amphetamines)

Tics typically begin in early primary school years (Cavanna and Rickards, 2013) and follow a waxing and waning course.

Approximately one quarter of people with TS find their tics nearly completely resolve as they approach adulthood, with a further one half reporting significant improvements (Erenberg et al., 1987).

The comorbid symptoms of ADHD often occur before the onset of tics, and symptoms such as inattention often persist beyond resolution of the tics. The OCD symptoms typically have their onset when the tics are most severe however compulsions can be the presenting symptoms (Mol Debes,

2013).

Interestingly, a longitudinal study of children with OCD conducted over nine years found that tics were actually protective against persistence of obsessive-compulsive diagnoses (Bloch et al., 2009).

2.2.1.4   Movement disorder phenotype

Tics are motor or vocal actions that are typically brief, repetitive without volition, although can often be temporarily suppressed. They tend to be preceded by a premonitory sensation and follow a waxing and waning course (Tamara, 2013). Exacerbating factors include stress, excitement and inter-current illness. The most common tics include eye-blinking, facial grimacing, and throat-clearing, however tics can be complex and consist of multiple motions. Whilst the general population often associates TS with compulsive swearing (coprolalia), this is an uncommon vocal tic. In a study of 250 cases receiving medical input for Tourette syndrome, which in itself is small subgroup of children with tics, only one third were found to have coprolalia (Comings and Comings, 1985). Other studies found coprolalia in ~4% of TS patients, mostly in adolescents and adults with TS. (McMahon et al., 1992)

2.2.1.5   Summary of associated psychiatric features

The rates of psychiatric comorbidity are high in tics and TS. The comorbidities include ADHD, ODD, OCD, anxiety (including separation anxiety, overanxious disorder, simple phobia, social phobia, agoraphobia) rage attacks, panic attacks and mood disorders (including mania, major depression) (Mol Debes, 2013, Pollak et al., 2009, Roessner et al., 2007, Gaze et al., 2006, Denckla, 2006, Termine et al., 2006, Kurlan et al., 2002, Ghanizadeh and Mosallaei, 2009). Pervasive developmental disorder, autism and Asperger Syndrome are more common in people with Tourette syndrome (Kerbeshian et al., 2009). The most commonly studied comorbidities are discussed in more detail below.

ADHD and tics are commonly occurring comorbidities (Groth et al., 2017a). Tics occur in about 10% of children with ADHD (Mol Debes, 2013) (Rizzo et al., 2013). Between 55 and 80% of children with TS also satisfy a diagnosis of ADHD (Cavanna and Rickards, 2013, Kerbeshian et al., 2009, Freeman, 2007).

Symptoms of tics and ADHD can overlap and the inattention and impulsivity of ADHD will often precede tics by 2-3 years (Rizzo et al., 2013). Children with ADHD tend to be diagnosed with TS earlier than children without the comorbidity. Recognition of comorbid ADHD is imperative, as it is the factor most related to impairment and poorer psychosocial outcome in children with Tourette (Rizzo et al., 2013, Eddy et al., 2012, Gorman et al., 2010). Children with ADHD are more likely to receive pharmacotherapy than children with TS alone (Debes et al., 2009).

The role of ADHD in prediciting outcome has been so well described that studies have taken to explore neuroanatomical similarities of 'Tourette and ADHD phenotypes' and 'ADHD alone', finding neuroanatomical commonalities that are not present in children with 'TS alone' (Denckla, 2006). The behavioural components of ADHD and the involuntary movements of Tourette can both be considered problems of inhibition. It is proposed that they share common pathways involving fronto-striatal structures (Mol Debes, 2013). It could be argued that tics and ADHD occur together by chance given that both conditions affect boys at a particular stage in development, however even when analysing lifetime risk in adult population, the lifetime incidence of tics was three times as common in adults who had ADHD compared with controls (Spencer et al., 2001).

There are familial studies supporting a hereditary nature to both TS and ADHD, with relatives of patients with either or both of these conditions being more likely to have TS and/or ADHD (Freeman, 2007, O'Rourke et al., 2011). One study of 239 probands and 692 first degree relatives found that for patients with TS only, the increased rate of ADHD in relatives was explained by its comorbidity to TS, in that there was not a higher rate of ADHD only; instead the ADHD + TS rate was increased. This suggests that the genetic component of TS also creates a predisposition to ADHD, rather than the conditions representing one genotype (O'Rourke et al., 2011).

For children with TS, comorbid ADHD is a risk factor for other comorbidities including OCD, oppositional-defiant disorder, depression, anger control, sleep issues, and learning disability (Rizzo et al., 2014, Freeman, 2007, Roessner et al., 2007). Whilst stimulant treatment for ADHD can exacerbate

existing tics when administered at high doses, the increased incidence of tics in children with ADHD is independent of stimulant use (Spencer et al., 2001).

Approximately half of all people with TS have some features of obsessive-compulsive behaviour with most observers describing approximately 40% incidence (Como et al., 2005, Lebowitz et al., 2012).

Parallels can be drawn between compulsions in OCD and the described 'need to tic.' The two disorders are both associated with dysfunction of the basal ganglia and it has been theorised that both conditions may be manifestations of a single pathophysiology with varying complexities (Cummings and Frankel, 1985). According to some authors, the main distinction between a tic and a compulsion is the complexity of the urge. Compulsions result from more complex feelings of anxiety whereas tics involve a different urge; 'I need to tic'. The urge associated with the tic tends to be more sensory, like an itch, than the psychological process of the compulsion (Cavanna and Rickards, 2013).

The types of compulsions in Tourette-OCD are considered to be distinct from 'idiopathic' OCD. In Tourette-OCD, there is a commonly expressed need to have things 'just right', with patients feeling a compulsion to repeat an action over and over until it is 'just so'. Symmetry and counting are often involved in Tourette-OCD (Cavanna and Rickards, 2013, Neal and Cavanna, 2013, Gomes de Alvarenga et al., 2012) (Como et al., 2005). By contrast contamination obsessive-compulsions are uncommon in Tourette-OCD unlike 'idiopathic' OCD. Comorbid OCD is associated with more severe tics (Lebowitz et al., 2012) and higher rates of anxiety, depression, ADHD, conduct disorder, and poorer overall functioning (Lebowitz et al., 2012, Wanderer et al., 2012, Gorman et al., 2010, Gomes de Alvarenga et al., 2012).

Depression has been reported to be increased in patients with Tourette syndrome (Robertson, 2006) with one study finding that nearly two thirds of patients satisfied diagnosis for major depression at least once in their lifetime (Gorman et al., 2010). Risk factors for depression include more severe tics and comorbid OCD (Cavanna and Rickards, 2013). In another study of 57 people with TS, 40% had engaged in self-injurious behaviour.

The association of depression and TS is not reported as consistently as the ADHD and OCD comorbidities, and some authors have found no difference in the risk of depressive symptoms between TS groups and controls (Termine et al., 2006, Eddy et al., 2013). Anxieties other than OCD, such as generalized anxiety disorder and separation anxiety, are not uncommon in Tourettes. OCD itself is a risk factor for other anxiety comorbidities (State, 2010, Lebowitz et al., 2012).

One study of 399 patients with TS found comorbid schizophrenia in 10 people (2%). Six of these children had their onset of positive psychotic symptoms before the age of 13 years and the mean age of diagnosis for schizophrenia was 8.2 years. In all but one patient, the onset of tics preceded the onset of psychosis (Kerbeshian et al., 2009). Psychosis is therefore considered marginally elevated in TS.

2.2.1.6 Treatment and prognosis

Most patients with tics will not require medication. There is increasing interest in the use of Comprehensive Behavioural Intervention for Tics (CBIT) and Habit Reversal Therapy (HRT), as they are non-pharmacological and have a good evidence base (Woods et al., 2000). Severe and persistent tics and TS can be managed with several pharmacological approaches. First line therapies are alpha agonists, such as clonidine, that act by inhibiting norepinephrine release and turnover (Coffey et al., 2000). It is worth noting that clonidine can result in sedation. Second line therapies for tics are typically anti-psychotics such as risperidone and aripiprazole, although these have a worse side effect profile. Other agents such as topirimate, tetrabenazine, benzodiazepines and baclofen can occasionally be helpful. Deep brain stimulation has been used for severe refractory tics in adulthood. Botox can also be used for localised severe tics such as 'whiplash' neck tics.

Stimulants such as methylphenidate remain a potential therapy for comorbid ADHD and have been shown not to aggravate tics except in very high doses (Rizzo et al., 2013). Stimulants do not improve comorbid obsessive-compulsive disorder and treatments such as selective serotonin reuptake

inhibitors and cognitive behaviour therapy may be incorporated into a therapeutic model when OCD is present.

The common refrain from the TS literature is that psychiatric and behavioral comorbidities are common and should be actively screened in patients with tic disorders and Tourette syndrome. As the comorbidities are often a greater cause of impairment than the tics themselves, the psychiatric and behavioural issues may present the initial treatment priority (Tamara, 2013).

2.2.2 Stereotypies

2.2.2.1 Disease overview

Stereotypies are rhythmic, repetitive movements that tend to occur in moments of stress, excitement and fatigue (Muthugovindan and Singer, 2009). They are estimated to occur in about 20-25% of neurotypical infants, and almost half of the population diagnosed with autistic spectrum disorder. (Singer, 2009, Peter et al., 2017).

2.2.2.2 Pathogenesis in brief

The cause of stereotypies is not well understood. The fact that they occur in higher rates of children with developmental disorders suggests some disruption of the neurological pathways (Muthugovindan and Singer, 2009). Animal studies have suggested that neurotransmitter abnormalities are contributory (Peter et al., 2017) and there is evidence to suggest there is a genetic cause, as 25% to 39% of typically developing children with stereotypies have a positive family history (Harris et al., 2008, Oakley et al., 2015).

2.2.2.3 Clinical course and diagnosis

Motor stereotypies are usually noted before the age of 3 years. They are observed frequently in children with developmental disorders such as autistic spectrum disorder, however they also occur in neurotypical children (Muthugovindan and Singer, 2009). They can be primary (physiological) or

secondary (pathological) to conditions such autistic spectrum disorder (ASD) (Singer, 2009, Peter et al., 2017).

2.2.2.4 Movement disorder phenotype

Stereotypies may present as any of a broad range of repetitive movements. Some of the common examples are hand shaking, arm flapping, body rocking and head nodding (Singer, 2011). They have been divided into two subtypes including common (such as hair twisting) and complex (hand flapping). Primary stereotypies are far more prevalent, and complex stereotypies are often associated with developmental disorders (Singer, 2009).

2.2.2.5 Spectrum of psychiatric symptoms

The prevalence of psychiatric symptoms is high in children with stereotypies and has been noted as greater than 90% in one study (Oakley et al., 2015). Rates of anxiety, ADHD, OCD, tics/TS and behavioural problems are all elevated amongst children with stereotypies (Oakley et al., 2015, Cardona et al., 2016). Another large study of 100 typically developing children with stereotypy found that nearly half have psychiatric comorbidities. ADHD was present in 30%, tics occurred in 18% and obsessive-compulsive behaviours/obsessive-compulsive disorder was noted in 10% (Harris et al., 2008).

2.2.2.6 Treatment and prognosis

Treatment is not generally required for children with stereotypies. Parental and patient education as to the diagnosis is often sufficient. Parents are often keen to know whether the stereotypies will cease over time and studies to date demonstrate that most stereotypies persist into late childhood and adulthood, however the children often become cognitively aware of their stereotypies and may do them in private, or reduce their visibility as they get older (Harris et al., 2008, Oakley et al., 2015).

In cases where stereotypies are causing detriment, a cognitive behaviour therapy approach has been applied with some success. This requires willing participation on the part of the child and is therefore

not practical for children with intellectual disorder or moderate to severe ASD. It is an unfortunate paradox that the children who prove most refractory to psychological therapies are often those with the most burdensome stereotypies (Peter et al., 2017, Miller et al., 2006).

There are no well-established pharmacological therapies for children with stereotypies. However, for children with self-injurious stereotypies, such as repetitive head banging in ASD, there is an argument to trial medication. Both anti psychotics and selective serotonin re-uptake inhibitors (SSRIs) have been studied in this context. They have generally been found to be ineffective, however limited benefits have been observed with haloperidol, risperidone, olanzapine and some SSRIs (Doyle and McDougle, 2012, Peter et al., 2017).

2.3   Neurotransmitter disorders
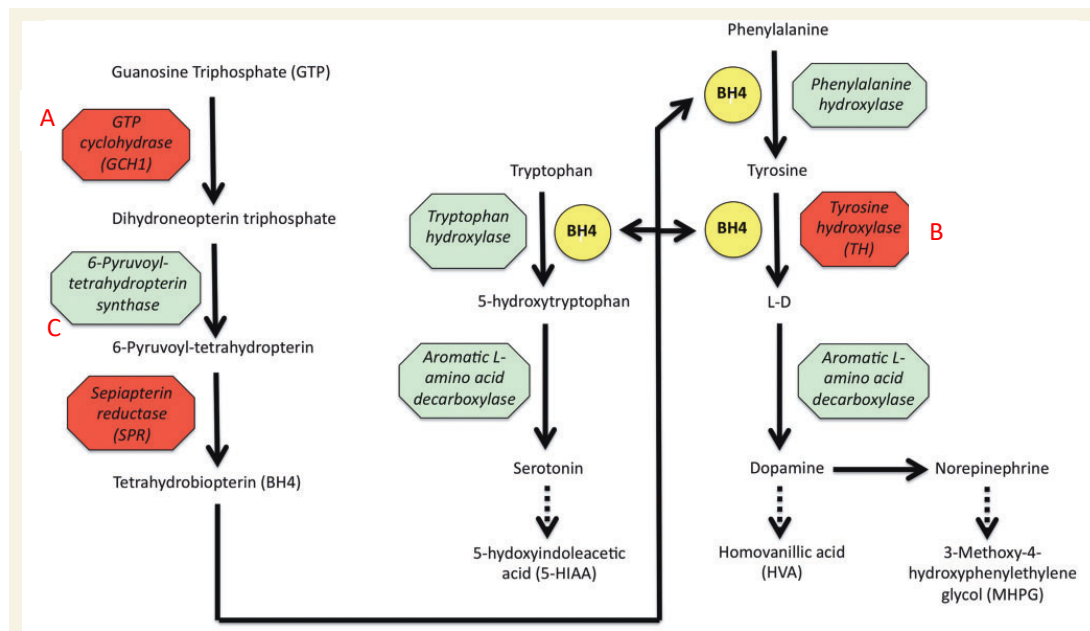
Figure 2.1 Pathways of neurotransmitter synthesis from (Charlesworth et al., 2013) p 2029

Figure 2.1 above is useful in demonstrating the pathways of neurotransmitter synthesis relevant in the section. Point A represents GTP-cyclohydrolase (GCH1), a gene essential for dopamine synthesis. Mutations in GCH1 lead to dopa responsive dystonia. Point B represents tyrosine hydroxylase (TH), Mutations in this gene are responsible for tyrosine hydroxylase deficiency (THD). Point C represents 6 pyruvoyl-tetrahydropterin-synthase (6PTPS), and deficiency in this enzyme prevents formation of tetrahydrobiopterin, an early precursor of tyrosine which later gets converted to dopamine.

2.3.1   Dopa responsive dystonia

2.3.1.1   Disease overview

The dopa responsive dystonias are a group of inherited dystonias that share the feature of marked improvement when treated with exogenous levodopa (Wijemanne and Jankovic, 2015).

2.3.1.2 Pathogenesis in brief

There are several subtypes of DRD, however the most common form is DYT5 (Segawa disease), which is caused by a heterozygous mutation of GTP-cyclohydrolase (GCH1). GCH1 is required in the early stages of neurotransmitter synthesis, (see Figure 2.1 above) and mutation of GCH1 results in a depletion of dopamine, an essential neurotransmitter in movement regulation. More than 100 different mutations in GCH1 have been identified (Asmus and Gasser, 2010).

2.3.1.3 Clinical course and diagnosis

Whilst the course is variable, DRD typically begins in childhood with lower limb dystonia as the presenting complaint. Generalised dystonia can develop over time. There is a strong diurnal fluctuation and this pattern (good in the morning, worse in the afternoon, and improvement after sleep) should prompt consideration of the DRD.

Diagnosis can usually be obtained on the basis of clinical findings followed by a trial of levodopa. Improvement in this setting is strongly in favour of DRD, and the response to L-Dopa is typically complete (in contrast to other dystonic syndromes, where there may be a less dramatic effect). Ancillary investigations include abnormal CSF neurotransmitters and genetic investigation (Wijemanne and Jankovic, 2015). However, testing for mutations in the implicated genes will yield a diagnosis in only 80% of cases and variable penetrance means that asymptomatic patients with a mutation in GCH1 may not always develop the clinical syndrome. (Asmus and Gasser, 2010).

2.3.1.4 Movement disorder phenotype

The early stage of DRD is characterised by focal dystonia in a single lower limb, typically resulting in pes equinovarus, therefore impairing mobility. The dystonia generalises slowly over the following decade, (Segawa et al., 2003) resulting in varying severity; some patients become wheelchair dependant, whereas other cases remain very mild. In addition to dystonia, patients may experience parkinsonism, postural tremor and myoclonus (Asmus and Gasser, 2010, Segawa et al., 2003, Muller, 2009).

2.3.1.5 Spectrum of psychiatric symptoms

Whilst the motor entity of DRD has been widely reported, only limited studies have explored associated psychiatric symptoms. Depression has been the most commonly described psychological symptom, (Theuns et al., 2012, Timmers et al., 2017) and anxiety and obsessive compulsive disorder have been occasionally reported. A study of a large Belgian autosomal dominant DRD family found that out of 12 patients, depression was present in 4, anxiety in 8, and obsessive-compulsive disorder was reported in 3 (Theuns et al., 2012). A study of 34 DRD patients found depression requiring treatment in 6, and severe mood swings in 12. (Trender-Gerhard et al., 2009). However, one study of 23 patients found that depression and anxiety were not more common than in healthy controls (Bruggemann et al., 2014).

A recent study focusing on non-motor symptoms in DRD evaluated 28 patients from 10 families (18 adults and 10 children), and compared this with matched controls. Patients with DRD were more than twice as likely to experience a lifetime psychiatric disorder (61% vs 29%), and mood and anxiety disorders were most common. ADHD and body dysmorphic disorder were occasionally seen (Timmers et al., 2017).

2.3.1.6 Treatment and prognosis

DRD responds well to levodopa and this is usually prescribed in combination with a decarboxylase inhibitor (DCI). The improvement is typically dramatic and immediate, however residual dystonia can persist in some individuals (Wijemanne and Jankovic, 2015). Tolerance can occur necessitating doses to be increased with duration of use (Trender-Gerhard et al., 2009), however patients typically remain highly responsive to L-Dopa.

1.1.1. Tyrosine hydroxylase deficiency

2.3.1.7 Disease overview

Tyrosine hydroxylase deficiency (THD) is a rare disease with fewer than 70 patients described to date (Willemsen et al., 2010, Yeung et al., 2011, Leuzzi et al., 2017) An autosomal recessive disorder, the

phenotype results from a disruption to the synthesis of dopamine, a neurotransmitter essential for movement regulation. (Kurian et al., 2011)

2.3.1.8   Pathogenesis in brief

Dopamine, norepinephrine and epinephrine are all catecholamines produced primarily in the brain and adrenal medulla (Willemsen et al., 2010). Tyrosine hydroxylase is the rate-limiting enzyme required for the biosynthesis of catecholamines (Asmus and Gasser, 2010), specifically the conversion of L tyrosine to L-dihydroxyphenylalanine (L-Dopa) (see Figure 2.1 above). L-dihydroxyphenylalanine is then the precursor for dopamine. It has been observed in mice, that absence of tyrosine hydroxylase is lethal. In humans, the disease state tends to occur with tyrosine hydroxylase activities of 10-20% of normal (Asmus and Gasser, 2010).

Resulting from an autosomal recessive mutation on chromosome 11p.15.5 (Willemsen et al., 2010), THD is characterised by a disturbance of neurotransmitter synthesis that results in a deficiency dopamine (Yeung et al., 2011).

A large review of THD patients (n=36) described 24 different TH mutations in the promoter sequence, and exons 3, 5-14 and intron 11 of the TH gene. A total of 100 mutated alleles were reported in the 36 individuals. Five of these involved mutations caused protein truncation, whereas others were missense mutations. There have been no patients homozygous for 2 truncating alleles observed, suggesting that an absolute absence of tyrosine hydroxylase is incompatible with life (Willemsen et al., 2010).

Studies refute a clear genotype-phenotype correlation. A recent paper describing 12 Chinese patients with THD found that those with a previously reported genotype clinically varied from those already described in the literature (Yeung et al., 2011). Willemsen's study described clinical features of 36 patients and categorised them into the two main subtypes of THD, described in detail below. They also found that patients with the same mutations could develop different subtypes (Willemsen et al., 2010).

2.3.1.9 Clinical course and diagnosis

Several distinct phenotypes have been described, including a severe early onset encephalopathy, a progressive dystonia responsive to dopa therapy (Grattan-Smith et al., 2002, Leuzzi et al., 2017, Willemsen et al., 2010) and a phenotype with myoclonus and dystonia (Gardiner et al., 2012). The motor component of each type is discussed in further detail in the following section.

Deficiency of the TH enzyme results in decreased levels of the downstream products beyond the enzyme deficiency, specifically decreased metabolites homovanillic acid (HVA) and 3-methoxy- 4 hydroxyphenylethylene (MHPG) (see figure 2.1). Diagnosis can therefore be confirmed by reduced amounts of these metabolites in CSF (Kurian et al., 2011). The parallel metabolic pathway for serotonin synthesis does not involve tyrosine hydroxylase as an enzyme, enabling normal levels of this pathway's end metabolite (5HIAA) to form. As such, CSF of patients with THD demonstrates decreased concentrations of HVA and MHPG with decreased HVA/5HIAA ratios (Willemsen et al., 2010). Raised serum prolactin caused by lack of suppression from dopamine deficiency has been noted but is an inconsistent finding (Yeung et al., 2011).

The clinical picture of the dystonic subtype may be confused with Dopa Responsive Dystonia (Segawa Syndrome). An important diagnostic difference is that CSF biopterin and neopterin will be decreased in DRD and normal in Tyrosine hydroxylase deficiency (Yeung et al., 2011).

Imaging is normal in the majority of patients with THD (Willemsen et al., 2010, Yeung et al., 2011). Abnormalities that are occasionally observed tend to be nonspecific, mild white matter changes and increased volume of extra cerebral CSF has also been reported. Despite the pathophysiology being associated with the basal ganglia, there have been no structural changes in the basal ganglia noted on MR (Willemsen et al., 2010).

Movement disorder phenotype

Progressive hypokinetic rigid syndrome with dystonia (Type A):

These patients tend to have uncomplicated antenatal and neonatal period. Whilst the initial cases described onset between 2 to 5 years, it has since been found that many have clinical signs during the first 2 years of life. Initial abnormalities are noted in 1 lower limb, then both lower limbs then the upper limbs. Manifestations include bradykinesia, rigidity and hypokinesia (Willemsen et al., 2010). Patients become hypokinetic and rigid followed by a dystonia of the limbs as described above. Parents may report abnormal posturing and regression of the child's walking ability (Willemsen et al., 2010). Untreated the dystonia can be significantly debilitating with patients becoming wheelchair bound or bedridden (Yeung et al., 2011). Other parkinsonism features are common including slurred speech and mask face. Oculogyric crisis has been observed. Diurnal fluctuation of dystonia is often noted (Willemsen et al., 2010) and in some cases has not been observed until as late as 10 years (Yeung et al., 2011).

Severe early onset encephalopathy (Type B):

With onset as early as a few weeks of age, (Willemsen et al., 2010) the signs of this subtype may be misattributed to antenatal causes and mislabelled as cerebral palsy. Abnormalities are usually noted before 6 months of age (Leuzzi et al., 2017, Yeung et al., 2011). Unlike the dystonic subtype described above, limb dystonia is uncommon in the encephalopathy form, and when dystonia does occur, it is a late sign. Common presentations include truncal hypotonia, global developmental delay, hypokinesia, oculogyric crisis and pyramidal tract signs with weakness and hyper-reflexia (Grattan-Smith et al., 2002, Yeung et al., 2011).

Syndrome of myoclonus and dystonia due to THD:

This has recently been described in one set of siblings (Gardiner et al., 2012) with compound heterozygosity of a point mutation in the promoter region of the TH gene and a novel nonsynonymous substitution in exon 12. The three siblings (2 female and 1 male) had unremarkable births and were noted to have poor head control at 6 months. Developmental delay persisted with the children unable

to walk or sit. Myoclonic jerks were noted in limbs, neck and trunk. Dystonia was also present, and most prominent in upper limbs and the face. There was no diurnal fluctuation (Gardiner et al., 2012).

2.3.1.10 Summary of associated psychiatric symptoms

Whilst cognitive deficit has been well described, especially in the encephalopathic subtype (Type B) (Willemsen et al., 2010, Giovanniello et al., 2012) psychiatric manifestations in THD have not been explored.

2.3.1.11 Treatment and prognosis

The neurological deficit from THD is expected to be permanent in the absence of treatment. L-Dopa is the primary pharmacotherapy, usually administered with a peripheral L-Dopa decarboxylase inhibitor to prevent loss of dopa in the in the circulation (Willemsen et al., 2010). Alternatives or additions to L-Dopa include a monoamine oxidase B (MAO-B) inhibitor, to prevent breakdown of dopamine or an anticholinergic, such as trihexyphenidyl (Singer H. S., 2010).

Doses are initially conservative as tolerance for L-Dopa is low in THD patients (Singer H. S., 2010), especially in the encephalopathic subtype (Willemsen, Verbeek et al. 2010). Doses may need to start as low as <0.5mg/kg /day, and titrate gradually over weeks or months. Side effect such as dyskinesia may be observed. (Willemsen et al., 2010).

Response to treatment is a point of difference for Type A and Type B patients. Outcomes for Type A patients are generally very good with approximately 88% able to walk independently. Type B patients have a less promising prognosis both in terms of motor and cognition (Willemsen et al., 2010). The siblings with THD associated with myoclonus and dystonia all responded well to L Dopa therapy (Carecchio et al., 2017).

It is suggested that the motor problems are improved more by therapy than the cognitive deficits (Giovanniello et al., 2012), and that earlier treatment results in a more favourable prognosis (Willemsen et al., 2010).

2.3.2 6-pyruvoyl-tetrahdropterin synthase deficiency

2.3.2.1 Disease overview

6-pyruvoyl-tetrahdropterin synthase (6PTPS) deficiency is a rare form of hyperphenylalaninemia resulting from tetrahydrobiopterin (BH4) deficiency (see Figure 2.1) and this in turn causes reduction in neurotransmitters, resulting in dystonia and other movement disorders. Untreated, hyperphenylalaninemia leads to encephalopathy, disability and other system disorders.

2.3.2.2 Pathogenesis in brief

6PTPS is an autosomal recessive disorder caused by mutations in in the PTS gene, which is located on chromosome 11q23.1, and codes for the enzyme 6 pyruvoyl tetrahdropterin synthase (Shintaku and Ohwada, 2013). 6 pyruvoyl tetrahydrobiopterin is required for the production of tyrosine hydroxylase and tryptophan hydroxylase and these enzymes form part of the pathway for the production of dopamine and serotonin. In addition, BH4 is important in the forming of phenylalanine hydroxylase and nitric oxidise synthase so that deficiency results accumulation of phenylalanine at toxic levels (Kao et al., 2004, Shintaku et al., 2000).

2.3.2.3 Clinical course and diagnosis

Untreated, 6PTPS results in parkinsonism and dystonia, axial hypotonia, microcephaly and intellectual disability (Kao et al., 2004) and hormonal abnormalities such as delayed or partial puberty. Respiratory failure and cardiac arrhythmias have also been reported (Roze et al., 2006).

6PTPS deficiency can be diagnosed from genetic mutation analyses of the PTS gene. Newborn screening can diagnose hyperphenylalaninemia and BH4 deficiency can be differentiated from PKU by analysis of the dihydropteridine reductase activity on the blood spot. Other supportive investigations include deranged neurotransmitters in CSF (although these may be normal in mild cases) and elevated urine pterins (Shintaku and Ohwada, 2013).

2.3.2.4 Movement disorder phenotype

The movement disorder phenotype is consistent with other dopamine deficient disorders and includes dystonia and choreo-athetosis. Less commonly bradykinesia, tremor and myoclonus have been described (Ye et al., 2013).

2.3.2.5 Spectrum of psychiatric symptoms

A study of 18 patients with 6PTPS found psychiatric disturbances in 2, specifically obsessive-compulsive disorder and depression with panic attacks and it was postulated that these may be manifestations of serotonergic disturbance (Leuzzi et al., 2010).

2.3.2.6 Treatment and prognosis

Treatment involves exogenous provision of BH4, thereby enabling the degradation of phenylalanine. And reducing neurotoxicity. BH4 does not cross the blood brain barrier and therefore additional treatment with 5-hydroxytryptophan and levo-dopa are also essential to moderate the symptoms resulting from dopamine deficiency (Shintaku and Ohwada, 2013).

2.4 Genetic disorders

2.4.1 Torsion dystonia or early onset dystonia (DYT1)

2.4.1.1 Disease overview

DYT1 was considered the most common genetic cause of early onset dystonia, although it is possible KMT2B is a more common dystonia outside of Ashkenazi Jewish populations. DYT1 typically presents in childhood or adolescence although it can occur in early adulthood. The primary symptom is an isolated dystonia of an arm or leg and the clinical spectrum is broad, however, the classical course is a slowly progressive dystonia. The prevalence of DYT1 is particularly common in the Ashkenazi Jew population (Bressman, 2004, Segawa and Nomura, 2014).

2.4.1.2   Pathogenesis in brief

DYT1 is caused by an autosomal dominant mutation of the TOR1A gene, which is located on chromosome 9 and includes 5 exons. The typical mutation is a 3 base pair deletion resulting in the loss of glutamic acid (Ozelius et al., 1998, Segawa and Nomura, 2014, Granata and Warner, 2010).

2.4.1.3   Clinical course and diagnosis

The classical presenting scenario is a previously well child who presents with a history of arm or leg dystonia most notable during an action, such as writing or walking. There may also be an associated postural tremor. A positive family history of dystonia makes the diagnosis more likely, but the absence of heredity does not exclude the diagnosis. The neurological exam and neuroimaging should be otherwise normal (Bressman et al., 2000, Ozelius and Lubarr, 1993).

Over time the dystonia tends to become more persistent and may progress to a fixed deformity and generalise to other limbs.

2.4.1.4   Movement disorder phenotype

The dystonia is generally focal or segmental and most noted during activity. Commonly, when a lower limb is affected, there may be involuntary muscle contraction causing ankle inversion and impairing gait. Upper limb dystonia with involuntary flexion and rotation of the wrist, is another typical pattern. Less frequently trunk or cervical dystonia may be the presenting symptom (Opal et al., 2002). Dystonia associated with DYT1 usually persists with age, and becomes more constant and generalised (Bressman, 2004) .

2.4.1.5   Spectrum of associated psychiatric symptoms

The literature reports increased rates of major depression in both symptomatic and asymptomatic carriers of TOR1A (Heiman et al., 2004). A single study of 13 patients with DYT1 and 13 healthy controls found an increase in risk taking behaviour in the dystonia patients (Heiman et al., 2004).

2.4.1.6 Treatment and prognosis

Symptomatic treatment options include anticholinergics, benzodiazepines and baclofen, which may be beneficial (Albanese et al., 2011, Albanese et al., 2006). A trial of levodopa may be indicated during the diagnostic process however a marked improvement makes DYT1 unlikely and suggests a diagnosis of dopa responsive dystonia. Deep brain stimulation has proved efficacious in severe cases (Panov et al., 2013, Miri et al., 2014).

2.4.2 Myoclonus dystonia

2.4.2.1 Disease overview

Myoclonus dystonia (DYT11) is a rare syndrome characterised by sudden "lightening like" jerks that tend to occur in the neck and upper limbs. There is often an associated focal dystonia, and symptoms have been found to be responsive to alcohol in some patients (Asmus et al., 2005b). Familial cases or sporadic cases are associated with mutation on the epsilon sarcoglycan gene (SGCE) (Rachad et al., 2017, Charlesworth et al., 2013).

2.4.2.2 Pathogenesis in brief

More than 50 mutations in SGCE have been described in myoclonus dystonia (Charlesworth et al., 2013). In familial cases of myoclonus dystonia an autosomal dominant loss-of-function mutation in the SCGE gene on chromosome 7q21-22 has been implicated as the most common cause, occurring in up to 50% of myoclonus-dystonia patients (Asmus et al., 2005b, Kim et al., 2017, Rachad et al., 2017). Variable penetrance has been observed, and a maternal inheritance with reduced expression of myoclonus dystonia (asymptomatic) is often noted. Most patients with a familial form of myoclonus dystonia inherit their mutation from their father (Asmus et al., 2005b).

2.4.2.3 Clinical course and diagnosis

The onset usually occurs in early childhood (Asmus et al., 2005b, Peall et al., 2016) and the clinical course is thought to be non-progressive (Rachad et al., 2017). Diagnosis is typically made on the

characteristic distribution of myoclonus and dystonia. Radiological investigations should be normal. The myoclonus is subcortical and therefore an EEG should not show cortical epileptic discharges during myoclonic attacks. In terms of genetic testing, finding an SCGE may confirm diagnosis of myoclonus dystonia.

2.4.2.4   Movement disorder phenotype

Myoclonus of the upper limbs is the dominant feature, and is usually localised to the upper limbs, neck or head, and primarily involves the proximal upper limbs or the neck. Cervical or upper limb dystonia frequently accompanies the myoclonus. Lower limb myoclonus and dystonia can also occur (Asmus et al., 2005b).

2.4.2.5   Spectrum of psychiatric symptoms

Psychiatric symptoms have been established as frequent comorbidities in myoclonus dystonia (Kim et al., 2017, Peall et al., 2016). Obsessive compulsive disorder and generalised anxiety have been noted to occur in higher rates than in the general population (Hess et al., 2007, Peall et al., 2013), and depression has been observed in 30% of myoclonus dystonia patients (Hess et al., 2007, Weissbach et al., 2013). Patients with myoclonus dystonia are also more likely to be affected by alcohol dependence, which can be partly explained by the alcohol responsive nature of the myoclonus (Charlesworth et al., 2013). In some cases, patients have reported psychiatric symptoms prior to the onset of myoclonus (Weissbach et al., 2013). There has been some disagreement in the literature as to whether the psychiatric symptoms in myoclonus dystonia are more severe in patients with SGCE mutations or whether the genotype is irrelevant to severity (Kim et al., 2017, Peall et al., 2016).

2.4.2.6   Treatment and prognosis

Generally, a non-progressive condition, some patients find temporary relief from GABA-ergic agents such as benzodiazepines. However, as with alcohol, benzodiazepines are prone to abuse in patients that find them beneficial (Charlesworth et al., 2013). There have been limited reports of levodopa

proving effective, and some authors advocate a levodopa trial (Luciano et al., 2009). Treatments for cortical myoclonus are not useful. (Roze et al., 2008, Charlesworth et al., 2013). Symptomatic therapy may be required for impairing psychiatric symptoms.

2.4.3   Benign hereditary chorea

2.4.3.1   Disease overview

Benign hereditary chorea (BHC) is a rare form of chorea that presents in childhood and is very slowly progressive, or stable, into adulthood (Gras et al., 2012, Peall and Kurian, 2015). It is associated with mutations in the NKX2-1 gene or ADCY5 genes (Chen et al., 2015, Mencacci et al., 2015, Peall et al., 2014).

2.4.3.2   Pathogenesis in brief

BHC has been attributed to autosomal dominant mutations in the NKX2.1 gene (also known as TITF-1) located on chromosome 14q13 (Kumar and Dixon, 2014, Peall et al., 2014). Studies of BHC suggest that approximately 60% of cases are de novo (Gras et al., 2012, Peall et al., 2014). Mutations in ADCY5 on chromosome 3 have been identified in familial and sporadic cases with child-onset chorea when they have been NKX2.1 negative chorea (Mencacci et al., 2015).

2.4.3.3   Clinical course and diagnosis

Patients typically present with hypotonia and motor delay within infancy. Chorea occurs within the first decade. Myoclonus and dystonia can also occur (Gras et al., 2012). NKX2.1 is required for genesis of the brain, lungs and thyroid and haplo-insufficiency of this gene results in respiratory dysfunction such as recurrent infections or infant respiratory distress, thyroid disease and movement disorder. Various combinations of these disease processes have been described including a classical triad with all 3 systems affected. In a study of 10 patients with confirmed NKX2.1 related chorea, only 3 demonstrated the triad of chorea, pulmonary insufficiency and hypothyroidism (Peall et al., 2014).

2.4.3.4   Movement disorder phenotype

Chorea generally starts within the first decade. Myoclonus may be associated and dystonia, tremor, motor tics and ataxia have been reported (Gras et al., 2012) (Peall et al., 2014). The ADCY5 chorea is sometimes more severe than NKX2.1 chorea and is exacerbated by stress or action (Mencacci et al., 2015). Commonly, patients with ADCY5 mutation experience dyskinesias that interrupt sleep or occur during drowsiness thereby preventing sleep initiation or increased movements upon waking. (Chang et al., 2016).

2.4.3.5   Spectrum of psychiatric symptoms

There is limited data on psychiatry in BHC. One study of 28 patients showed ADHD in a quarter of the cohort. Symptoms of impairing hyperactivity and aggression have been reported in other studies (Kumar and Dixon, 2014). Peall et al studied 10 children and found one to have severe obsessive compulsive disorder (Peall et al., 2014). Psychosis has been described (Glik et al., 2008).

Intellectual disability is not uncommon, occurring in 20 of the 28 BHC patients in the study by Gras et al (Gras et al., 2012). Other studies have found intellectual ability to be within the normal range (Peall et al., 2014). There are similar studies suggesting a range of cognitive abilities in the ADCY5 cohort with intellectual delay and normal development reported (Chang et al., 2016, Mencacci et al., 2015). The psychiatric profile of ADCY5 has not been investigated to date.

2.4.3.6   Treatment and prognosis

In NKX2.1 associated BHC the chorea has been described as remaining stable or improving into adulthood, however accompanying myoclonus or dystonia may continue to impair (Gras et al., 2012). In ADCY5 some studies have suggested the chorea may worsen in adulthood.

Tetrabenazine has been shown to be effective in reducing chorea and improving motor function in some studies of patients with NKX2.1 (Gras et al., 2012), and Levodopa has also provided benefit (Asmus et al., 2005a). Improvement has been reported from treatment with clonazepam and trihexyphenidyl. Sodium valproate and sulpiride have been tried with limited efficacy (Peall et al.,

2014). There is limited information of treatment for ADCY5 chorea, although tetrabenazine may be useful.

2.4.4 Paroxysmal dyskinesia

2.4.4.1 Disease overview

Paroxysmal dyskinesia is the collective name for episodic movement disorders, with the most common being paroxysmal kinesiogenic dyskinesia (PKD). PKD is estimated to affect approximately 1 in 150,000 people (Bruno et al., 2004).

In PKD, the episodes of dyskinesia are precipitated by a voluntary movement (Charlesworth et al., 2013, Gardiner et al., 2015). Other subtypes of paroxysmal dyskinesia include paroxysmal non-kinesiogenic dyskinesia and exercise induced dyskinesia (Bruno et al., 2004, Gardiner et al., 2015).

2.4.4.2 Pathogenesis in brief

Paroxysmal kinesiogenic dyskinesia has been linked to mutations in PRRT2 (located on chromosome 16p11.2). This gene is thought to be important in the release of neurotransmitters at the synapse. Other genetic associations include SLC2A1, which is associated with exercise induced dystonia, and PNKD which is associated with paroxysmal non-kinesiogenic dystonia (Ebrahimi-Fakhari et al., 2015). Genetic mutations are found in approximately half of all families with paroxysmal dyskinesia (Gardiner et al., 2015).

2.4.4.3 Clinical course and diagnosis

PKD usually presents within the first 2 decades of life (Bruno et al., 2004). Patients experience brief and frequent attacks of dyskinesia triggered by voluntary and usually sudden movements, such as moving from sitting to standing (Gardiner et al., 2015). Consciousness is preserved during episodes and the neurological examination should be otherwise normal. There is often a warning or 'aura' immediately prior to the onset of dyskinesia which may consist of paraesthesia to the affected limb (Charlesworth et al., 2013).

2.4.4.4 Movement disorder phenotype

The dyskinesic episodes in paroxysmal dyskinesia may be dystonia, chorea or athetosis, however the movements must resolve between events (hence paroxysmal). Events are brief and usually last 5 to 10 seconds, although they may last up to 5 minutes in exceptional situations. In PKD, events are triggered by voluntary movement (Becker et al., 2013).

2.4.4.5 Spectrum of psychiatric symptoms

Psychiatric symptoms have not been well described in conjunction with the paroxysmal dyskinesias. There is one case report describing comorbid anxiety in a man with diagnosed and treated PKD (Kunii et al., 2017).

2.4.4.6 Treatment and prognosis

PKD responds well to antiepileptic medications such as carbamazepine and topiramate. Prognosis is excellent (Bruno et al., 2004). Given the paroxysmal nature, and response to anti-epileptics, some neurologists consider PKD more akin to epilepsy than a movement disorder.

2.4.5 Glutaric aciduria type 1

2.4.5.1 Disease overview

Glutaric aciduria type 1 (GA 1) is an organic aciduria that manifests as infant onset dystonia, usually as the result of a metabolic encephalopathy. It is a rare disorder with an estimated prevalence of 1 in 100,000 newborns (Lindner et al., 2004, Kolker et al., 2011).

2.4.5.2 Pathogenesis in brief

Glutaric aciduria is an autosomal recessive disorder caused be a deficiency in glutaryl-CoA dehydrogenase. The gene is located on chromosome 19p13.2 and more than 200 mutations have been described. The deficiency of glutaryl-CoA dehydrogenase impairs the catabolism of L-lysine, L-

hydroxylysine and L- tryptophan and results in elevated glutaric aciduria (Goodman et al., 1998, Boy et al., 2017).

2.4.5.3 Clinical course and diagnosis

Without treatment, approximately 90% of patients with GA1 develop neurological disease within the first 3 years of life. This typically occurs following an encephalopathic crisis precipitated by an infantile illness or stress. The sequelae of this crisis may include acute striatal injury, manifesting as dystonia and choreoathetosis (Kolker et al., 2011). Seizures may occur during periods of encephalopathy. Macrocephaly, subdural haemorrhages and subarachnoid cysts are also associated with GA 1 (Boy et al., 2017). Less commonly, a more insidious course has been reported with neurological symptoms evolving in the absence of an encephalopathic crisis (Boy et al., 2017).

In some countries including Australia, GA1 is included in the newborn screening program. This involves testing the metabolite glutarylcarnitine in the dried blood spot. Where there is a clinical suspicious of GA1, quantitative analysis of organic acid is preferred for diagnosis. Mutation analysis of GHDH gene in fibroblasts or leukocytes confirms the diagnosis (Kolker et al., 2011).

2.4.5.4 Movement disorder phenotype

As outlined above, the hallmark movement dystonia of GA1 is dystonia, which may be superimposed on truncal hypotonia. Athetosis may also be present, and later in life, parkinsonism may be observed (Kolker et al., 2011).

It is not uncommon for patients to be misdiagnosed as has having dystonic or athetoid cerebral palsy, particularly in the absence of a careful history and metabolic investigations.

2.4.5.5 Spectrum of psychiatric symptoms

There has been limited research in to the psychiatric manifestations of GA1, however some studies have considered psychiatric symptoms in organic acidaemias in general. One study found that patients

with organic acidaemias are 2.5 times as likely to have an emotional or behavioural problem than neuro-developmentally normal children (Jamiolkowski et al., 2016).

2.4.5.6 Treatment and prognosis

When treatment is initiated in the newborn period, patients typically remain asymptomatic (Kolker et al., 2011, Boy et al., 2017). This treatment includes adherence to a low lysine diet and carnitine supplementation as well as emergency treatment during crises (Boy et al., 2017). Supportive treatment includes benzodiazepines, baclofen and anticholinergic drugs to treat dystonia as well as other pharmacological and allied health treatments for symptoms, as indicated (Kolker et al., 2011).

2.4.6 Wilson's Disease

2.4.6.1 Disease overview

Wilson's disease (WD) is an inherited disorder that results in copper accumulation and therefore hepatic, haematological, neurological and psychiatric dysfunction (Bandmann et al., 2015, Medici et al., 2007).

2.4.6.2 Pathogenesis in brief

An autosomal recessive mutation of the WD gene (OMIM 277900), which codes for a copper transporting ATP-ase, ATP7B, has been identified as the cause (Bandmann et al., 2015). This ATP-ase is essential in excreting copper from the liver for elimination. More than 200 mutations have been identified (Ferenci, 2005).

2.4.6.3 Clinical course and diagnosis

A disorder of copper accumulation, WD commonly presents anytime from adolescence to the fourth decade of life although it can occur at any age. Presenting symptoms vary, with psychiatric, neurological and hepatic symptoms all seen at first presentation. The disease may be multi-system (in about 25% of patients) or affect one system only (Medici et al., 2007, Bandmann et al., 2015).

Neurologic dysfunction typically presents as a parkinsonian type with bradykinesia, dystonia, tremor and incoordination. Hepatic symptoms may vary from mild hepatomegaly, to acute hepatitis and fulminant liver failure. Haemolysis is relatively common. Endocrine, cardiac and musculoskeletal conditions are less frequently observed (Medici et al., 2007). Psychiatric symptoms will be discussed in greater detail in section 2.4.6.5.

Diagnosis is achieved by observing typical clinical features (such as the pathopneumonic Kaiser Fleisher rings in the cornea) and biochemical testing. The latter may include serum free copper and caeruloplasmin levels, and 24-hour urinary copper excretion. Imaging may demonstrate copper deposition within the basal ganglia on MRI Brain. In some patients, hepatic copper concentrations may be required. Mutation analysis is complex given the large number of mutations known to cause Wilson's disease and therefore not often practical, although exome sequencing makes this more practical recently (Ferenci, 2005). Screening of family members following a positive index case is advised.

2.4.6.4   Movement disorder phenotype

Up to one third of patients with neurological Wilson's have dystonia which may be generalised or focal (Svetel et al., 2001), and dysarthria with slow tongue movements is typical in Wilson's. Bradykinesia and other parkinsonian symptoms are commonly observed. Patients with WD may also present with tremor and classically this is a flapping tremor, however intention tremors and rest tremors may also be seen (Bandmann et al., 2015).

2.4.6.5   Spectrum of psychiatric symptoms

Psychiatric manifestations of Wilson's have been well documented, and 30-40% of patients with WD have a psychiatric symptom at the time of diagnosis (Zimbrean and Schilsky, 2014).

A large study retrospectively analysing 195 patients with WD found psychiatric dysfunction in half the cases (Dening and Berrios, 1989). Twenty percent of all the cases required psychiatric input prior the diagnosis of Wilson's disease suggesting the symptoms occurred early in the disease process. Similar

rates have been reported elsewhere (Zimbrean and Schilsky, 2014). Specific psychiatric problems identified in studies include personality and behavioural change, and mood disorders such as major depression (Carta et al., 2012, Portala et al., 2000). Psychosis is less common (Dening and Berrios, 1989) however there are reports that bipolar disorder occurs more frequently in WD than in the general population (Woerwag-Mehta et al., 2011, Carta et al., 2012). Mania was the presenting symptom of WD in a single case report (Machado et al., 2008).

2.4.6.6   Treatment and prognosis

Treatment options for Wilson's disease include chelation therapies such as D-penicillamine or Trientine and therapies aimed at reducing uptake such as zinc salts (Medici et al., 2007). A paradoxical worsening of neurological symptoms following initiation of chelation has been well documented. The mechanism of this worsening is unclear but it is thought to be due to toxic effects of free copper and it has been suggested that starting chelation at lower doses may decrease the likelihood of this iatrogenic deterioration (Bandmann et al., 2015).

Liver transplant is a definitive treatment for hepatic WD however it is generally contraindicated, or at the very least controversial, in patients with neuropsychiatric syndromes. Many patients with neuropsychiatric Wilson's will require symptomatic treatment of their dystonia or psychiatric condition (Bandmann et al., 2015).

2.4.7   Juvenile Huntington's disease

2.4.7.1   Disease overview

Huntington's disease is a rare neurodegenerative disease caused by an inherited expansion of the HTT gene. Juvenile Huntington's (JH) applies when the onset is before 21 years. Expansions of HTT gene increase with each generation of inheritance and larger repeats generally lead to an earlier onset of symptoms. Triplet repeat sizes of more than 60 repeats typically result in Juvenile Huntington's disease (Monrad and Renaud, 2013).

2.4.7.2   Pathogenesis in brief

JH is caused by an autosomal dominant inheritance by way of large triplet repeat expansions at one end of the Huntington gene. Expansion leads to neurotoxicity and degeneration of striatal neurons (Zuccato et al., 2010).

2.4.7.3   Clinical course and diagnosis

By definition, JH is clinically recognisable by 21 years of age. Children and young people with JH typically present with parkinsonian symptoms including bradykinesia and dystonia although other movement disorders may occur (Gatto et al., 2016). Other symptoms of neurological dysfunction such as behaviour change and cognitive decline are common, and seizures may be observed (Wojaczynska-Stanek et al., 2006). Imaging demonstrates bilateral atrophy of the basal ganglia however this may normal in the early stages. The diagnosis is confirmed by genetic diagnosis (Monrad and Renaud, 2013).

2.4.7.4   Movement Disorder phenotype

Whilst chorea is a common presenting disorder in adults with Huntington's, children tend to present with bradykinesia, tremor and rigidity (Monrad and Renaud, 2013) and postural instability and dysdiadochokinesia may be present. Involuntary movements such as chorea and myoclonus also may be observed (Gatto et al., 2016).

2.4.7.5   Spectrum of psychiatric symptoms

Psychiatric disorders have been widely described in Huntington's, albeit not specific to JH, with rates of lifetime diagnosis being approximately 60% (Vassos et al., 2008). Mood disorders are the most common psychiatric feature, and psychotic and anxiety disorders are also seen frequently (Craufurd et al., 2001, Vassos et al., 2008). Drug and alcohol addiction have been associated, and apathy and loss of energy are regarded as common associated symptoms (Craufurd et al., 2001).

There is limited literature pertaining to psychiatry in the JH cohort specifically. One study examined data from 29 cases of JH and 9/29 had a psychiatric symptom as their presenting feature. For 3 patients this symptom was depression, for 3 it was behavioural change (such as psychotic or obsessive-compulsive behaviour), and for 3 it was addiction. During the course of follow up (mean 11 ±6 years) 79% demonstrated behavioural disturbance (Ribai et al., 2007).

An interesting clinical question is whether the gene responsible for HD could independently lead to psychiatric problems even in the absence of causing classic motor JH symptoms. Whilst psychiatric symptoms can precede the onset of motor symptoms, one study comparing the rates of psychiatric diagnosis in pre-symptomatic carriers found they were not significantly different from matched controls (Julien et al., 2007).

2.4.7.6 Treatment and prognosis

Treatment of JH is supportive. Movement disorder medications such as tetrabenazine may be indicated for chorea. Anti-psychotics such as risperidone and quetiapine may be beneficial for psychosis and anxiety. Anti-depressants are frequently required and antiepileptic medication may be indicated for seizures (Sung et al., 2018).

2.4.8 Emerging genotypes in paediatric movement disorders

During the time that this study has been in progress, several new genes for movement disorders were discovered and tested in our cohort of patients, including KMT2B, TBC1D24 and GNB1. The literature on each is limited, however overviews have been provided below.

2.4.8.1 KMT2B

KMT2B was first described in 2016 as a cause of child onset progressive generalised dystonia (DYT28) (Meyer et al., 2017, Zech et al., 2016). In a review of 38 patients with KMT2B dystonia, 4 patients had psychiatric comorbidities including ADHD and anxiety. (Gorman et al., 2018)

2.4.8.2 TBC1D24

Autosomal recessive inheritance of TBC1D24 has been associated with several epilepsy phenotypes however it has more recently been found in patients with myoclonus and dystonia. Disability and intellectual impairment are commonly described, however psychiatry has not been established (Ngoh et al., 2017).

2.4.8.3 GNB1

Neuro-disability has recently been attributed to mutations in the guanine nucleotide binding protein, beta 1 (GNB1) gene and dystonia may form part of the phenotype. Hypotonia and seizures are other features described however psychiatric comorbidities have not been studied. (Steinrucke et al., 2016)

2.5 Immune mediated disorders

2.5.1 Sydenham's chorea

2.5.1.1 Disease overview

Sydenham's chorea (SC), historically known as St Vitus Dance, is a movement disorder defined by new onset chorea following infection with beta haemolytic Group A Streptococcus, and is the brain component of the multi-system autoimmune disorder Rheumatic fever. It is broadly accepted that Sydenham's chorea can result in chorea and other motor dysfunction as well as neuropsychiatric symptoms (Ridel et al., 2010, Teixeira et al., 2007b, Moore, 1996). Sydenham's chorea is a sign of acute rheumatic fever (ARF), and its presence in isolation can satisfy the major criteria.

According to the World Health Organisation, the annual incidence of acute rheumatic fever is 0.5 per 100,000 school aged children (Batzloff, 2004). Current estimates are that between 10-30% of children with ARF are affected by Sydenham's chorea (Ben-Pazi et al., 2011).

2.5.1.2   Pathogenesis in brief

Sydenham's chorea is an autoimmune disorder resulting from an immunological phenomenon known has molecular mimicry. It is hypothesised that antibodies that previously formed in response to Group A Streptococcus react with structures in the basal ganglia and disrupt regulation of movement, by affecting basal ganglia cortical-circuits (Church, 2002, Stollerman, 1997) (Dale et al., 2004, Ridel et al., 2010), although the exact immunopathogenesis is not clear.

2.5.1.3   Clinical course and diagnosis

Sydenham's chorea is classically non-degenerative and self-limiting. Time to resolution is thought to be between 3 months and 2 years, however chronic cases have been described (Walker, 2010). Cardoso reported persistent chorea in 50% (n= 32) of Sydenham's chorea patients at 2 years. (Cardoso et al., 1999).

Sydenham's chorea is a clinical diagnosis. It is characterised by purposeless, involuntary and unpredictable movements that may affect the limbs, trunk and face. According to the revised Jones criteria for ARF, diagnosis requires two major criteria (chorea, carditis, polyarthritis, erythema marginatum, subcutaneous nodules) or one major and two minor criteria (fever, arthralgia, elevated acute phase reactants, prolonged PR interval on electrocardiogram). For most clinical presentations, the diagnosis also requires evidence of a recent streptococcal infection via culture, rapid antigen or antibody titres (Special Writing Group of the Committee on Rheumatic Fever, 1992).

In the case of chorea however, which can present several months after the initial streptococcal infection, it is accepted that evidence of recent infection may be difficult to demonstrate and is not considered necessary. Diagnosis should involve reasonable exclusion of other causes of chorea such as toxins, systemic lupus erythematosus and Wilson's (Burke and Chang, 2014).

2.5.1.4   Movement disorder phenotype

The hallmark of Sydenham's chorea is the acute onset of involuntary, jerky, non-rhythmic and

unpredictable movements. Other motor signs such as hypotonia, dysarthria and slowing of saccades may accompany the chorea (Teixeira et al., 2007a, Stollerman, 1997).

2.5.1.5 Summary of associated psychiatric symptoms

Sydenham's chorea has been associated with several neuropsychiatric conditions including obsessive-compulsive disorder, generalised anxiety disorder, depression, attention deficit hyperactivity disorder and psychosis (Ben-Pazi et al., 2011, Fibbe et al., 2012).

In 1993, Swedo assessed 11 children with Sydenham's chorea via clinical assessments and structured interviews. Of these children, 81% were found to have obsessive-compulsive symptoms and 36% satisfied the DSM criteria for diagnosis of obsessive-compulsive disorder (Swedo, 1993). This association has been reiterated across several studies undertaken during the two decades that followed.

In one study examining 30 patients with Sydenham's chorea, a sudden onset of obsessive -compulsive symptoms was noted in 21 patients (70%). Five patients (16.7%) had symptoms that were severe enough to satisfy diagnosis for obsessive-compulsive disorder (Asbahr, 1998).

In a separate cohort of 20 patients with acute rheumatic fever without chorea there were no cases of obsessive-compulsive symptoms in that group (Asbahr, 1998). This supports the hypothesis that direct immunological effect on the brain, as opposed to other systemic involvement, influences emotionality in these patients. However, this hypothesis was refuted in the study of 59 ARF patients performed by Hounie et al. In this study the rates for obsessive-compulsive disorder were higher in patients with and without Sydenham's chorea, than in control patients from an orthopaedic clinic. Results between the chorea and non-chorea group were not statistically different (Hounie, 2004).

A further study assessed 72 Sydenham's chorea patients, and found symptoms consistent with OCD in 38.4% (Asbahr et al., 2005). Maia's 2005 paper involved 156 patients including 56 with Sydenham's chorea, 50 with ARF and no chorea, and 50 healthy controls. Maia reported obsessive- compulsive behaviours in 19% of Sydenham's patients and 11% fulfilled criteria for obsessive-compulsive disorder.

Rates in healthy controls were 11% and 4% respectively (Maia, 2005). Dale et al reported OCD rates of 10% in their study of 20 patients with Sydenham's chorea (Dale et al., 2004).

An important issue is the distinction between Sydenham's chorea and PANDAS; patients with Sydenham's chorea by definition have chorea and they generally do not have tics. Patients diagnosed with PANDAS often have tics and should not have chorea. Both disorders are associated with increased rates of OCD however de Alvarenga and Floresi have demonstrated the obsessive-compulsive symptoms differ (de Alvarenga et al., 2009).

It is worth noting that Asbahr and Garvey's review of 73 children with Sydenham's chorea found that none of these children had tics, although more than one third met DSMIV criteria for OCD. The obsessive-compulsive symptoms in Sydenham's chorea were also different from the profile of OCD in children with tics, and more in keeping with children who have primary OCD (de Alvarenga et al., 2009).

Three studies referred to anxiety disorders in Sydenham's chorea patients. Dale et al found generalized anxiety disorder in 25% of the Sydenham's chorea patients (n=20) (Dale et al., 2004). One study of 28 children with Sydenham's chorea found increased rates of anxiety (panic, separation, phobic, avoidant) during and after the onset of movement disorder. Interestingly, there was also an increased rate of anxiety compared to the general population before the onset of the movement disorder in these children, a question of neuropsychiatric susceptibility in children who develop neurological sequelae from streptococcal infection (Ridel et al., 2010).

The literature provides some evidence of an association with Sydenham's chorea and depression. Ridel found that patients with Sydenham's chorea have a premorbid prevalence of depression of 13%. During the acute episode of chorea this percentage increases to 31% and falls only slightly to 27% after the chorea resolves (Ridel et al., 2010). Dale reported increased rates of major depression (20 % of n= 20) (Dale et al., 2004).

In contrast to these trends, Teixeira assessed 32 patients with Sydenham's chorea and 32 aged and gender matched asymptomatic controls. This study found that depressive symptoms were not increased in the Sydenham's chorea group. (Teixeira et al., 2007a).

There are two case reports detailing psychosis following Sydenham's chorea. One described a 13yo diagnosed with Sydenham's chorea who developed acute comorbid visual and auditory hallucinations along with anxiety. The patient was commenced on penicillin and risperidone and the psychotic symptoms resolved within 2 weeks. The movement disorder and anxiety settled after a period of 3 months (Teixeira et al., 2007b).

The second case report demonstrated a chronic and refractory psychiatric course commencing at five years of age with chorea. More than twenty years later, the patient developed auditory hallucinations and visions of God, and she was hospitalised ten years later due to delusions of persecution (Casanova, 1995). Such isolated case studies cannot account for all the confounding factors that may predispose an individual to psychosis, and may oversimplify the apparent causality.

However, given the accepted association between psychosis and other chorea disorders such as Huntington's disease, it seems reasonable to suggest that antibody disruption to the basal ganglia may in turn lead to psychotic symptoms in patients with preceding Sydenham's chorea (Teixeira et al., 2007b). One further retrospective study has been performed. Medical histories were reviewed for 600 psychotic and 369 nonpsychotic subjects. There were significantly more past cases of ARF in psychotic patients than non-psychotic (Wilcox, 1986).

Elevated rates of ADHD have been reported in Sydenham's chorea. Maia described rates of 30.4% in patients with Sydenham's compared to 8% of healthy controls. ADHD was more frequent in patients whose chorea was persistent (Maia, 2005). Ridel found that rates of ADHD were not only elevated (37%) in patients with Sydenham's Chorea but that the prevalence was higher than the general population prior to, and following resolution of chorea. This again raised the question of biological susceptibility (Ridel et al., 2010).

2.5.1.6 Treatment and prognosis

Currently treatment of Sydenham's chorea remains aligned with general treatment of acute rheumatic fever, along with symptomatic therapy for neuropsychiatric symptoms. Patients diagnosed with Sydenham's chorea should be treated with 10 days of penicillin (Walker, 2010). Secondary prophylaxis with penicillin (or erythromycin in the case of penicillin allergy) is recommended for cardiac protection. Efficacy of ongoing penicillin treatment in preventing relapses of Sydenham's chorea remains controversial (Walker, 2010). The duration of prophylaxis is dependent of several factors including age of patient, evidence of cardiac disease and time lapsed since last event (Dajani, 1995).

The literature recommends symptomatic therapy aimed at controlling the chorea and associated psychiatric or behavioural symptoms. For the chorea, dopamine receptor antagonists such as haloperidol are effective but if used, should be commenced slowly due to adverse effects. One study demonstrated that patients with Sydenham's chorea have an increased rate of neuroleptic side effects (Teixeira et al., 2003). Valproate, carbamazepine and benzodiazepines remain alternatives (Walker, 2010).

Immunotherapy has been gaining increasing evidence, with steroids and IVIG each showing promising results in small studies (Fusco and Spagnoli, 2018). Barash treated five children with Sydenham's chorea with a short course of steroids resulting in marked improvement within 24-48 hours and resolution by 12 days post treatment without relapse (Barash et al., 2005). A double-blind control study of children with Sydenham's chorea, randomized children to receive 2 mg/kg/day corticosteroid for 4 weeks, followed by a gradual discontinuation (n=22), or placebo (n=15). The steroid group showed a greater improvement in symptoms at one week and a shorter time to remission. No statistical difference was observed with regards to rate of relapse (Paz, 2006). More recently other forms of immunomodulation have been recommended for the treatment of Sydenham's chorea. A

randomised study of 18 patients with SC found that patients treated with IVIG or plasma exchange received greater clinical improvement than patients treated with oral steroids (Garvey et al., 2005).

The outcome of psychiatric symptoms is less well understood. In Swedo's study demonstrating increased rates of OCD in Sydenham chorea patients, the cohort improved by 18 months so that none of them fulfilled criteria for OCD by this stage (Swedo, 1993). Of the 70% of Sydenham's chorea patients who developed obsessive compulsive symptoms in Asbahr's study, 28.6% still had obsessive compulsive symptoms at 5-6 months (Asbahr, 1998). Asbahr went on to publish a series of 4 cases the following year and amongst that cohort of 4 adolescents, symptoms of OCD occurred simultaneously with the first episode of chorea in 2 patients. All 4 patients had recurring chorea and associated obsessive-compulsive symptoms up to 3 years later posing the question of increased vulnerability with repeated chorea episodes (Asbahr, 1999).

Amid the limited studies of depression, anxiety, psychosis and ADHD in Sydenham's chorea there is a suggestion that the psychiatric symptoms outlast the movement disorder (Ridel et al., 2010, Casanova, 1995, Teixeira et al., 2007b) however the literature examining this hypothesis is lacking.

2.5.2 Paediatric autoimmune neuropsychiatric disorder associated with streptococcus

2.5.2.1 Disease overview

Of all the disorders featured in this review, the one that attracts the greatest scepticism and controversy is paediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS).

As early as 1894 William Osler was commenting on the historical misunderstandings surrounding chorea (Osler, 1894) and eventually it became accepted that streptococcus infection could cause neuropathology. Over a century later Sydenham's chorea holds its place as an established post-infectious entity. However, PANDAS has yet to be established broadly. The existence and classification of psychological manifestations occurring after streptococcus continues to attract debate in the

medical literature and the topic deserves analysis here, as children with PANDAS typically have both movement disorders and psychiatric diagnoses.

Estimation of the actual prevalence of PANDAS is not well described and this is complicated by the inconsistencies of inclusion criteria in various studies. Epidemiological data of related conditions such as Tourette's Disorder and OCD find that 0.3%-3% of children are affected with these conditions (Murphy et al., 2010a) suggesting that a smaller subset may fulfil criteria for PANDAS. The criteria for PANDAS dictates pre-pubertal onset (Swedo, 2001) and few if any patients are reported under the age of 3 years (Pavone et al., 2004).

2.5.2.2   Pathogenesis in brief

PANDAS refers to a specific constellation associated with infection due to Group A Streptococcus (GAS). GAS is a commonly acquired organism and resulting clinical infections include pharyngitis, impetigo, scarlet fever and septicaemia. There are numerous non-suppurative conditions including rheumatic fever and glomerulonephritis. (Murphy et al., 2010a).

PANDAS implies an immune mediated pathophysiology that results in a disorder of the central nervous system. The most widely accepted theory refers to molecular mimicry, similar to the mechanism described in rheumatic carditis. In PANDAS, it is proposed that antibodies produced in response to streptococcal exposure mistake brain tissue for streptococcal antigen and become disease causing (Murphy et al., 2010a).

This hypothetical pathophysiology is supported by several studies demonstrating auto-antibodies against the basal ganglia antigens of patients with PANDAS (Murphy et al., 2010a). Various theories have been postulated as to the more detailed pathophysiology including direct impact on basal ganglia receptors, either stimulating or inhibiting, or forming immune complexes that actually damage the brain parenchyma (Lewin et al., 2011, Giedd et al., 1996). Further consideration of anatomic basis is given by Giedd et al who compared the MRI brains of 34 children with PANDAS to 82 'normal healthy' controls. This study noted that the average sizes of the caudate, putamen and globus pallidus were

significantly smaller in the PANDAS group when compared to the healthy controls (Giedd et al., 1996),

In view of the widespread colonisation of GAS in childhood populations, the question emerges as to why certain children develop the PANDAS sequelae. The issue of genetic susceptibility is discussed in several studies, both in terms of susceptibility to autoimmunity as well as predisposition to anxiety and related disorders. The rate of autoimmunity as determined by a structured medical interview in mothers of children with tics, OCD and PANDAS was 17.8%, which was quoted to be significantly greater than the general prevalence. Rates of autoimmunity were greater again in the subgroup that had features suggestive of PANDAS (Murphy et al., 2010b),

In terms of genetic predisposition for neurological deficit, one study examined pedigrees of 54 children with PANDAS and found that 39% had at least one first degree relative with a history of tic and 26% had at least one first degree relative with OCD (Lougee et al., 2000).

A further study illustrated PANDAS in two siblings with the onset of disease separated by 3 years.. (Dranitzki, 2007). These familial studies can provide some basis to a multifactorial disease with environmental and genetic susceptibility.

Caution in terms of attributing too great an emphasis to genotype is offered by Lewin and Storch et al who analysed 3 children with PANDAS and their genetically identical twin or triplet and found variation in the clinical phenotype, from full PANDAS to asymptomatic. This suggests that the pathogenesis is more complex than a linear interaction between the organism and genetics, as is true for all multifactorial diseases (Lewin et al., 2011).

Another interesting observation is that when children with PANDAS were analysed retrospectively in a study by Murphy and Storch, they were found to have a higher rate of tonsillectomies and adenoidectomies than children without PANDAS. (Murphy et al., 2012). A recent epidemiological study in Denmark performed streptococcal throat testing in more than 600,000 children. This study found that a positive streptococcal test was associated with increased rates of OCD and tics than children without a streptococcal infection. Interestingly children with non-streptococcal throat

infections were also at increased risk compared to children without any infection. (Orlovska et al., 2017). Various interpretations for these associations have been offered including that cumulative streptococcal infections were factors in the child developing PANDAS. It has also been suggested that the absence of lymphoid tissue post-surgery rendered these children more vulnerable to future infections.

2.5.2.3 Clinical course and diagnosis

The diagnosis of PANDAS requires a temporal correlation with streptococcal infection and should adhere to the 5 point criteria outlined below. This issue deserves emphasis in terms of clinical practice as well as research methodology. A recent assessment of children diagnosed with PANDAS found that more than half did not strictly meet the NIH criteria for PANDAS (Gabbay et al., 2008). Typically the streptococcal infection will precede the onset of OCD by a few days to 2 weeks, however a simple demonstration of positive anti-streptolysin O titre does not suffice, as some children are chronic carriers (Murphy et al., 2010a). A correct diagnostic process should thoroughly enquire about the onset and sudden presentation of symptoms as well as recurrent infections or suggestions of GAS, throat infections or scarlet fever. Streptococcal titres should be taken at symptoms onset and retested in 4-6 weeks looking for a rise in titre (Murphy et al., 2010a, Swedo, 2004, Murphy et al., 2012).

2.5.2.4 Movement disorder phenotype

The term PANDAS defines a range of brain-related deficits and the symptoms that are most widely described include OCD, anxiety and tics.

In the seminal study by Swedo in 1998 - 5 clinical characteristics were outlined to provide diagnostic criteria for PANDAS. These include:

1. prepubertal onset usually between 3 years and 12 years

2. obsessive compulsive disorder, a tic disorder (lifetime diagnostic criteria)

3. sudden explosive onset of symptoms and course of recurrent sudden exacerbations and remissions

4. temporal relationship of exacerbations with streptococcal infections

5. presence of neurological abnormalities during periods of symptom exacerbation (tics, hyperactivity)

(Swedo, 1998)

The tics commonly include eye blinking, tongue protrusion, shoulder shrug, facial grimacing, lip sucking and neck jerking (Mabrouk and Eapen, 2009). Distal choreiform movements have been described in PANDAS and may occur up to 3 months following a tic exacerbation (Murphy et al., 2010a). Choreiform movements have also been seen in general childhood onset OCD, tics, and ADHD and it has been raised that the neurological symptoms may simply reflect the comorbidities seen in other children with TS and OCD (Hirschtritt et al., 2009).

2.5.2.5 Summary of associated psychiatric features

Children with PANDAS typically have psychiatric manifestations that include anxiety, and specifically, there is a high rate of obsessive-compulsive disorder. Features that distinguish PANDAS patients from other children with OCD include the sudden onset of the disorder, with children who were previously unaffected developing a sudden manifestation of psychiatric concerns. Emotionality is characteristic with separation anxiety, nightmares, personality changes and rage episodes all observed. There can also be psychotic symptoms although these are atypical (Murphy et al., 2010a). Other symptoms include secondary nocturnal enuresis and stuttering which may be anxiety related (Swedo, 1998) as well deterioration in handwriting (Mell et al., 2005).

Several authors have drawn distinctions between the OCD in PANDAS to the OCD seen in other children. Bernstein analysed children between 6-14 years and assigned diagnosis of PANDAS-OCD on the basis of Swedo et al's criteria (described in section 2.5.2.4 above). Comparisons were drawn between non-PANDAS OCD using several questionnaires including Children's Yale-Brown Obsessive Compulsive Scale and Anxiety Disorders Interview Schedule for DSM-IV. Separation anxiety, deterioration in handwriting, and decline in school performance were all more prevalent in the initial

episode of children with PANDAS–OCD (Bernstein et al., 2010). Other studies found that the neuropsychiatric symptoms of PANDAS patients were in keeping with, and not distinct from, the primary neuropsychiatric presentation, such as OCD or Tourette syndrome (Hirschtritt et al., 2009).

Variations to PANDAS have been offered including PANDAS manifesting as anorexia nervosa (Puxley et al., 2008), infantile onset PANDAS and adult onset PANDAS (Pavone et al., 2004). Descriptions remain limited with approximately 20 cases of PANDAS anorexia and 3 cases of possible PANDAS in children under 3 years, however these entities are not broadly accepted or well studied to date.

Whilst there is debate in the literature as to the extent to which PANDAS psychiatry can be distinct from non-PANDA-OCD and TS, the more accepted point of difference is the fulminant onset and 'saw-tooth' fluctuation. The classical clinical picture of PANDAS depicts a sudden deterioration in a previously high functioning and unaffected child with severe changes noted over 24-72 hours, such that parents might describe 'a different child' overnight (Murphy et al., 2010a). Following the sudden change in anxious behaviour, the OCD and tics may improve or completely resolve. There may be complete remission or recurrent exacerbations. For the latter group it is not uncommon for the interval between exacerbations to become briefer with each episode (Murphy et al., 2010a).

Murphy and Storch's study examined 109 patients with tics, OCD or both. They were subsequently classified as PANDAS and non-PANDAS via clinical interview, neurological exam, autoimmune tendencies and serology. They found that children in the PANDAS group were more likely to have definite remissions in neuropsychiatric symptoms and have dramatic onset of symptoms (Murphy et al., 2012).

2.5.2.6   Treatment and prognosis

Patients with PANDAS should receive conventional therapy for their OCD, tic and other neuropsychiatric disorders, including cognitive behaviour therapy and SSRIs for OCD, stimulants for ADHD, and clonidine, guanfacine, or a dopamine receptor antagonist for tics (Murphy et al., 2010a,

Singer et al., 2012). Cognitive behaviour therapy is regarded as a standard therapy for general OCD and success has been demonstrated in 7 patients with PANDAS-OCD (Storch et al., 2006).

Both penicillin and azithromycin prophylaxis have been studied (Murphy et al., 2010a) and in one study, 23 subjects with PANDAS were enrolled in a double blind trial comparing antibiotic prophylaxis with penicillin compared to azithromycin over a 12-month period. Both the antibiotic groups demonstrated a decrease in neuropsychiatric presentations compared with the previous year, however there was no placebo arm to allow for consideration of that effect (Snider et al., 2005). Garvey studied 37 children with PANDAS comparing penicillin to placebo and found no difference in obsessive compulsive or tic severity, although compliance was problematic (Garvey, 1999).

Given the hypothesis of autoimmunity as a key factor in PANDAS it is not surprising that IVIG and plasmapheresis have been trialled. Perlmutter's study looked at 29 children with severe, infection-triggered exacerbations of OCD or tic disorder and randomly assigned them to plasma exchange, IVIG or placebo. Follow up was at 1 month and then 12 months. Perlmutter reported improvements in obsessive-compulsive symptoms, anxiety and overall functioning (Perlmutter et al., 1999). Singer pronounced strong criticism of this study in view of limited control patients; the placebo was only for IVIG and after one month these children were placed in open trials. Singer also highlights that several of the improved patients continued on their psychotropic medications, several without achieving dose reduction (Singer, 1999). Singer articulated the caution that should be applied when considering these treatments given the potential adverse effects that are weighed against limited evidence for efficacy. Whilst the medical and scientific scholars debate the criteria and mere existence of PANDAS, the general community have become intrigued by this post-infectious disorder that seems to change the thoughts and emotions of their children overnight. Tanya Murphy outlines the astonishing statistic that there are approximately 100,000 Internet sites featuring the streptococcus-OCD association (Murphy et al., 2010a).

During the last decade there has been a broadening of the understanding of acute onset neuropsychiatric syndromes similar to PANDAS with a de-emphasis of streptococcal as the causative

agent. Childhood acute neuropsychiatric syndrome CANS) (Singer et al., 2012) and Paediatric acute-onset neuropsychiatric syndrome (PANS), which does not require a streptococcal trigger, (Murphy et al., 2014) are now proposed entities, in addition to PANDAS.

2.6 The auto-immune encephalitis syndromes

2.6.1 Anti-NMDA Receptor (NMDA-R) Encephalitis

2.6.1.1 Disease overview

The autoimmune encephalitis conditions are known to cause a spectrum of clinical syndromes involving movement disorder and psychiatric manifestations (Hacohen et al., 2013). NMDA Receptor encephalitis is likely to be more common than originally thought, and it has been shown that approximately 4% of patients hospitalised for encephalitis are NMDA R Ab positive (Granerod et al., 2010). Despite initially been described as a para-neoplastic syndrome in adult women with ovarian teratoma it is now recognised that up to 40% of patients are 18 years or younger (Florance et al., 2009).

2.6.1.2 Pathogenesis in brief

Anti-NMDA R encephalitis is caused by hypofunction of the NMDA receptor secondary to autoantibodies targeting the NR1a subunit (Dalmau et al., 2011). The clinical picture implicates dysfunction of cortical subcortical structures, limbic regions, amygdala, and fronto-striatal circuitry (Dalmau et al., 2011, Gable et al., 2012).

2.6.1.3 Clinical course and diagnosis

The typical clinical course is characterized by a prodrome that may include headache, fever, nausea, vomiting and respiratory symptoms. Within two weeks patients commonly develop psychiatric symptoms. This is often followed by development of a movement disorder and encephalopathy with possible seizures and mutism is common. There is typically progression to a catatonic state, and following this, patients may require intensive care for autonomic instability (Dalmau et al., 2011, Gable

et al., 2012).

MRI abnormalities are seen in up to 50% of patients with non-enhancing T2 lesions in the temporal lobes, cerebral cortex, cerebellum, brainstem and basal ganglia (Dalmau et al., 2008, Dalmau et al., 2011, Hacohen et al., 2013). The lesions are usually transient however, and atrophy has been noted in follow up at six months in a minority. EEG demonstrates generalized slowing or less frequently epileptiform changes (Hacohen et al., 2013). Commonly in the CSF there is lymphocytic pleocytosis with raised protein and oligoclonal bands. Most patients have intrathecal production of anti-NMDA R antibodies when tested (Dalmau et al., 2011).

2.6.1.4 Movement disorder phenotype

After an initial period of altered level of consciousness and agitation, abnormal movements are generally noted and oro-lingual-facial dyskinesia is a hallmark feature. Other movement disorders are common, and include choreoathetosis, dystonia, rigidity and oculo-gyric crisis (Baizabal-Carvallo et al., 2013). Several movement disorders may occur simultaneously and repetitive stereotyped movements are often observed (Mohammad et al., 2014, Dalmau et al., 2011).

2.6.1.5 Summary of associated psychiatric symptoms

The spectrum of psychiatric symptoms is broad. The psychiatric symptoms that are well established in the literature include anxiety and psychosis, specifically delusions of grandeur, hyper-religosity and paranoia. Social withdrawal may be an early symptom. Mood disturbances including mania and irritability are frequently described (Dalmau et al., 2011, Maneta and Garcia, 2013, Dalmau et al., 2008).

Paediatric patients experience behavioural and personality change as an initial feature, however this may be difficult to detect in the younger patient and the diagnosis may be delayed until movement disorders or encephalopathy develop (Florance et al., 2009, Dalmau et al., 2011). There have been cases of NMDA R encephalitis with psychiatric symptoms only (Kayser et al., 2013).

2.6.1.6 Treatment and prognosis

For patients with ovarian tumours, removal of the tumour is the primary treatment. Otherwise first line treatment includes immunotherapy such as corticcosteroids, IVIG or plasma exchange (Ingram and Robertson, 2013). Some patients require second line immunotherapy including rituximab, cyclophosphamide, mycophenolate or azathioprine (Dalmau et al., 2011). Patients who are tumour negative are more likely to require second line immunotherapy.

The clinical course is long, with patients often requiring hospitalization for three months or more. Recovery often occurs in reverse order to symptom onset; patients awake from the catatonia, develop autonomic instability and then recover verbal functions (Dalmau et al., 2011). Outcome is variable with approximately 50% to 75% of patients demonstrating recovery or mild residual deficits (Dalmau et al., 2011, Titulaer et al., 2013, Hacohen et al., 2013, Dalmau et al., 2008). At follow up of 12-60 months from onset, 50% of patients had ongoing behaviour or cognition issues and 33% had ongoing seizures (Hacohen et al., 2013). The mortality rate is estimated to be 3% (Gable et al., 2012).

2.6.2 Basal ganglia encephalitis

2.6.2.1 Disease overview

Basal ganglia encephalitis is a clinic-radiological syndrome with dystonia-akinesia plus radiological basal ganglia inflammatory lesions. Antibodies to dopamine 2 (D2) receptors have been implicated in basal ganglia encephalitis and may result in this acute neuropsychiatric syndrome.

2.6.2.2 Pathogenesis in brief

D2 receptors are expressed in the basal ganglia as well as in the cortex. Autoantibodies targeting these receptors are thought to disrupt the basal ganglia circuitry (Dale et al., 2012, Ingram and Robertson, 2013).

2.6.2.3 Clinical course and diagnosis

Basal ganglia encephalitis is characterized by lethargy, movement disorder (dystonia-akinesia) and psychiatry. Brain MRI may be normal or show inflammatory lesions in the basal ganglia and brainstem. EEG can be unremarkable or demonstrate changes suggestive of encephalopathy. Antibodies may be detected on serum (Dale et al., 2012).

2.6.2.4 Movement disorder phenotype

The movement disorders are typically dystonic, possibly with dystonic tremor. Parkinsonism and chorea are other common symptoms, and ataxia and oculogyric crisis have occasionally been described. (Dale et al., 2012)

2.6.2.5 Spectrum of psychiatric symptoms

Psychiatric disturbance occurs in most patients. These symptoms included agitation, emotional lability, anxiety and psychotic symptoms. Sleep disorders and mutism have also been observed (Dale et al., 2012).

2.6.2.6 Treatment and prognosis

Treatment is often commenced empirically during the diagnostic process. Preliminary observations have found high dose steroids and intravenous immunoglobulin to be beneficial. Symptomatic treatment of motor and psychiatric symptoms is often required. Although small numbers limit extrapolation, full recovery has been noted in under half of the D2R patients presented in the literature. Chronic sequelae include dystonia, cognitive problems and psychiatric comorbidity. One study that followed 4 patients for 3 to 13 years post disease, found all 4 had ongoing executive dysfunction, fine motor difficulties and anxiety at final follow up (Pawela et al., 2017).

2.6.3   Opsoclonus myoclonus ataxia syndrome

2.6.3.1   Disease overview

Opsoclonus-myoclonus ataxia syndrome (OMAS) is a rare and serious neurological disorder of auto-immune aetiology. Its hallmark features are opsoclonus, myoclonus and ataxia and OMAS may occur as a paraneoplastic syndrome, classically associated with neuroblastoma.

2.6.3.2   Pathogenesis in brief

Whilst the exact mechanism is not clear, OMAS is understood to be an auto-immune disorder with the adaptive immune system targeting CNS structures such as the cerebellar and basal ganglia (Pranzatelli and Tate, 2016). This response is thought to be provoked by paraneoplastic or para-infectious processes (Galstyan et al., 2017).

2.6.3.3   Clinical course and diagnosis

OMAS generally occurs in early childhood, usually before 3 years of age (Brunklaus et al., 2011). It is common for the neurological symptoms to be preceded by a prodrome of irritability resembling a viral illness. Children then present with ataxia or frequent falls, tremor and myoclonus. Opsoclonus, hypotonia and speech difficulties can present later along with behavioural issues (Tate et al., 2005). Children lose motor control and deteriorate cognitively (Turkel et al., 2006). The diagnosis is clinical with supporting data such as neuro-inflammation evident in the CSF (Pranzatelli and Tate, 2016). Unfortunately, the time from first presentation to diagnosis is often several months (Tate et al., 2005). If left untreated, and indeed even in the setting of treatment (Pranzatelli and Tate, 2016), long term neurocognitive deficits occur frequently.

Neural crest tumours has been diagnosed in approximately forty per cent of cases of OMAS (Brunklaus et al., 2011, Tate et al., 2005) and therefore a crucial step after making the diagnosis is screening for occult neuroblastoma or neuroganglioma.

2.6.3.4 Movement Disorder phenotype

The movement disorders seen in OMAS include myoclonus, tremor and opsoclonus the latter being essentially pathognomonic for OMAS when occurring in the appropriate clinical setting. The myoclonus and tremor are typically generalised (Tate et al., 2005). Families often report dysarthria and speech regression.

2.6.3.5 Spectrum of psychiatric symptoms

Irritability and mood dysfunction are common in the initial phase of OMAS, and night terrors have been observed at or soon after diagnosis (Turkel et al., 2006). Neuropsychiatric symptoms are also commonly observed as part of the chronic disease process. An American study of 100 children with OMAS found that psychiatric symptoms were present in most patients. Rage attacks were reported in 79%, oppositional defiant disorder in 65%, obsessions and compulsions in 58% and hyperactivity, depressions and ADHD were also more common. Behaviour problems have been recognised in several studies (Brunklaus et al., 2011), and impulsivity and emotional instability are noted (Klein et al., 2007, Pranzatelli et al., 2005). Aggressiveness and self-injurious behaviour have also been reported (Papero et al., 1995, Turkel et al., 2006, Tate et al., 2005).

2.6.3.6 Treatment and prognosis

Until recently, publications examining the long-term prognosis of OMAS demonstrated poor outcome. Early immunosuppressive treatment has been shown to improve prognosis. Recommendations now direct provision of corticosteroid or ACTH and IVIG, with a disease modifying agent such as Rituximab for moderate-severe cases (Galstyan et al., 2017, Pranzatelli and Tate, 2016), and this has been associated with better preservation of functioning and cognition.

2.6.4 Antiphospholipid chorea

2.6.4.1 Disease overview

Antiphospholipid chorea is a rare manifestation of chorea that occurs in the presence of

antiphospholipid antibodies (Peluso et al., 2012).

2.6.4.2 Pathogenesis in brief

The exact pathophysiology involved in antiphospholipid chorea is not well understood. Studies have suggested that antibodies cross the blood brain barrier and form immune complexes with antigens in cerebral tissue (Bresnihan et al., 1979, Ho et al., 2016, Sokol et al., 2007). Previous suggestions that the mechanism was a pro-thombotic assault on basal ganglia vasculature have given way to a hypothesis based on endothelial dysfunction, inflammation and direct neural injury caused by aPL antibodies (Peluso et al., 2012).

Antibodies implicated in antiphospholipid chorea include lupus anticoagulant, anticardiolipin antibodies, antinuclear antibodies, anti-DNA, anti-Ro, anti-RNP, anti-La, and anti-Sm (Cervera et al., 1997) (Chapman et al., 2003, Ho et al., 2016). Antiphospholipid syndromes tend to occur mostly commonly in systemic autoimmune disease, specifically SLE, however, viral infections such as HIV and herpes have also been associated (Peluso et al., 2012). Less frequently antiphospholipid syndrome can occur as a primary process without systemic or viral trigger.

2.6.4.3 Clinical course and diagnosis

Antiphospholipid syndrome may result in a range of symptoms including thromboembolic events or stroke, or broader neuropsychiatric symptoms including migraine, seizures or dementia. Antiphospholipid syndrome can either be primary (occurring with no other inflammatory syndrome) or secondary to a systemic inflammatory disease such as systemic lupus erythematous. Unlike other neuropsychiatric presentations occurring in SLE, which may or may not be associated with raised antibody titres, antiphospholipid and lupus chorea is almost invariably associated with antiphospholipid antibodies (Benseler and Silverman, 2007). Other neurological symptoms that can occur in this syndrome include headache, cerebrovascular disease, seizures, transverse myelitis, and ataxia (Sanna et al., 2003, Arnson et al., 2010). The diagnosis relies on clinical recognition of chorea and detection of antibodies in serum. Neuro-imaging is not generally useful although can be important

to exclude other pathologies. Because of the implications for treatment it is important to differentiate the diagnosis from other causes of chorea such as Sydenham's chorea, BHC and Wilson's disease (Peluso et al., 2012).

2.6.4.4   Movement disorder phenotype

Anti-phospholipid chorea presents as a typical chorea, characterised by random, dance-like dyskinesia. It is more often unilateral than bilateral (Benseler and Silverman, 2007), or the chorea may start on one side then affects the contralateral side in succession. Interestingly most patients with antiphospholipid chorea have only one episode of chorea (Peluso et al., 2012).

2.6.4.5   Spectrum of psychiatric symptoms

There have been several studies examining neuropsychiatric symptoms in antiphospholipid syndromes with mood disorders, anxiety and psychosis all found to be associated, although there have been no dedicated studies to explore psychiatry in antiphospholipid chorea specifically (Sanna et al., 2003, Hallab et al., 2018, Montero-Olvera et al., 2017, Gris et al., 2015). Anti-phospholipid screening may form part of the work-up for new onset psychiatric symptoms, and a study of hospital patients with psychosis found that one third had antiphospholipid antibodies, however the significance of this is uncertain (Schwartz et al., 1998). One case of pathological gambling has also been described with antiphospholipid chorea {Barros, 2011 #1951.

2.6.4.6   Treatment and prognosis

Treatment options include immunosuppressive treatment such as steroids and other immune suppressants, for example, cyclophosphamide (often in combination, particularly if monotherapy does not lead to remission). Symptomatic treatment including neuroleptics such as haloperidol may be required for the chorea {Peluso, 2012 #1811}.

2.6.5 Rasmussen and dystonia – a rare phenotype in a rare disease

Rasmussen encephalitis is an uncommon inflammatory process affecting one cerebral hemisphere and it most commonly associated with epilepsia partialis continua and progressive cerebral atrophy on MRI. Rarely hemidystonia and hemiathetosis have been described. (Bhatjiwale et al., 1998, Frucht, 2002) Progressive intellectual impairment may result however psychiatric comorbidities remain largely unknown Varadkar, 2014 #2072}.

2.7 Other

2.7.1 Essential tremor

2.7.1.1 Disease overview

Essential tremor (ET) is one of the most common movement disorders seen by physicians and yet its pathophysiology is not well understood. Traditionally described as an isolated tremor syndrome, more recently the condition has been expanded to include gait ataxia. Credence has also been granted to the concept that essential tremor may actually be an umbrella for several different disease processes (Louis, 2014).

2.7.1.2 Pathogenesis in brief

The cause of ET is not well understood however it is generally accepted to be a disorder of cerebellar dysfunction (Chunling and Zheng, 2016). Studies have strongly supported a genetic basis and several genetic loci have been presented (Lorenz and Deuschl, 2007).

2.7.1.3 Clinical course and diagnosis

Essential tremor is characterised by a tremor, and this may be accompanied by other symptoms including sleep disturbance, mild cognitive and memory impairment (Chunling and Zheng, 2016, Chandran and Pal, 2012). The diagnostic approach is primarily concerned with clinical criteria and excluding other causes of trauma such as Parkinson's disease and hyperthyroidism (Lorenz and Deuschl, 2007).

2.7.1.4   Movement Disorder phenotype

Essential tremor is typically a kinetic tremor of 4 Hz and 12 Hz occurring primarily in the upper limbs. A postural tremor may be noted, however this is less marked than the kinetic tremor. The tremor tends to be exaggerated during voluntary movements such as eating or writing (Louis, 2005). The impact is variable with some people describing very subtle symptoms, and patients at the more severe end of the spectrum may be unable to dress or feed themselves. Overall the tremor is thought to be slowly progressive (Louis, 2005, Benito-Leon and Louis, 2006).

2.7.1.5   Spectrum of psychiatric symptoms

Despite its relatively common incidence, essential tremor has not been extensively studied with regards to psychiatric symptoms. Depression has been found in 40 to 55% of patients (Louis et al., 2007, Fabbrini et al., 2012). A prospective analysis also found that people with depression were more likely to develop essential tremor, suggesting this may be a primary process rather than a reactive mood disorder (Louis et al., 2007). Social phobia, anxiety, sleep disturbance and fatigability have all been reported to be increased in people with essential tremor (Schneier et al., 2001, Sengul et al., 2015). A study of patients who had been treated with deep brain stimulation for essential tremor found that the patient's own perception of tremor severity was the strongest predictor of depression and anxiety (Achey et al., 2018).

2.7.1.6   Treatment and prognosis

Treatment options for ET include pharmacotherapy options, such as propanolol, topirimate and gabapentin. Pregabalin, benzodiazepines, botox injections and zonisamide may also show some improvement in tremor. Deep brain stimulation and thalatomy have been found to be effective in severe cases (Lorenz and Deuschl, 2007, Zesiewicz et al., 2005).

2.7.2 Dystonic cerebral palsy (CP)

2.7.2.1 Disease overview

Dystonic CP refers to a group of heterogeneous conditions that result in non-progressive disturbance of movement with varying degrees of dystonia. As a subset of cerebral palsy, dystonic CP is far less common than spastic CP, and dystonic CP accounts for approximately 15% of the broader cerebral palsy cohort (Himmelmann et al., 2005, Lin et al., 2014).

2.7.2.2 Pathogenesis in brief

Dystonic CP can result from a range of pathologies although most involve injury to the basal ganglia as a common mechanism. Frequent causes include (in order of prevalence) neonatal hypoxic ischaemic encephalopathy, prematurity and kernicterus followed by less frequent metabolic and infectious processes (Lin et al., 2014). Sometimes there is no apparent cause of dystonic CP, and genetic causes are increasingly identified.

2.7.2.3 Clinical course and diagnosis

The course of cerebral palsy is, by definition, non-progressive and related to the anatomical distribution and extent of brain injury. Patients may be mild or severely affected. Despite the static nature of the movement disorder, associated complications from neurological disease such as contractures, scoliosis, respiratory infection and gastrointestinal complications may cause impairment that worsens over time. In some patients, particularly those with injury extending to the cerebral hemispheres, intellectual impairment and epilepsy may occur (Himmelmann et al., 2007).

2.7.2.4 Movement disorder phenotype

Patients with dystonic cerebral palsy are affected by dystonia as the name implies. The location of the dystonia is related to the underlying pattern of injury and may manifest as hemidystonia or bilateral involvement. Athetosis, dysarthria and spasticity may accompany the dystonia (Himmelmann et al., 2005).

2.7.2.5 Spectrum of psychiatric symptoms

Studies of dystonic CP have explored cognition and quality of life, however few have investigated psychiatry. One study of 22 children with dystonic CP found high levels of social and emotional difficulties, as well as hyperactivity and attention problems (Adegboye et al., 2017). Literature looking at CP in general reports higher rates of psychological problems than in the general population (Ramstad et al., 2012, Foster et al., 2010, Parkes et al., 2008). Children with CP are more likely to be affected by depression, impulsivity, adjustment disorder and emotional lability than healthy cohorts (Foster et al., 2010, Fevang et al., 2017).

2.7.2.6 Treatment and prognosis

Supportive and multi-disciplinary treatment (including physiotherapy, orthotics and orthopaedic intervention) is important for decreasing the burden of immobility and preventing complications in dystonic CP. Symptomatic treatment of dystonia can include clonidine, benzodiazepines, baclofen or Trihexyphenidyl. Botox, baclofen pumps and tendon release are sometimes needed. Severe cases may benefit from deep brain stimulation, although the benefit is sometimes modest (Cif, 2015).

3 Method

3.1 Aims

1. To describe the prevalence of psychiatric co-morbidities in children (5-16 years) with diagnosed movement disorders from an Australian and British tertiary hospital population

2. To compare the prevalence of psychiatric co-morbidities in children (5-16 years) with a movement disorder to children who have no neurological disease or any other chronic disease (emergency department hospital control group)

3. To compare the prevalence of psychiatric co-morbidities in children and young people (5-16 years) with children with a neurological disorder distinct from a movement disorder, specifically a peripheral neuropathy or epilepsy (neurology control)

4. To compare within the movement disorder group, the prevalence of psychiatric comorbidities of children with Tourette syndrome to children with movement disorders distinct from Tourette syndrome including dystonia, chorea, tremor, myoclonus, stereotypy and bradykinesia.

5. To identify correlations between specific movement disorders (grouped by aetiology and/or clinical patterns) and specific types of psychiatric disorders

3.2 Hypothesis

I hypothesised that children and young people with movement disorders were significantly more likely to have a psychiatric disorder than children without a movement disorder. I expected that children

with movement disorders other than Tourette syndrome (such as dystonia and chorea) will have elevated rates of psychiatric comorbidity similar to children with Tourette Syndrome

3.3   Study design overview

A multi-centre clinical project, the study systematically compared the prevalence of psychiatric diagnoses from children in the study group (children with diagnosed movement disorders) to children from distinct control groups (Emergency control and Neurology control). The movement disorder study group consisted of patients known to The Children's Hospital at Westmead, Australia. To increase the size of our study group we also recruited movement disorder patients from Great Ormond Street Hospital (GOSH), London UK. All patients from the control groups were recruited from the Children's Hospital at Westmead (CHW), Sydney Australia. Control patients were only sought in Australia, as a large UK based normative sample already existed from a previous published study using the same assessment tool applied in this study. (Ford et al., 2003) I utilised this existing normative data for comparative purpose in our analysis.

Psychiatric assessment occurred through the use of a structured questionnaire called the Development and Wellbeing Assessment (DAWBA) tool and I have described this tool in detail below. The psychiatric diagnoses were made in line with DSMV criteria and determined by a Psychiatrist.

Figure 3.1 Overview of study design
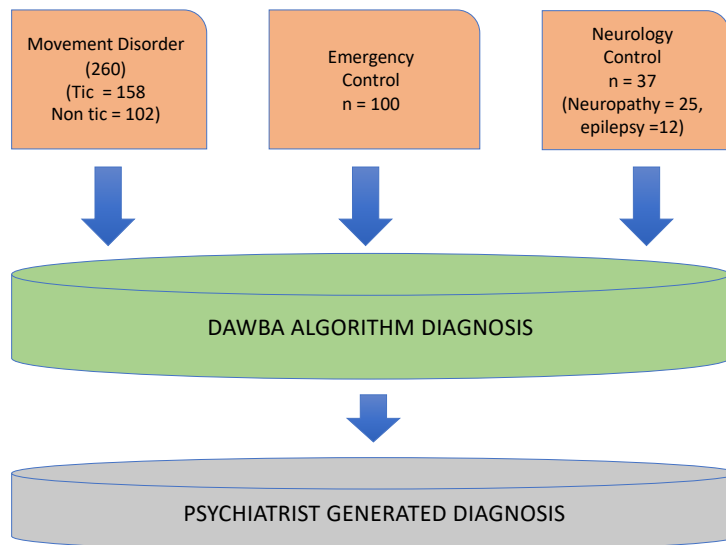
DAWBA; Development and Well-Being Assessment

3.3.1 Hospital context 1: The Children's Hospital at Westmead, Sydney, Australia

The majority of movement disorder subjects and all the control subjects were recruited from the Children's Hospital at Westmead (CHW). CHW is the largest paediatric hospital in New South Wales, Australia and services the Sydney area and regional New South Wales. There is a tertiary neurology service with a dedicated movement disorder clinic, tic clinic, complex epilepsy service and a peripheral neuromuscular clinic. Patients from the movement disorder group and the neurology control group, including neuropathy and epilepsy patients, were recruited through these services. The hospital Emergency Department services children from birth to 16 years of age with a range of urgent medical and surgical needs, and the emergency department predominantly sees children local to hospital with acute and emergency conditions. Patients from the Emergency control cohort were recruited through this emergency department.

3.3.2 Hospital context 2: Great Ormond Street Hospital, London, United Kingdom

Great Ormond Street Hospital (GOSH) is a large tertiary hospital located in Central London, the United Kingdom. In addition to a 24 bed inpatient neurology ward, the hospital runs multiple neurology clinics and a multidisciplinary Tourette Syndrome clinic.

3.3.3 Selection of cohorts

Three patient groups were selected for the study:

The study group consisted of patients with movement disorders (n=260). Within that group there were patients with tic movement disorders (Tic MD, n=158) and patients with movement disorders other than tics (Non-tic MD) such as dystonia, chorea, tremor, myoclonus (n=102). Of the tic patients 75/158 were recruited in the UK, and 83/158 were recruited in Australia. Within the Non-tic cohort 5/102 were recruited in the UK and the remaining 97/102 were Australian patients. The decision to define patients as Tic or Non-tic was important because cohorts of tics and Tourette have previously been the subject of extensive research into psychiatric comorbidities, and served as a positive control group against the less common movement disorders.

The first control group was a Hospital Emergency control group (n=100).

These are patients who presented to the Emergency Department at The Children's Hospital at Westmead with an acute presentation. These children had no movement disorders or neurological conditions, but presented with a range of medical and surgical problems. This group should not be considered a 'normal' group of children, but instead a 'hospital' group without neurological disorders, for comparison.

The second control group was a neurology control group (n=37).

These patients had a diagnosed peripheral neuropathy (n=25) or epilepsy (n=12) but did not have a movement disorder. This group provided an interesting comparator because it crudely controlled for

confounding factors such as disability and medical intervention for neurological disease during childhood. Patients in this control group had neurological impairments without a movement disorder.

3.3.4 Inclusion criteria

All patients recruited for the study were between 5 and 16 years. They were all required to have verbal skills, to the extent that they could communicate in sentences and therefore facilitate some understanding of their behaviour and psychiatry in the detail required to complete the DAWBA. Detailed inclusion criteria specific for each of the subgroups has been outlined in later sections.

3.3.5 Exclusion criteria

Patients were excluded if they were outside the age of 5-16 years, if they were non-verbal or if they or their parent or guardian were unable to understand English to the extent that an informed consent was made difficult or completion of the DAWBA was not possible (see below).

3.4 The assessment tool – The Development and Well-Being Assessment tool

Extensive consideration was given to the selection of an assessment tool suitable for the screening of psychiatric diagnoses. The Development and Wellbeing Assessment Tool (DAWBA), Child and Adolescent Psychiatric Assessment (CAPA), Diagnostic Interview Schedule for Children IV (DISC IV), Children's Interview for Psychiatric Symptoms (ChIPS) and Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) were identified as potential means of assessment and interrogated for their strengths and limitations.

3.4.1 Description of the DAWBA

The Development and Wellbeing Assessment Tool is a validated and structured screening questionnaire designed to determine psychiatric diagnosis in a population setting. Applicable to children between the ages of 2 and 17 years, it consists of multiple choice and open-ended questions that investigate psychiatric, emotional and behavioural aspects of a child's development and

functioning. There is a mandatory component for parents to complete and an optional component for young people over the age of 11 to complete. (Goodman, 2000)

Outcomes from the DAWBA are depicted as DSMIV, DSMV or ICD diagnoses. The following disorders are screened: separation anxiety, specific phobia, social phobia, panic disorder / agoraphobia, post-traumatic stress disorder, obsessive compulsive disorder, generalised anxiety disorder, body dysmorphic disorder, disruptive mood dysregulation disorder, major depression, ADHD / hyperkinesia, oppositional defiant disorder, conduct disorder, eating disorders, including anorexia, bulimia and binge eating, autism spectrum disorders, tic disorders, including Tourette Syndrome and bipolar disorders (Ford et al., 2003).

A computer algorithm within the DAWBA determines the probability of diagnoses and a qualified child and adolescent psychiatrist reviews the entire questionnaire with responses and provides a final diagnosis. These final diagnoses were the basis of psychiatric prevalence examined in the study. The emphasis on DSMV diagnosis as opposed to quality of life or functioning domains was one of the characteristics of the DAWBA that led us to use the DAWBA for this psychiatric study.

3.4.2 Description of considered alternatives: CAPA, K-SADS, ChIPS, DISC IV

The Child and Adolescent Psychiatric Assessment (CAPA) screens for behaviour, mood, anxiety, sleep, eating, elimination, substance abuse, tic and psychotic disorders (Angold and Costello, 2000). It demands interviewers to be trained to recognise various psychiatric symptoms that have been defined in a customised glossary. A combination of open and closed questions form screening, mandatory or discretionary probes are used (Angold and Costello, 2000). Symptoms screened are in accordance with DSM III, DSM IV, ICD-10 criteria, and in the case where symptoms are recognised, questions are then asked about the level of impact caused (Angold and Costello, 2000) (Angold et al., 2012). The intensity of symptoms is generally rated on a 3 or 4 point scale (Angold and Costello, 2000). A computer algorithm generates the diagnosis based on coded data that has been derived from the interview scoring (Angold et al., 2012).

Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) is a semi-structured interview that screens for affective disorders such as anxiety, depression and bipolar disorder (Renou et al., 2004). K-SADS is administered by a health professional or trained researcher who can provide interpretation of questions and responses.

Children's Interview for Psychiatric Symptoms (ChIPS) is a structured interview also to be administered by trained interviewers, preferably with at least a bachelor's degree in mental health. Symptoms and diagnoses are in accordance with the DSM symptom. ChIPS screens for 20 disorders and parallel child and parent versions exist. A detailed scoring system requires the interviewer to document responses and scores in a scoring booklet, which can then be calculated to determine the presence or absence of a DSMIV diagnosis (Weller et al., 2000).

Diagnostic Interview Schedule for Children IV (DISC IV) is a structured diagnostic tool that contains approximately 3000 questions. It is administered by lay interviewers who require training, and screens for more that 30 psychiatric diagnoses using DSMIV and ICD-10 criteria. Like the CAPA, a computer-scoring program generates the diagnosis (Angold et al., 2012). Parallel parent and youth questionnaires are combined for analysis (Shaffer et al., 2000).

3.4.3   Selection of the DAWBA

As a research screening tool, the DAWBA offered several benefits. Unlike the CAPA, ChIPS, DISC and K-SADS, the DAWBA can be self-administered without the need for a trained interviewer. The vast majority of patients that we recruited completed the DAWBA remotely on a computer connected to the internet. This allowed parents and patients the freedom to participate in the study at their chosen time and location, thereby improving acceptability to families, and therefore compliance. Many patients completed the study on a hospital iPad during hospital admissions, or following clinic appointments. For families who did not wish to complete on the internet, I interviewed them over the phone or in-person using the DAWBA format. All questions included in the DAWBA are listed in the appendix (Appendices 2 and 3).

The DAWBA has been created to be user-friendly and relatively short. In a comparative study of the DAWBA, the DISC IV Diagnostic Interview Schedule for Children Version IV, and the CAPA, the DAWBA took significantly less time (33 minutes) than the DISC IV and CAPA for lay interviewers to complete (55 minutes and 60 minutes respectively) (Angold et al., 2012). Consisting of simply-phrased questions that are mostly multiple-choice, the DAWBA can be completed by the parent and youth without the need for a skilled interviewer. 'Skip rules' are included in the DAWBA, allowing the questionnaire to 'skip' ahead if a particular session is deemed irrelevant for the participant on the basis of previous responses. In our study, the time for completion varied depending on the extent of psychological impairment depicted in the answers, the time for consideration taken by the participant, and other factors such as additional conversation had during face-to-face interview or level of computer literacy for those who completed the DAWBA online.

The DAWBA is a validated and peer reviewed tool that has been widely reported in the medical literature, and applied to more than 10,000 children in the United Kingdom (Goodman, 2011) (Goodman, 2000). In an early study assessing its validity as a screening tool, the DAWBA was applied to a community setting (n=491) and clinic setting (n=39). The DAWBA was found to be excellent in differentiating the community and clinic samples. When comparing DAWBA to clinician-based diagnoses, the DAWBA demonstrated strong reliability. In cases where the clinician had diagnosed one psychiatric disorder, the DAWBA agreed in 93% of cases. The DAWBA had a tendency to diagnose more comorbid disorders than the clinician, however on review of the case notes, the clinician diagnosed the DAWBA diagnoses as 'possible' rather than absent (Goodman, 2000).

A later study examining the clinical utility of the DAWBA was performed on 270 new referrals to a large child and adolescent psychiatric service in Zurich. The DAWBA diagnosis was randomly disclosed prior to clinical assessment in approximately half the cases. Diagnostic agreement was noted in 77% of disclosed internalising disorders, such as generalised anxiety and major depression, and 68% of the

non-disclosed cases. Rates for externalising disorders, such as ADHD and oppositional defiant disorder were similar (Aebi et al., 2012).

Precedent exists to illustrate the utility of DAWBA in assessing psychiatric issues in children with neurological disorders such as Sydenham's Chorea (Dale et al., 2004) and across a range of other paediatric studies as described in table 3.1

Table 3.1 Utility of DAWBA in previous studies

Author	Year	Area of study	Age range	Cohort descriptors	Chief findings
Halabi et al (Halabi et al., 2017)	2017	Bullying and psychosocial correlates in Lebanese population	11-17y	Random (geographical clustering) sample of youth in Beirut (n=510)	Anxiety disorder and disruptive behaviour disorder were associated with being bullied
Santos et al (Santos et al., 2017)	2017	Gestational age at birth and behavioural problems	6-11y	Population based birth cohort (n=4231)	No significant correlation between behaviour problems and gestational age at birth
Jesmin et al (Jesmin et al., 2016)	2016	Psychiatric Disorders in children attending Paediatric Outpatients of Tertiary Hospitals	5-16y	Patients attending outpatient appts at tertiary hospital in Bangladesh (n=240)	18% had a psychiatric disorder
Groth et al (Groth et al., 2017b)	2017	Comorbidities in Tourette Syndrome	5-19y	Patients at a Danish National Tourette Clinic (n=227)	63% had psychiatric comorbidities at a 6 year follow up
Maalouf et al (Maalouf et al., 2016)	2016	Psychiatric disorders in adolescents among Lebanon	11-17y	Cluster sampling across Beirut (n=510)	30-day prevalence for psychiatric diagnosis was 26.1%
Elberling et al (Elberling et al., 2016)	2016	Psychiatric Disorders in Danish children	5-7y	Sample from Copenhagen Child Cohort (n=1585)	Prevalence of any ICD-10 disorder was 5.7%
Alvarenga et al (Alvarenga et al., 2016)	2016	Psychiatric comorbidities in children obsessive compulsive symptoms	6-12y	OCD (n=77) OCS (n=488) Unaffected (n=1947) Total (2512)	OCD group had higher rates of comorbid psychiatric disorders than the OCS or unaffected

Xiaoli et al (Xiaoli et al., 2014)	2014	Prevalence of psychiatric disorders among children and adolescents in north east China	6-17y	School students in Northeast China (9806)	9.49% of the sample had a DSMIV diagnosis
Machnes-Maayan et al (Machnes-Maayan et al., 2014)	2014	Psychiatric comorbidities in children with recurrent headache or abdominal pain	5-17y	Children attending tertiary medical centre for Migraine (n=32), tension headache (n=32), recurrent abdominal pain (n=32) Healthy matched controls (f/u for brief acute illness) (n=33)	All 3 study groups had higher rates of psychiatric diagnoses than the control group (Migraine 65.6%, Tension headache 75%, abdo pain 52% and control 21%)
Rabin et al (Rabin et al., 2013)	2013	Emotional and behavioural comorbidities in children with epilepsy	5-17y	Patients with epilepsy in Bangladesh (n=50) Age matched controls (n=50)	Psychiatric disorders were noted in 44% of children with epilepsy and 22% of controls
Dale et al (Dale et al., 2004)	2004	Psychiatric comorbidities in children with post-streptococcal dyskinesia		Patients with post streptococcal dyskinesia presenting to a tertiary centre (n=40)	62.65% of patients had a psychiatric comorbidity
Ford et al (Ford et al., 2003)	2003	Prevalence of psychiatric disorders in British children and adolescents	5-15y	Systematic sampling across a range of postal areas from a national register (n=10438)	9.5% had a DSMIV diagnosis

ADHD; attention deficit hyperactivity disorder, ODD/CD; oppositional defiant/ conduct disorder, TDC; typically developing cohort, OCD; obsessive compulsive disorder, OCS; obsessive compulsive symptoms, ICD-10; International Statistical Classification of Diseases and Related Health Problems, DSM-IV; Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

To promote credibility of the research findings in my study, an effort was made to select a tool that under-diagnosed rather than over-diagnosed psychiatric disorders (and was therefore more rigorous). Angold et al compared the DAWBA to the CAPA and DISC in for children aged 9 to 16 who attended a primary care paediatric clinic (n=646) in North Carolina. The DAWBA detected 1 or more diagnoses in 17.7% of youth, suggesting it was a far more conservative than the DISC and CAPA which diagnosed disorders in 47.1% and 32.4% of youth respectively (Angold et al., 2012).

The DAWBA has the provision for a nominated teacher to participate in a supplementary survey. Following significant consideration, I decided not to incorporate this section of the questionnaire in this study, as it was hypothesised that a requirement to provide school contact details may reduce the number of parents who agreed to participate in the study. The likely outcome of this was that we underdiagnosed behaviour disorders that may have been reported by teachers more than parents.

3.5 Ethics

Ethics approval was obtained for the study. A National Ethics Application Form and site-specific application was completed in accordance with the National Health and Medical Research Council. Applications were also made to the Sydney Children's Hospital Human Research Ethics Committee (H REC/11/CHW/14) and Governance office (SSA/11/CHW/62) to ensure protocols were followed with the Hospital. Separate and parallel applications were submitted to the UK Health Research Authority (15/LO/0239) for the Great Ormond Street component of recruitment.

3.6 Study cohorts in detail

3.6.1 Study cohort 1 – Movement disorder: Tic and Non-tic cohorts

3.6.1.1 Explanation and rationale

We aimed to have a large group of children 5-16 years with a wide range of movement disorders in the study. Due to the established medical literature depicting high rates of psychiatric comorbidity in

children with Tourette Syndrome, we were determined to have 2 subgroups – the first being children with tics and TS movement disorder (Tic MD cohort) as a positive control given the increased incidence of psychiatry has been established in the literature), and the second being children with other movement disorders other than Tourette Syndrome (Non-tic MD cohort).

An effort was made to recruit all eligible children with diagnosed movement disorders to the study. This included all patients with that demonstrated hyperkinetic movements (chorea, dystonia, myoclonus and tremor), hypokinetic movement disorders (bradykinesia), tics, or stereotypies. The movement disorders included primary (genetic or suspected genetic) and secondary disease processes. A concerted effort was made to avoid selection bias so that all eligible patients, not only those with suspected psychiatric vulnerabilities, were selected for the study, as they were seen in the movement disorder clinics.

3.6.1.2   Inclusion criteria and exclusion criteria for movement disorder group

In addition to the general criteria outlined in the study description above, pertaining to age and verbal ability, the following criteria applied:

- patients needed to have a diagnosis of a movement disorder made by a neurologist

3.6.1.3   Recruitment

Patients with diagnosed movement disorders were recruited through patient encounters at CHW and GOSH from services such as movement disorder clinic, Tourette clinics, general neurology clinics and neurology inpatient wards. Within the Australian site, an effort was made to recruit all eligible patients with movement disorders that presented to Neurologist and project supervisor, Professor Russell Dale between 2012 and 2015. After that time, it became evident that the study had a sufficient cohort of patients with Tourette Syndrome (the most common movement disorder), so recruitment of tic patients ceased, and recruitment of less common movement disorder patients continued to the end of 2017. There was an attempt to recruit all consecutive patients with movement disorders, rather than only those suspected to psychiatric symptoms, to minimise selection bias. In the UK, emphasis

was placed on recruiting patients with dystonia, as dystonia is the most common Non-tic movement disorder in the paediatric population. The Tourette patients from the UK were extracted from a previously consented group seen at Great Ormond Street Hospital tic clinic service. 75 patients with Tourette from GOSH who were eligible and completed the DAWBA during the same interval as the Australian patients (2012-2015) were included in our analysis.

Record was kept of those patients who were approached who declined participation on the Australian site. Overall 239 patients with movement disorders were approached about the study on the CHW site, and of them, 180 (75.3%) completed the DAWBA. The majority of patients who did not participate were lost to follow up after initially consenting, or their expression of willingness to complete the DAWBA did not eventuate into action despite phone calls to remind them. For a very small number of patients (n=5) there were stated reasons not to participate, and this was cited as lack of time in all but one case. In the latter case the parent described that their child was self-conscious about their neurological symptom and the parent did not want to draw greater attention to it by taking part in a study.

3.6.1.4   Administration of the tool

Patients and their parents were informed of the study by Professor Russell Dale or myself. They were provided with written information and written consent was obtained. Parents were directed to the DAWBA website with a de-identified and confidential log-in number and asked to complete the questionnaire online.

The majority of parents of movement disorder patients completed the DAWBA online from home. For families where this was difficult due to their computer access or computer literacy, I completed the questionnaire with the parent over the phone.

For some specific patients, I was able to complete the questionnaire in a face-to-face capacity following clinic appointments or on the ward. In these situations, I assisted the parent complete the DAWBA on a tablet.

3.6.2 Study cohort 2 – Hospital Emergency control

3.6.2.1 Explanation and rationale

Selection of a hospital control group was one of the most challenging aspects of the study design. The purpose of the control group was to ensure that a locally relevant prevalence rate could be compared to the rates of psychiatric comorbidities found in the neurological patients. Normative data already exists for the DAWBA in terms of British or Norwegian children in population studies. (Aebi et al., 2012, Goodman, 2000) However, it was felt that a local and culturally comparable group would be valuable. Initial plans for the healthy control group included the children of staff working at the Children's Hospital at Westmead. The intention was to involve staff from varied departments including medical officers, nursing staff, clerical staff and allied health. There were two obstacles that prohibited the success of this approach. Firstly, it was decided that the children of hospital staff were not an ideal representation of children in the general population. There was no way of ensuring that educational levels, places of residence and cultural backgrounds would be comparable to the children with movement disorders who were the focus of the study. Furthermore, utilising children of hospital staff required staff members to provide detailed and potentially sensitive information about their child's strengths and vulnerabilities, social and developmental history, to colleagues within a working environment. I was concerned that this may affect the rate of recruitment of healthy controls or the accuracy of information provided by the parents.

An alternative control group that I considered was children with fractures who were waiting to be seen in fracture clinic. This option was dismissed due to the concern that a cohort of children with fractures was likely to include a high number of active and impulsive boys whose activity may have predisposed them to injury. It was felt that this might inflate the rates of ADHD in the control group

above what may be expected in the general population. A practical limitation also included the efficient processes of fracture clinic with very short waiting times, therefore limiting the opportunities to recruit these patients whilst prior to their appointments. Consideration was also given to recruiting children through local schools however the logistical issues involved in navigating the various ethical and administrative processes required to access school students and parents for research led us conclude that such an option was untenable.

Following extensive discussion and consideration, we decided to recruit patients from the Children's Hospital emergency department. I spent two days each week from January 2015 to December 2015 in the Emergency Department and approached all eligible patients to discuss the study.

Use of the Emergency Department population as study group posed several challenges. The first was the availability of patients, as the emergency Department is busy with primarily very young and very unwell children, and there was frequently a paucity of patients who fit the eligible criteria.

For those patients with less severe medical conditions there was an arguable overlay of parental and/or patient anxiety contributing to the reasons for presentation. For example, a parent who brings an 8-year-old child to Emergency for a 24-hour history of a sore throat may be motivated by anxiety that prevents them from managing at home or visiting a primary care practitioner. This poses questions as to whether the familial rates of anxiety of children presenting to Emergency may be higher than the average population. Also, children presenting with chronic but mild medical complaints such as a recurrent headache or abdominal pain are perhaps more likely to experience co-existing anxiety or mood issues. Chronic headache or abdominal pain are known to be frequent somatic presentations of a non-organic paediatric issue. Common chronic and 'less-critical' symptoms presenting in children such as headache and recurrent abdominal pain are also known to occur in children with anxiety and mood disorders. Overall it seemed that there were definite factors suggesting that children in Emergency departments were an imperfect representation of the general population. However, they served as a practical and feasible group that can provide an additional comparison to the European normative data. However, we felt it was important to note that this group

be referred to as the 'hospital medical control' group, noting that these patients had medical issues rather than a 'normal paediatric population-based' control group.

3.6.2.2 Inclusion criteria and exclusion criteria of hospital Emergency control cohort

In addition to the general criteria outlined in the study description above, pertaining to age and verbal ability, the following exclusion criteria applied:

- Patients were excluded if they had a significant chronic illness that resulted in frequent hospitalisations or time away from school such as severe inflammatory bowel disease or an oncological history, or had a syndrome such as velo-cardiofacial syndrome. We created this exclusion because the Emergency cohort was ideally a group of otherwise normal children who had short-lived medical illnesses, although some patients had ongoing medical issues. For example, patients with asthma, allergy or a history of occasional headaches were included as it felt these would occur in local general population.

- Patients were excluded if they presented to Emergency with a critical medical or surgical issue that required urgent intervention (within 30 minutes) or if they were experiencing significant pain or distress, as it was considered unethical to recruit these children

- Patients presenting to Emergency primarily for a mental health reason were excluded. However, patients who presented with an acute medical condition on a background history of a behavioural or psychiatric diagnosis were included in the study, as we felt it would be inappropriate to exclude these patients, as it may create bias.

3.6.2.3 Recruitment

I approached patients in the Emergency Department and discussed the study with the parents and the patient. Written information was provided, and a consent form offered for signature. The majority of parents invited were agreeable to completing the DAWBA. A small number (n<10) of patients were eligible but refused to participate in the study and they cited being tired and stressed due to their child's illness or they had other young children present who required their attention.

3.6.2.4   Administration of the tool

Following attainment of consent, parents were directed to the DAWBA website with a de-identified and confidential log-in number and asked to complete the questionnaire online. The questionnaire was then completed by the parent on an iPad or laptop. If the patient was 11 years or older they were also invited to participate in the study, and if they agreed they completed the questionnaire on an iPad.

3.6.3   Study cohort 3 – Neurology control group (Charcot Marie Tooth neuropathy and epilepsy)

3.6.3.1   Explanation and rationale

A concerted effort was made to ensure that a neurological control group would be included. Children with Charcot Marie Tooth (CMT) neuropathy have a chronic illness that impacts their life in similar ways to their children with other neurological diseases. A significant distinction between the children with CMT and movement disorders is that the children with CMT are less likely to have central nervous system involvement. This presents an interesting comparison because the children have similar shared experiences of disability or impairment, with different biology.

We felt it was important to consider how patients with movement disorders compared to children with other neurological disorders. As epilepsy is the most common category of disorders seen to the Neurology Department at the Children's Hospital, we included epilepsy in the neurological controls in addition to the peripheral neuropathy group.

3.6.3.2   Inclusion criteria and exclusion criteria

In addition to the general criteria outlined in the study description above, pertaining to age and verbal ability, the following exclusion criteria applied:

- To be included, patients needed to have a diagnosis of a peripheral neuropathy or epilepsy

- Patients with a co-existing movement disorder were excluded

3.6.3.3 Recruitment

Recruitment of CMT proved more difficult than initially anticipated, primarily due the small numbers of patients presenting to the hospital. Patients were approached at monthly CMT clinics. Typically, 4 patients with CMT were seen at each monthly clinic. Several patients were outside the eligible age range. Initially a target of 100 patients was determined for the CMT group however this was soon assessed as unachievable and the goal was reduced to 50 patients. As factors such as researcher maternity leave interfered with recruitment, this target was again reduced to 25. A supplementary epilepsy subgroup was added, and I was able to achieve 37 neurology controls in total (25 CMT and 12 epilepsy) until I closed the study.

Of those neurology control patients that were contacted, all except two agreed to participate in the study. One of those that refused to participate cited having insufficient time to complete the questionnaire and the other parent cited being overwhelmed by issues pertaining to CMT.

I attended monthly peripheral neuromuscular clinics between 2012 and 2017 and approached eligible patients and their parents. Epilepsy patients and parents were approached on the wards during epilepsy monitoring admissions and clinic reviews in 2016.

3.6.3.4 Administration of the tool

Following attainment of consent, parents were directed to the DAWBA website with a de-identified and confidential log-in number and asked to complete the questionnaire online. The questionnaire was then completed by the parent on an iPad or laptop at the hospital. If the patient was 11 years or older, they were also invited to participate in the study and if agreed they completed the questionnaire on an iPad.

3.7 Data collection

3.7.1 Data collected across all cohorts

The following aspects of clinical and demographic information were collected on all patients in the study and entered in to a secure database.

3.7.1.1 Patient demographic details

- Gender of patient

- Age of patient at the time of DAWBA completion

- Highest level of education obtained by mother and father performed as a proxy for socio-economic status. This question was asked directly as part of the study recruitment process and answers.

3.7.1.2 Patient intellectual functioning

Intellectual ability was captured by way of 2 parameters

- The clinical notes describing as intellectual ability as within normal range or below. Such information was obtained from the Neurologist's letters or correspondence from schools and paediatricians, or direct reports of psychometric testing included in the files.

- Type of schooling and learning support. Options included normal class and normal school, normal class with support teacher or aide, support class in normal school, special school. (This question was directly asked as part of the study recruitment process and answers were documented in the patient file.)

3.7.2 Data collected from the movement disorder (tic and Non-tic) cohorts

The following aspects of clinical and demographic information were collected on all patients in the movement disorder cohorts.

3.7.2.1 Clinical diagnosis

Initially patients were divided into the Tic on Non-tic subgroups. All patients with tic as their primary movement disorder were allocated to the Tic cohort and all patients whose primary movement disorder was not a tic were placed in the Non-tic MD cohort.

The actual diagnosis was extracted by recording the disease name documented in patient notes and clinic letters. A verification meeting was held with the treating Neurologist to confirm the accuracy of each diagnosis.

Diagnoses in the Tic cohort were further defined as follows:

3.7.2.1.1 Tourette syndrome

Tourette syndrome referred to patients who had a combination of vocal and motor tics for a duration of at least one year and not attributable to another cause. The tics must have started before the age of 18 years. (American_Psychiatric_Association, 2013)

3.7.2.1.2 Tic disorder

Chronic tic disorder *(motor)* was defined in context with DSMV

The patient needed to have vocal or motor tics (but not both) that occur multiple times or daily or on and off for at least one year (American_Psychiatric_Association, 2013)

3.7.2.1.3 Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

PANDAS was used to name acute neuropsychiatric disease following a diagnosed streptococcal infection. Patients in this group needed to fulfil the recognised criteria presented by Swedo:

1. prepubertal onset usually between 3 years and 12 years

2. obsessive compulsive disorder, a tic disorder (lifetime diagnostic criteria)

3. sudden explosive onset of symptoms and course of recurrent sudden exacerbations and remissions

4. temporal relationship of exacerbations with streptococcal infections

5. presence of neurological abnormalities during periods of symptom exacerbation (tics, hyperactivity) (Swedo, 1998)

3.7.2.1.4 Paediatric acute-onset neuropsychiatric diagnosis

PANS was used to describe patients with an abrupt onset of obsessive-compulsive symptoms and other neuropsychiatric symptoms (motor tics were essential due to the movement disorder focus of this study) but without the association with streptococcal infection related to PANDAS above. (Murphy et al., 2014)

Patients in the Non-tic group had diagnoses defined as follows:

3.7.2.1.5 Neurotransmitter disorders

3.7.2.1.5.1 Dopa-responsive dystonia (DRD)

DRD referred to patients who had a dystonic syndrome with convincing therapeutic benefit from exogenous dopamine, plus evidence of dopamine depletion on CSF neurotransmitter analysis or genomic testing (Segawa, 2011)

3.7.2.1.5.2 Tyrosine Hydroxylase deficiency (THD)

Tyrosine hydroxylase deficiency (THD) referred to patients who have a hypokinetic rigidity syndrome with dystonia, abnormalities in cerebrospinal fluid neurotransmitter profile and a genetic testing detecting a mutation in the TH gene. (Willemsen et al., 2010)

3.7.2.1.5.3 6-pyruvoyl-tetrahydropterin synthase (6PTPS) deficiency

6-pyruvoyl-tetrahydropterin synthase (6PTPS) deficiency referred to patients with an early onset movement disorder and biochemical profile consistent with hyperphenylalaninemia followed by genetic testing demonstrating an abnormality in the PTS gene. (Leuzzi et al., 2010)

3.7.2.1.6 Genetic disorders

3.7.2.1.6.1 DYT1 dystonia

DYT1 referred to patients who had dystonia and the presence of the common mutation in the TOR1A gene. (Ozelius and Lubarr, 1993)

3.7.2.1.6.2 Myoclonus dystonia

Myoclonus dystonia referred to patients with myoclonus occurring in the upper limbs, head or neck with or without dystonia. Patients also tested positive for the SCGE mutation on genetic testing. (Peall et al., 2016)

3.7.2.1.6.3 Benign hereditary chorea

Benign hereditary chorea referred to patients with non-progressive chorea and a family history or genetic testing consistent with the diagnosis (mutation in TITF1/NKX2.1 gene) or where other causes of chorea had been reasonably excluded and genetic testing was pending (Gras et al., 2012)

3.7.2.1.6.4 Paroxysmal kinesiogenic dyskinesia

Paroxysmal kinesiogenic dyskinesia referred to patients who have brief (seconds to minutes) episodic movement disorders (typically dystonia or chorea) precipitated by voluntary movements such as moving from sitting to standing (Gardiner et al., 2015). The syndrome is often associated with PRRT2 mutations, although gene testing was not essential for a diagnosis of PKD, if fulfilling criteria of Bruno et al. (Bruno et al., 2004)

3.7.2.1.6.5 Glutaric aciduria

Glutaric aciduria referred to patients presenting with early onset dystonia, who were diagnosed as part of the newborn screening program on the basis of raised glutarylcarnitine in the dried blood spot. Diagnosis was confirmed by mutation in the GHDH gene. (Kolker et al., 2015)

3.7.2.1.6.6 Wilson's disease

Wilson's disease referred to one patient with dystonia, tremor and dysarthria and abnormalities in serum copper, caeruloplasmin and urinary copper excretion. (Ferenci, 2005)

3.7.2.1.6.7 Juvenile Huntington's disease

Juvenile Huntington's referred to one patient with a progressive dystonia and a degenerative discourse and genetic testing confirming a triplet repeat expansion in the Huntington gene. (Geevasinga et al., 2006, Gonzalez-Alegre and Afifi, 2006, Monrad and Renaud, 2013)

3.7.2.1.6.8 Newly recognised genes (KMT2B, TBC1D24, GN1B1)

A genotypic diagnosis consistent with KMT2B, TBC1D24, GN1B1 was provided for patients who had primary dystonias and genetic confirmation (de novo) on testing.

3.7.2.2 Suspected genetic (gene negative)

3.7.2.2.1.1 Suspected genetic movement disorder

A descriptive term of either a gene negative dystonia, gene negative chorea, gene negative myoclonus or gene negative tremor were used to label those patients whose disease presented with a typical genetic course but without positive gene testing.

3.7.2.2.2 Immune

3.7.2.2.2.1 Sydenham's chorea

Sydenhams Chorea was applied to patients who presented with new onset chorea (purposeless, involuntary and unpredictable movements) in the context of a recent group A beta haemolytic streptococcal infection (Ridel et al., 2010).

3.7.2.2.2.2 Basal ganglia encephalitis

Basal ganglia encephalitis referred to patients with an acute neuropsychiatric illness in the context of a highly specific basal ganglia radiological encephalitis and positive D2 receptor antibodies (Dale et al., 2012). The clinical syndrome presented as dystonia, parkinsonism, and associated behavioural change,

and the MR imaging demonstrated caudate and putamen inflammatory lesions.

3.7.2.2.2.3   Opsoclonus myoclonus ataxia syndrome (OMAS)

OMAS referred to one patient with a clinical triad of opscoclonus, myoclonus and ataxia and evidence

of neuroinflammation as evidenced by cerebrospinal fluid studies and response to immunotherapy.

(Pranzatelli and Tate, 2016, Tate et al., 2005)

3.7.2.2.2.4   Rasmussen encephalitis

Rasmussen encephalitis referred to one patient with dystonia and dystonic tremor and evidence of

inflammatory hemispheric injury on the basis of MRI abnormalities and raised cerebrospinal fluid

neopterin. (Granata and Andermann, 2013)

3.7.2.2.2.5   Anti-phospholipid chorea

Anti-phospholipid chorea referred to patients with chorea in the presence of antiphospholipid

antibodies, fulfilling criteria for antiphospholipid syndrome (Peluso et al., 2012).

3.7.2.2.3   Multifactorial (dystonic cerebral palsy)

Dystonic CP referred to patients who had experienced a known or presumed cerebral insult in the

antenatal period or shortly after a birth and who developed subsequent non-progressive impairment

of movement associated with dystonia. (Himmelmann et al., 2007, Kyllerman et al., 1982) This

diagnosis was further subdivided into one of the following aetiologies:

Prematurity defined as cause of CP

Vascular event (in utero or neonatal) defined as cause of CP

Kernicterus as cause of CP

Hypoxic ischaemic encephalopathy or traumatic delivery as cause of CP

Unknown cause of CP

3.7.2.2.4 Developmental syndromes with movement disorders

3.7.2.2.4.1 Stereotypy

Stereotypy referred to a clinical symptom rather than a diagnosis, which featured in a range of developmental disorders as well as neuro-typical children. However, the term stereotypy was listed as a diagnostic descriptor for children in whom this was the primary movement disorder, namely primary motor stereotypy in neurotypical children. Stereotypy was defined as rhythmic, fixed, repetitive and suppressible movements including head banging, body rocking, hand flapping (Fernandez-Alvarez, 2001).

3.7.2.2.5 Psychogenic

Psychogenic referred to patients whose movement disorder has been clinically determined to have a psychological cause for their symptoms and whereby other reasonable diagnoses have been excluded.

3.7.2.3 Movement disorder phenomenon

In addition to aetiological classification (as above), we also classified patients according to the movement disorder subtypes or 'phenomena', such as dystonia or chorea. I recorded the chief or most impactful movement disorder as the primary movement disorder, and then listed co-existing movement disorders as secondary and tertiary. Criteria for categorising the movement disorders were derived from the International Parkinson and Movement Disorder Society definitions. There were 2 categories, specifically stereotypy and mirror movements, for which the IPMDS did not provide a definition. For these categories I referred to the text Movement Disorders in Children by Fernandez and Aicardi (Fernandez-Alvarez, 2001).

3.7.2.3.1 Tic

Tic described involuntary, stereotypical, and repetitive, abrupt movements that are often preceded by an urge or uncomfortable feeling that may be relieved following the movement. (Fernandez, n.d)

3.7.2.3.2 Dystonia

Dystonia referred to involuntary muscle contractions that can result in abnormal posture and often repetitive movements that are twisting in nature.

(International_Parkinson_and_Movement_Disorder_Society, 2016).

3.7.2.3.3 Chorea

Chorea was defined random, 'dance-like' movements that are often fast, brief, irregular and unpredictable (Ho, 2016).

3.7.2.3.4 Myoclonus

Myoclonus referred to a series of very brief, jerk-like or 'electric shock-like' involuntary movements resulting from contraction or relaxation of muscles (Merello, n.d-a).

3.7.2.3.5 Tremor

Tremor was defined an involuntary, rhythmic oscillation in fixed plane (Verhagen, n.d).

3.7.2.3.6 Bradykinesia

Bradykinesia described slowness with decrement and degradation of repetitive movement (Merello, n.d-b)

3.7.2.3.7 Stereotypy

Stereotypy referred to a repetitive and suppressible movement that include, but are not limited to, hand waving, arm flapping, body rocking (Fernandez-Alvarez, 2001). The movements are sometimes separated according to whether they occur in the context of normally developed children, or children with neurodevelopmental delay.

3.7.2.3.8 Functional

The term functional applies to one patient whose moment was thought to have a functional (non-organic) cause and the movement was unusual and inconsistent so that it could not be defined by the above categories

3.7.2.4 Clinician based psychiatric diagnoses

The details of any psychiatric comorbidities made by the treating neurologist that was documented in the patient letters were recorded. As an additional validation process, I met with the Neurologist to confirm my interpretation of his clinical assessments and to check that all clinician diagnoses were correctly recorded.

3.7.2.5 Additional data

Further clinical details including the age of onset of the movement disorder and significant neurological comorbidities were extracted from the patient files and listed in a spreadsheet. Family history was obtained in terms of any first degree relative (parent or sibling) with any neurological or psychiatric diagnosis. All specific diagnoses were recorded. A list of all medications prescribed for the patient at the time of the study was kept. In addition, any previously prescribed psychiatric or behavioural medications taken by the patient were also recorded. Note was made if the patient had sought psychotherapy or counselling.

3.7.3 Data collected from the Emergency cohort

In addition to the demographic data collected across all cohorts, the following were obtained from all patients in the Emergency cohort:

3.7.3.1 Reason for presenting to Emergency

The reason for presentation was captured and simplified in to one of the following categories:

3.7.3.1.1 Orthopaedic

A presenting problem related to fracture, musculoskeletal pain or soft-tissue injury.

3.7.3.1.2   Gastrointestinal

A presenting problem related to abdominal pain, vomiting, constipation.

3.7.3.1.3   Respiratory

A presenting problem related to cough, exacerbation of asthma, sore throat, ear pain.

3.7.3.1.4   Fever

A presenting problem related to fever or any acute cause.

3.7.3.1.5   Rash

A presenting problem related to rash of any acute cause.

3.7.3.1.6   Head injury

A presenting problem related to head injury not requiring urgent intervention (mostly minor injuries requiring a period of observation).

3.7.3.1.7   Dental

A presenting problem related to dental pain or infection.

3.7.4   Data collected from the Neurology cohort

In addition to the demographic data collected across all cohorts, the following were obtained from all patients in the Neurology cohort:

3.7.4.1   The type of peripheral neuropathy or type of epilepsy

The diagnosis as provided by a Neurologist was recorded for each patient.

3.7.5   Overview of cohorts

In total, 397 patients participated in the study including 260 movement disorder patients and 137 hospital control patients. The movement disorder patients were divided into 2 subgroups for analysis;

the tic and Tourette Movement Disorder cohort (Tic MD, n=158) and Non-tic Movement Disorder cohort (Non-tic MD, n=102). As explained in the method chapter, the Tic cohort was included as a positive control because of the established literature of psychiatry in tic patients.

The Tic MD cohort included patients with Tourette, chronic motor tics, PANDAS and PANS, and the Non-tic MD cohort was comprised of patients with all other movement disorders.

The 137 hospital control patients were also inclusive of 2 separate cohorts; the Emergency control patients (n=100) and Neurology control patients (n=37). The specific characteristics of each cohort are explained further detail in section 4.1.3. Finally, comparison was made with data from a pre-existing community control group comprised of 10,438 British children from a national mental health survey using the DAWBA (Ford et al., 2003).

The majority of patients across all study cohorts (n=318) were patients from CHW, Australia, as outlined in the method chapter. As the study was designed to increase cohort sizes via a multicentre collaboration, a subset of patients (n=80), were recruited from GOSH, UK. Of these GOSH patients, 5 had dystonia and formed part of the Non-tic MD cohort, whilst 75 had tic disorders and contributed to the tic cohort.

All study cohorts included patients between the ages of 5 and 16 years, however the UK community sample had only surveyed children to 15 years. I had opted to include children to 16 years to extend the coverage of rare genetic movement disorders that had not been interrogated previously in the literature. The mean age of all 397 hospital patients was 10.6y. There was a male predominance in the tic cohort which was in keeping with tics affecting more males than females in general, and gender was otherwise quite evenly distributed across all other groups. Table 3.2 below presents the basic demographic descriptors, including age, gender and Australian versus UK recruitment across each cohort.

Table 3.2 Demographic data across all cohorts in the study

	Tic cohort	Non-tic cohort	Emergency control	Neurology control	Community control (Ford et al., 2003)
Total (n=)	**158**	**102**	**100**	**37**	**10,438**
Australian (n=)	83	97	100	37	
UK (n=)	75	5	0	0	10.438
Gender Male	127 (80.4%)	46 (45.1%)	56 (56.0%)	19 (51.3%)	5,212 (49.9%)
Age range	5-16y	5-16y	5-16y	5-16y	5-15y
Mean age	10.6y	10.9y	9.8y	12.3y	11y

Additional demographic data was obtained at the time of recruitment to capture socio-economic status for which tertiary education of at least one parent served as a proxy. As this data was part of the recruitment process for this trial, information was unable to be obtained from the 75 tic patients that were included from the UK. This data is captured in table 3.3, below. Rate of tertiary education in at least one parent ranged from 37.3 to 51%. Gross academic ability was observed by type of schooling attended by the patient, with the vast majority of children in all groups attending mainstream school. Within the Tic MD and Non-tic MD cohorts there were 1 and 6 children, respectively, attending special schools for children with additional needs.

Table 3.3 Data across all cohorts with a focus on education

	Tic MD cohort	Non-tic MD cohort	Emergency control	Neurology control
Total (n=)	**158**	**102**	**100**	**37**
One parent with tertiary education	34/83* (41.0%)	38/102 (37.3%)	51 (51.0%)	17 (45.9%)
Child's school ability:				
mainstream	127 (80.4%)	65 (63.7%)	96 (96.0%)	35 (94.5%)
support teacher	20 (12.7%)	25 (24.5%)	4 (4.0%)	1 (2.7%)
support class	6 (3.8%)	11 (10.8%)	0	1 (2.7%)
special school	2 (1.3%)	1 (1.0%)	0	0
No school	0	0	0	0
Schooling not known	3 (1.9%)	0	0	0

*Data from the 75 UK TIC MD cohort unavailable due to retrospective inclusion

3.7.6 Family history in both MD cohorts

Parental history of psychological, behavioural or developmental disorders were present in 44.9% of patients with tic, and 23.5% of patients from the non -tic MD cohort. Sibling family history was less common, with 17.7% of the tic cohort having a sibling with a psychiatric history and 13.7% of the Non-tic MD cohort. In 10.8% of Tic MD patients, and 6.9% of Non-tic MD patients, both a parent and sibling had a history of psychiatric diagnosis. These rates are shown in table 3.4 below.

Table 3.4 Rate of family history in each cohort

	Parent history of psychiatric disorder	Sibling history of psychiatric disorder	Both parent and sibling history of psychiatric disorder
Tic MD cohort (n=158)	71 (44.9%)	28 (17.7%)	17 (10.8%)
Non-tic MD cohort (n=102)	24 (23.5%)	14 (13.7%)	7 (6.9%)

3.7.7   Descriptive data for Tic MD and Non-tic MD cohorts

Both movement disorder cohorts were comprised of children with heterogeneous diagnoses. The Tic MD cohort included all patients with tic related movement disorders as their primary diagnosis with Tourette being the most common (n=136), following by chronic motor tic, PANDAS and PANS. The distribution of each condition with gender and mean age is demonstrated in table 3.5.

Table 3.5 Breakdown of the tic cohort with demographic data including gender and age

Tic or Tourette Diagnosis	n =	Gender	Mean age at onset	Mean age at DAWBA
Tourette Syndrome	136	109 M (80.1%)	5.6 y	10.7 y
Chronic motor tic	10	6 M (60.0%)	6.8 y	10.7 y
PANDAS	7	7M (100.0%)	5.2 y	9.9 y
PANS	5	5M (100.0%)	4.6 y	7.7 y
Total	**158**	**130M (80.4%)**	**5.7 y**	**10.6 y**

The Non-tic cohort were even more diverse in terms of movement phenomenon and aetiologies. Patients had, as their primary movement disorder, dystonia (n=66), chorea (n=12), stereotypy (n=11), myoclonus (n=6), tremor (n=5), and bradykinesia (n=1). One additional patient (n=1) had an unusual

jerking movement that was inconsistent and appeared functional in nature and difficult to characterise by standard movement disorder definitions. In many cases there was a secondary movement disorder. Table 3.6 demonstrates the number of patients with each primary movement phenomenon, their secondary movement problem (if any), as well as demographic data such as gender, age of disease onset and age at the time of completing the DAWBA.

Table 3.6 Non-tic MD cohort by movement phenomenon with demographic data

Primary movement phenomenon	n =	Secondary movement phenomenon	n =	Gender (male)	Mean age at onset (y)	Mean age at DAWBA (y)
Dystonia	66	Chorea	4	2 M	4.5	9.3
		Myoclonus	3	1 M	2.5	14. 3
		Tremor	6	3 M	6	11.3
		Bradykinesia	4	1 M	4.2	10
		Stereotypy	2	0 M	2	12
		none	47	19 M	3.5	10.8
Chorea	12	Myoclonus	2	1 M	2.7	8
		none	10	5 M	5.5	12.5
Stereotypy	11	none	11	7 M	2.5	8.5
Myoclonus	6	Dystonia	3	2M	1.7	8
		none	3	3 M	4	10. 3
Tremor	5	none	5	2 M	10	12.4
Bradykinesia	1	none	1	0M	15	15
Other (functional)	1	none	1	0 M	1	16
Total	**102**			**46 M(45.1%)**		**10.9**

Of the 102 Non-tic MD patients, a range of aetiologies were identified as causing their movement disorders. 13 patients had an identifiable neurotransmitter pathology, whilst 42 had other genetic disease processes (24 patients were proven on genetic testing and 18 were suspected only). There were 22 patients with dyskinetic cerebral palsy where the cause was regarded as multifactorial but

could be described as primarily related to birth related events such hypoxic ischaemic encephalopathy, kernicterus or an in-utero vascular event. A further 11 patients were affected by an immune neurological disease and the remaining patients had developmental (n=11) or psychogenic (n=3) conditions. An outline of the diverse aetiological processes captured in this cohort and the corresponding demographic data, including age and gender, are included in table 3.7.

Table 3.7 Aetiologies in the Non- tic MD cohort

Type of aetiology	n =	Aetiology	n =	Gender	Mean age at onset (y)	Mean age at DAWBA (y)
Neurotransmitter	13	Dopa responsive dystonia (GTP cyclohydrolase deficiency)	4	1 M	4	11
		Dopa responsive dystonia (gene negative)	3	2 M	4.5	8
		Tyrosine hydroxylase deficiency	3	1 M	0	12.7
		6 PTPS deficiency	3	0 M	0	8.3
Proven genetic	24	KMT2B dystonia	2	1 M	4.5	11
		TBC1D24 dystonia	1	0 M	1	13
		Myoclonus dystonia (SCGE)	7	5 M	2.1	11.4
		GNB1 dystonia	1	0 M	4	11
		Glutaric acidura type 1	2	0 M	0	6y
		Paroxysmal kinesiogenic dystonia (PRRT2)	4	3 M	9.5	13.8
		Benign hereditary chorea	5	3 M	0.7	14.7
		Wilson's disease	1	0 M	11	13
		Juvenile Huntington's disease	1	0 M	1	17
Suspected genetic	18	Dystonia gene negative	11	6 M	4.3	11.5
		Chorea gene negative	1	1 M	5	14

Table 3.7 Aetiologies in the Non- tic MD cohort

		Myoclonus gene negative	2	2 M	4.2	12.5
		Tremor gene negative	4	2 M	8	11.5
Immune	11	Sydenham's chorea	2	0 M	13	14
		Antiphospholipid chorea	1	0 M	12	16
		Basal ganglia encephalitis (Dopamine 2 Receptor Antibody positive)	4	2 M	33	8.3
		Rasmussen encephalitis	1	0 M	13	14
		Opsoclonus myoclonus syndrome	2	1 M	1.3	11
		Acute immune akinetic psychotic syndrome	1	1 M	15	15
Multifactorial neonatal (dystonic cerebral palsy subgroup)	22	Prematurity defined as cause	7	1M	0.5	10.9
		Vascular event (in utero or neonatal)	4	1 M	1.5	11
		Kernicterus	3	2 M	0	10
		Hypoxic ischaemic encephalopathy or traumatic delivery	4	2 M	0.2	10.3
		Unknown	4	2 M	0	11.8
Developmental	11	Stereotypy	11	7 M	2.7	8.5
Psychogenic			3	O M	13.7	14.6
	3	Psychogenic movement disorder				
Total	**102**			**46 M**	**4.7y**	**10.9**

3.7.8 Descriptive data for the hospital control cohorts

The 100 patients in the Emergency cohort were children between the ages of 5 and 16y who had presented to the Emergency department at the Children's Hospital at Westmead for acute care of a routine non-chronic medical issue. Patients were excluded if they had a significant chronic disease or if they were very unwell at the time of presentation rendering them inappropriate for inclusion. The mean age of this cohort was 9.8y and 56% were male. Almost a third of patients (n=31) presented with an orthopaedic issue such as a fracture of soft-tissue injury and close to a quarter (n=24) had an acute gastrointestinal problem such as abdominal pain, vomiting or constipation. Other reasons for presentation including respiratory concerns, fever, rash, mild head injuries or dental pain. A table depicting reasons for presentations is included below (table 3.8)

Table 3.8 Reasons for presentation to the emergency department in the Emergency cohort

Type of presentation	n=	Descriptors and examples
Orthopaedic	31	Fracture, musculoskeletal pain, soft-tissue injury
Gastrointestinal	24	Abdominal pain, vomiting, constipation
Respiratory	22	Cough, exacerbation of asthma, sore throat, ear pain
Fever	11	Fever of any acute cause
Rash	6	Rash of any acute cause
Head injury	5	Head injury without intracranial pathology
Dental	1	Dental pain and infection
Total	**100**	

The Neurology control cohort comprised of 37 patients who had been treated by the neurology department at Children's Hospital for either a peripheral neuropathy (n=25) or epilepsy (n=12). Charcot Marie Tooth 1A was by far the most prevalent peripheral neuropathy (n=17) and temporal lobe epilepsy was the most common epileptic diagnosis. The specific diagnoses attributed to all patients in the Neurology hospital control cohort are listed in table 3.9. The mean age of this cohort was 12.3y and 51.3% were male.

Table 3.9 Diagnoses in the Neurology cohort

Type of neurology	n =	Diagnosis	n=
Peripheral neuropathy	25	Charcot Marie Tooth 1A	17
		Charcot Marie Tooth 4C	1
		Charcot Marie Tooth X3	3
		Brown-Vialetto-Van-Laere syndrome	4
Epilepsy	12	Genetic generalised epilepsy	2
		Temporal lobe epilepsy	6
		Childhood absence epilepsy with frontotemporal spikes	2
		Juvenile absence epilepsy	1
		Panayiotpoulos epilepsy	1
Total	**37**		**37**

3.8 Data analysis

For all participants in the study the results of the DAWBA were obtained as a DSMV diagnosis. Each diagnosis was recorded in an excel spreadsheet alongside the DAWBA ID and clinical details as specified above. The excel cells were combined to demonstrate how many DSMV diagnoses each patient fulfilled and what each of these diagnoses were. Data was again sorted to demonstrate the rates of DSMV diagnoses in each population cohort. For the Tic MD cohort, a diagnosis of tics was obviously not considered a comorbidity.

Prevalence rates of DSMV diagnoses were measured against the aetiology of the movement disorder, as well as movement disorder phenomenology.

Associations were examined by comparing the rates of DSMV diagnoses in those patients whose parents had at least one tertiary degree between them, as well those patients with a family history in terms of sibling, parent or both.

3.9   Statistical analysis

Prevalence rates were compared with the assistance of the hospital biostatistician and use of SAS software. Chi square probabilities were calculated to determine statistical validity of prevalence rates between groups. As the Non-tic cohort was the primary cohort of interest, for the reason that these disorders have not previously been interrogated for psychiatric comorbidities in the literature, statistical analysis concentrated on differences between the Non-tic cohort and each of the other cohorts respectively.

4 Results

4.1 Primary outcome

4.1.1 Primary outcome: rate of psychiatric comorbidity across cohorts

The rate of psychiatric comorbidity, in terms of any DSMV diagnosis determined by the DAWBA, across all 260 patients with movement disorders was 106/260 (40.8%).

Of the 158 patients within the Tic MD cohort, 66 (41.8%) satisfied at least one DSMV diagnoses and 36 (22.3%) qualified for 2 or more. Within the 102 patients with a Non-tic MD cohort, 40 (39.2%) were found to have at least 1 psychiatric diagnosis and 14 (13.7%) had 2 or more. The rate of psychiatry comorbidity was not statistically significant between the two movement cohorts (Tic MD v. Non-tic MD).

Importantly, the rate of psychiatric comorbidities across all movement disorder patients and across both tic and Non-tic patients, was more than four times the rate of psychiatric diagnosis observed in the large-scale community British study in 10,438 children (9.5%). (Ford et al., 2003)

Within the Emergency control cohort, 18/100 (18%) satisfied one or more psychiatric comorbidities and only 3% were found to have two or more diagnoses. The Neurology control rate was higher than the Emergency group, but lower than both MD cohorts, with 11/37 (29.5%) patients fulfilling a psychiatric diagnosis, and in the Neurology control group (16.2%) had 2 or more DSMV diagnosis. Table 4.1 outlines the rate of DSMV diagnoses across each cohort and includes the large community control for comparison.

Table 4.1 DSMV diagnoses across all cohorts

	Tic MD cohort	Non-tic MD cohort	Emergency control	Neurology control	Community control*
Total (n=)	158	102	100	37	10 438
Any DSMV	66 (41.8%)	40 (39.2%)	18 (18.0%)	11 (29.7%)	983 (9.5%)
1 diagnosis	30 (19.0%)	26 (25.4%)	15 (15.0%)	5 (13.5%)	691 (6.7%)
2 diagnoses	23 (14.6%)	10 (9.8%)	3 (3.0%)	4 (10.8%)	222 (2.0%)
3 diagnoses	10 (6.3%)	2 (2.0%)	0	2 (5.4%)	49 (0.5%)
4 diagnoses	3 (1.9%)	1 (1.0%)	0	0	17 (0.2%)
5 diagnoses	0	1 (1.0%)	0	0	4 (< 0.1%)

*(Ford et al., 2003)

Figure 4.1 depicts the rate of any psychiatric diagnosis across each cohort, demonstrating similar rates between the Tic MD and Non-tic MD cohorts. As the Non-tic cohort represents the primary group of interest in this thesis, statistical comparisons have been made between the Non-tic cohort and the other cohorts. The difference between the Non-tic MD cohort and the Tic MD cohort was not statistically significant. The difference between the Non-tic cohort and Emergency cohort was statistically significant ($p<0.001$). The difference between the Non-tic and Neurology cohorts was not statistically significant, and the difference between the Non-tic and Community control was statistically significant ($p<0.00001$).

Overall, when comparing the Non-tic cohort to the other cohorts in terms of any DSMV disorder, only the difference between the Non-tic to Emergency, and Non-tic to Community were statistically significant.

Figure 4.1 The percentage of patients from each group who had any psychiatric diagnosis

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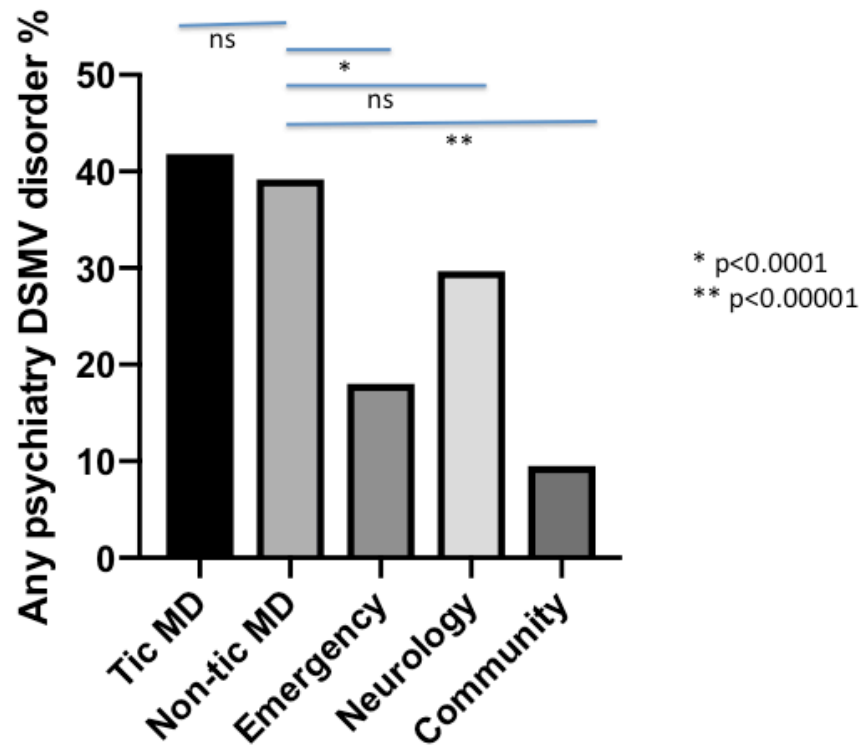
4.2   Secondary outcomes

4.2.1   Secondary outcome 1: Types of DSMV diagnoses found in each cohort

The type of psychiatric disorders identified across each cohort were calculated and compared. Due to the varying denominators, this data is presented by percentage as opposed to patient numbers.

The most common type of psychiatric disorder in the Tic MD cohort were anxiety disorders inclusive of OCD (32.3%), oppositional and conduct disorder (17.7%) and disruptive disorders such as ADHD (8.9%). In the Non-tic MD cohort, anxiety disorders (separation anxiety, generalised anxiety, social phobia and specific phobia) were the most frequent psychiatric diagnoses (28.4%). Disruptive disorders such as ADHD were the second most frequent (13.7%). There were no patients in the study who satisfied criteria for psychosis.

All psychiatric diagnoses established in both MD cohorts, and the number of patients affected by each, are listed in table 4.2.

Table 4.2 Specific diagnoses found in each cohort

	Tic cohort	Non-tic cohort	Emergency control	Neurology control	Community healthy control
Total (n=)	158.0	102.0	100.0	37.0	10 438
Any disorder (%)	41.8	39.2	18.0	29.7	9.5
Any Anxiety disorder (%)	32.3	28.4	11.0	27.0	3.8
Sep Anxiety	11.4	7.8	3.0	2.7	1.2
Social phobia	1.3	4.9	2.0	5.4	0.3
Agoraphobia	0.6	0.0	0.0	0.0	0.1
OCD	8.9	0.0	0.0	0.0	0.3
Gen anxiety	3.2	5.9	0.0	8.1	0.7
Specific phobia	3.8	3.9	4.0	2.7	1.0
Panic disorder	2.5	1.0	1.0	2.1	0.1
PTSD	0.0	1.0	1.0	0.0	0.1
Other anxiety	1.9	3.9	0.0	5.4	0.9
Depressive disorder (%)	3.2	4.9	1.0	2.7	0.9
Major depression	3.2	4.0	0.0	2.7	0.7
Other depression		0.0	0.0	0.0	0.2
Disruptive disorder (%)	8.8	13.7	5.0	13.5	5.9
ADHD combined	0.0	3.9	4.0	5.4	1.4
ADHD hyperactive	5.1	1.0	1.0	8.1	0.2
ADHD inattentive	3.8	9.8	0.0	0.0	0.7
Oppositional/conduct disorder (%)	17.7	2.9	4.0	2.7	3.8
ODD	17.7	6.9	4.0	2.7	2.3
Conduct	1.3	2.9	0.0	0.0	1.5

	Tic cohort	Non-tic cohort	Emergency control	Neurology control	Community healthy control
Social (%)	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Selective mutism	0.0	0.0	0.0	0.0	0.0
Attachment disorder	0.0	0.0	0.0	0.0	0.0
PDD/Autism (%)	**3.8**	**2.0**	**0.0**	**5.4**	**0.3**
Eating disorders (%)	**0.0**	**0.0**	**0.0**	**0.0**	**0.1**

The following graphs demonstrate the different rates of each category of disorders across all cohorts. The Non-tic cohort represents the primary interest group that has been largely unexplored in terms of psychiatric comorbidities in the past. Therefore, statistical comparisons have been performed only between the Non-tic cohort and the other cohorts.

Figure 4.2 The percentage of any anxiety disorder across all cohorts
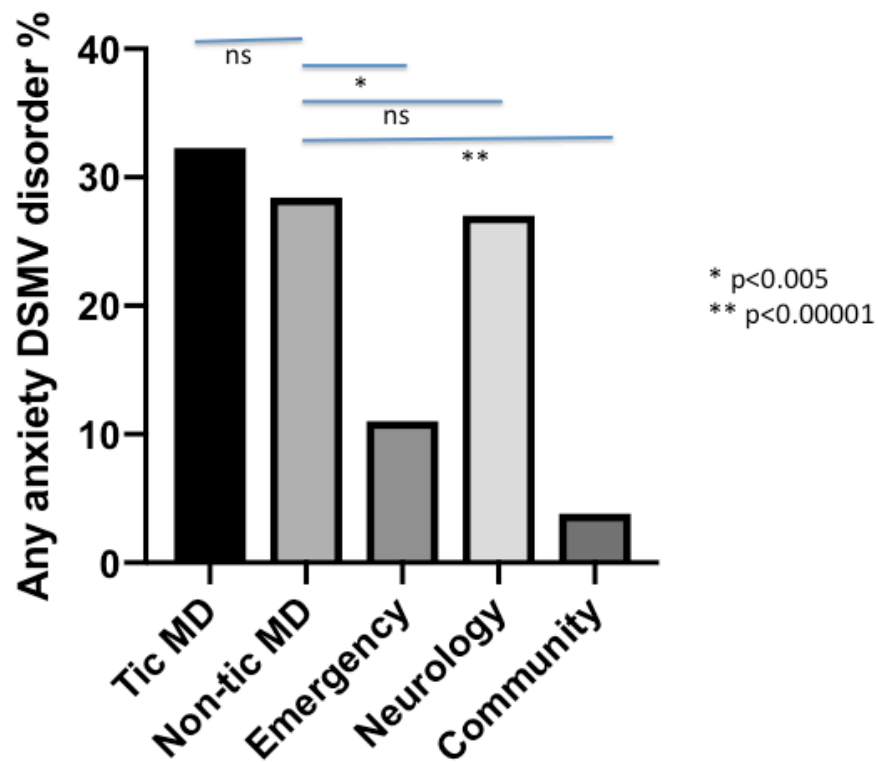
The rate of any anxiety diagnosis is shown in figure 4.2 above. Of the Non-tic MD cohort, 28.4% had any anxiety disorder, compared to 32.3% in the tic cohort. The difference between the Non-tic and Tic cohort was not statistically significant. Within the Emergency cohort 11.0% of patients had an anxiety disorder. The difference between Non-tic cohort and Emergency cohorts was statically significant (p<0.005). The rate of any anxiety disorder in the Neurology cohort was 27.0% and this was not statistically significant to the Non-tic cohort, however the rate of anxiety disorder in the community cohort was 3.8%, and this was statistically significant to the Non-tic cohort (p<0.00001). Overall when comparing the Non-tic MD cohort to the other cohorts, only the difference between the Non-tic cohort to Emergency cohort, and Non-tic cohort to Community cohort were statistically significant.

Figure 4.3 The percentage of any depressive disorder across all cohorts
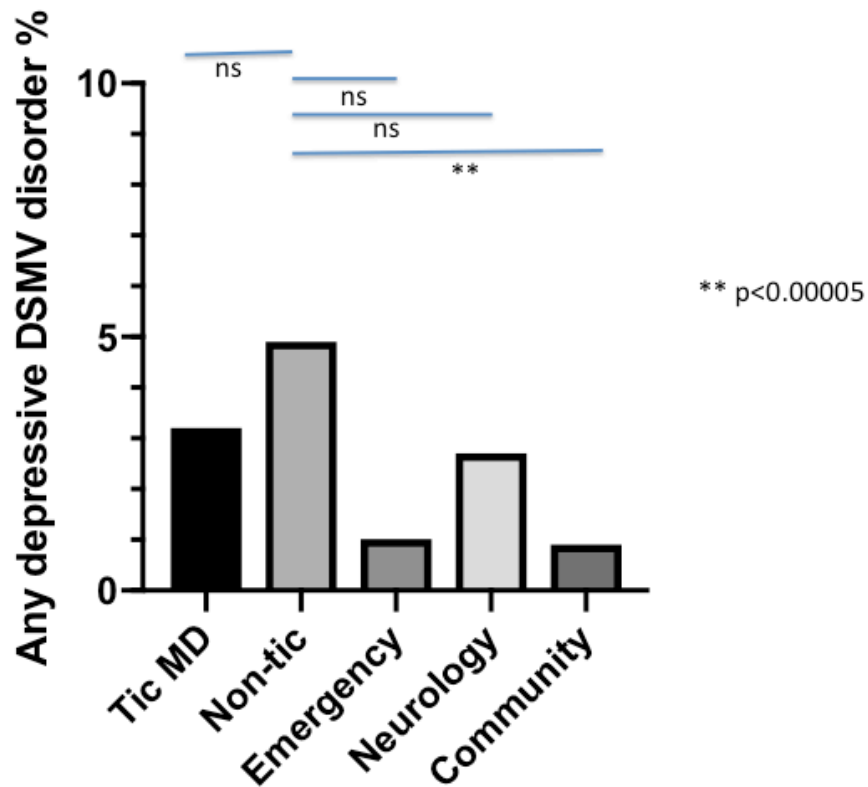
Figure 4.3 shows the rate of any depressive disorder. The rate of depressive disorder in the Non-tic cohort was 4.9%, and in the Tic cohort it was 3.2%. The difference was not statistically significant. Within the Emergency cohort the rate of depressive disorder was 1.0% and this was not statistically different to the Non-tic cohort. The rate of depressive disorder in the Neurology cohort was 2.7% and the difference with the Non-tic rate of depression (4.9%) was not statistically significant. The rate of any depressive diagnosis in the Community control was 0.9% and the difference between this cohort and the Non-tic was statistically significant. ($p < 0.00005$). Rates for depressive disorders in all cohorts were generally much lower than the anxiety disorders, and the differences between the Non-tic cohort and the other cohorts were not statically significant with the exception of the community cohort.

Figure 4.4 The percentage of any disruptive (ADHD) disorder across cohorts
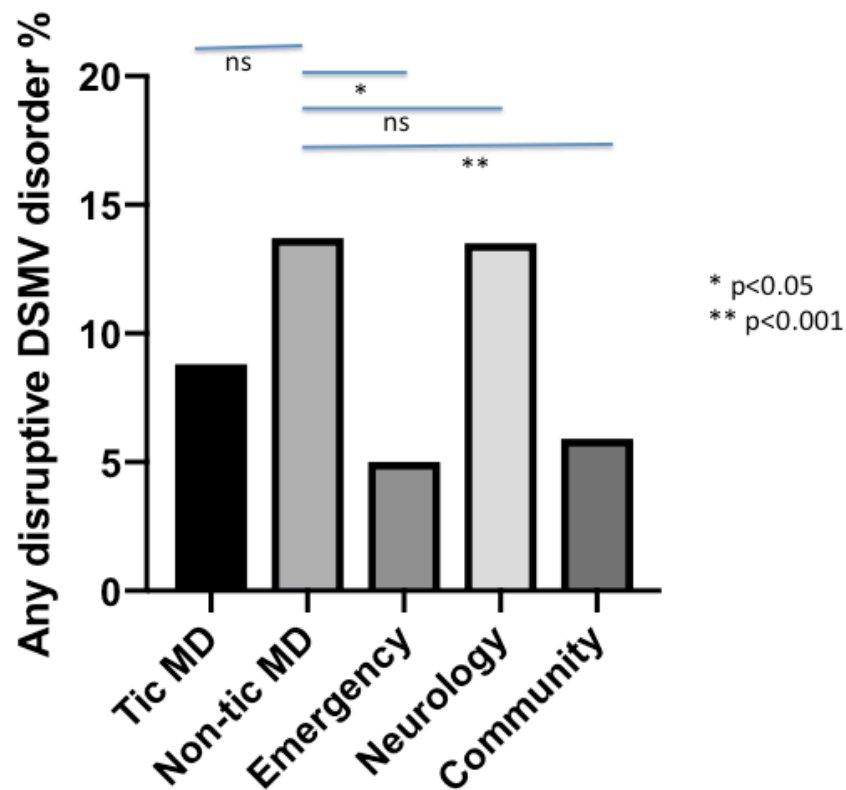
The rate of any disruptive (including ADHD) diagnosis across all cohorts is shown in Figure 4.4. The rate of any disruptive disorder in the Non-tic MD cohort was 13.7%, compared to 8.8% in the Tic MD cohort and this difference was not statistically significant. Within the Emergency control cohort the rate of any disruptive disorder was 5.0% and when comparing this the rate of 13.7% in the Non-tic cohort, the difference was statistically significant ($p < 0.05$). The rate of any disruptive diagnosis in the Neurology control cohort was 13.5% and this was not statistically significant to the Non-tic cohort. The rate of any disruptive diagnosis in the community control was 5.9% which was statistically significant to the Non-tic cohort (13.7%) ($p < 0.001$).

Figure 4.5 The percentage of any oppositional or conduct diagnosis across all cohorts
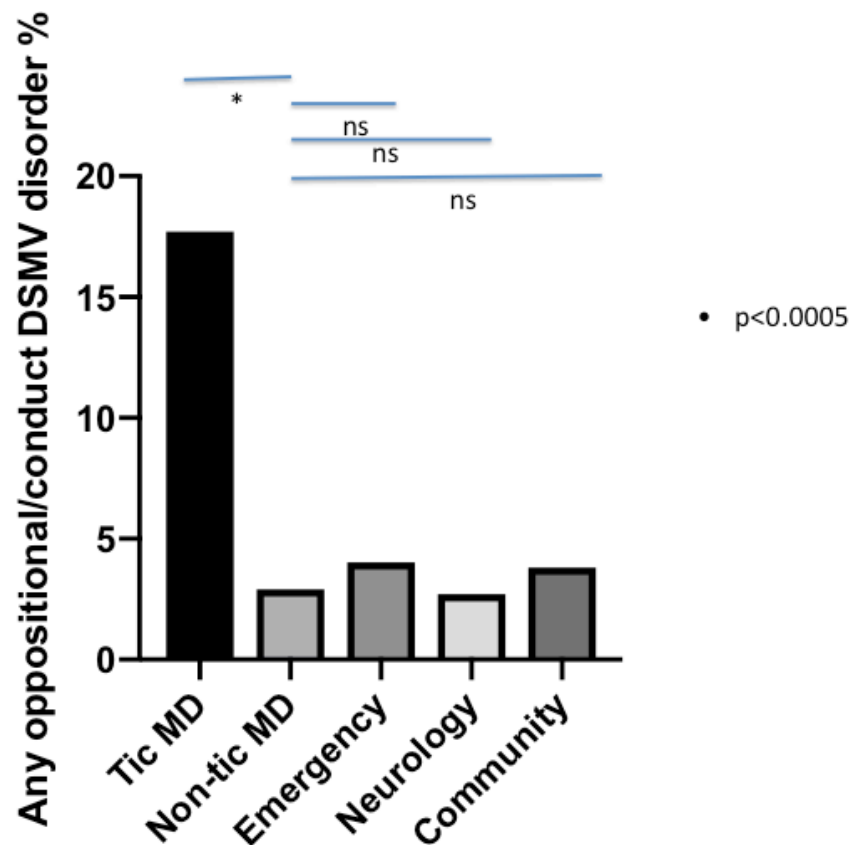
The rate of any oppositional or conduct diagnosis is shown in figure 4.5. The rate of any oppositional or conduct disorder in the Non-tic cohort 2.9%, compared to 17.7% in the Tic cohort. The difference between the Non-tic and Tic cohort was statistically significant ($p<0.0005$) Within the Emergency control cohort the rate of any oppositional or conduct diagnosis was 4.0% and the difference between this and the Non-tic cohort was not statistically significant. The rate of any oppositional or conduct diagnosis in the neurology control cohort was 2.7% and the difference between this rate and the rate in the Non-tic cohort was not statistically significant. Within the community control, the rate of any oppositional or conduct diagnosis was 3.8% and this was not statistically significant in difference to the Non-tic cohort. Overall, with respect to the rate of opposition or conduct disorders across all cohorts, the only statically significant difference was that between the tic and Non-tic cohorts.

4.2.2   Secondary outcome 2: Prevalence and type of DSMV diagnoses by tic disorder

Rate of psychiatry was examined within the different diagnostic entities of both Tic MD and Non-tic MD cohort. Within the Tic MD cohort, psychiatric comorbidities were found in all patients with PANDAS and PANS, and 40.0% of those diagnosed with chronic motor tic disorder. Of those patients with TS, 36.7% satisfied criteria for DSMV diagnosis. The range of specific diagnoses present were similar across the subgroups of diagnosis, with anxiety disorders, depression, disruptive and oppositional disorders seen most commonly. PDD/autism was demonstrated in the tic and chronic motor tic patients but absent in PANDAS and PANS subgroup, although the numbers of these latter subgroups are small, and so statistical comparisons were not performed. These findings are outlined in table 4.3.

Table 4.3 Rate of psychiatry and specific psychiatric diagnoses seen by tic disorder

Tic or Tourette Diagnosis	Patients with psychiatry (%)	Specific diagnoses present
Tourette Syndrome (n=136)	50 (36.7%)	ODD, (24), Separation anxiety (9), OCD (9), ADHD hyperactive (6), PDD/autism (5), specific phobia (4), panic disorder (3), other anxiety (3), social phobia (2), ADHD inattentive (2), conduct disorder (2), generalised anxiety (1), major depression (1)
Chronic motor tic (n=10)	4 (40%)	Separation anxiety (2), generalised anxiety (2), OCD (2), ODD (2) specific phobia (1), major depression (1), ADHD inattentive (1), PDD/autism (1)
PANDAS (n=7)	7 (100%)	Separation anxiety (5,) generalised anxiety (2), OCD (2), ADHD hyperactive (1)
PANS (n=5)	5 (100%)	Separation anxiety (4), ADHD inattentive (2), specific phobia (1), OCD (1), panic disorder (1), major depression (1), ODD (1)
Total (n=158)	**66 (41.8)**	**ODD (27), Separation anxiety (20), OCD (14), ADHD hyperactive (7), PDD/autism (6), specific phobia (6), ADHD inattentive (5), other anxiety (3), generalised anxiety (3), social phobia (2), , conduct disorder (2), major depression (3), panic disorder (1)**

4.2.3 Secondary outcome 3: DSMV prevalence and diagnoses by movement disorder phenomenon

When analysed by movement disorder phenomenon, and excluding the single functional patient, patients with chorea had the highest rate of psychiatric comorbidity (66.7%) followed by tremor (60.0%) then, stereotypies (45.5%) and dystonia (33.3%).

Within the dystonia subgroup of 66 children, anxiety disorders were the most common psychiatric comorbidity, including separation anxiety, generalised anxiety, social phobia and specific phobia. ADHD (including the hyperactive, inattentive and combined subtypes) was also found in the dystonia subgroup, along with ODD and major depression.

Patients with chorea were also found to have anxiety and mood disorders and disruptive/ADHD disorders. Only one patient with myoclonus as a primary movement disorder had a psychiatric comorbidity and this was ADHD combined. Patients who had myoclonus as a secondary movement disorder, with dystonia or chorea as their primary movement problem, were found to have anxiety disorders, ADHD and ODD. 60% of patients with tremor had a DSMV diagnosis, although the group was small (n=5 only). Anxiety disorder and mood disorders were also observed in the functional subgroup and this was also the only category in which PTSD was diagnosed.

The rates and specific types of psychiatric comorbidities are outlined in table 4.4 below.

Table 4.4 Rates and types of DSMV diagnoses by movement disorder in the Non-tic cohort

Primary movement disorder	Secondary movement	n =	Patients with DSMV psychiatry (%)	Specific diagnoses present
All dystonia		**66**	**22 (33.3%)**	**separation anxiety (5), social phobia (5), specific phobia (4), ADHD combined (3), ADHD inattentive (3), ODD (3), generalised anxiety (2), other anxiety (1), Major depression (1), ADHD hyperactive (1)**
Dystonia	Chorea	4	1	Major depression (1), ADHD combined (1), ADHD inattentive (1)
Dystonia	Myoclonus	3	2	Other anxiety (1), specific phobia (1), ADHD inattentive (1)
Dystonia	Tremor	6	4	Separation anxiety (2), social phobia (1), ADHD combined (1), ADHD hyperactive (1)
Dystonia	Bradykinesia	4	1	Separation anxiety (1)
Dystonia	Stereotypy	2	1	Generalised anxiety (1), specific phobia (1)
Dystonia	none	47	13	Separation anxiety (2), social phobia (4), specific phobia (2), generalised anxiety (1), ADHD combined (1), ADHD inattentive (1), ODD (3)
All chorea		**12**	**8 (66.7%)**	**Separation anxiety (1), other anxiety (1) bipolar/mania (1), major depression (2), ADHD inattentive (1), ODD (3) conduct disorder (1**
Chorea	Myoclonus	2	1	ODD (1)
Chorea	none	10	7	Separation anxiety (1), other anxiety (1) bipolar/mania (1), major depression (2), ADHD inattentive (1), ODD (2) conduct disorder (1)
All myoclonus		**6**	**1 (16.7%)**	**ADHD combined (1)**

Myoclonus	Dystonia	3	0	-
Myoclonus	none	3	1	ADHD combined (1)
All tremor	**none**	**5**	**3 (60.0%)**	**Generalised anxiety (1), panic disorder (1), major depression (1)**
All bradykinesia	**none**	**1**	**0 (0%)**	**-**
All stereotypy	**none**	**11**	**5 (45.5%)**	**Generalised anxiety (1), ADHD inattentive (3), ODD (1) PDD/Autism (2)**
All other (functional)	**none**	**1**	**1 (100%)**	**Generalised anxiety (1), PTSD (1), major depression (1) ADHD, conduct disorder**
		102	**40 (39.2%)**	

In addition to analysing the rate of psychiatric comorbidities by movement disorder phenomenon, I also evaluated the Non-tic cohort with respect to aetiology.

Within in the Non-tic cohort, psychiatric comorbidities were most common in patients with disorders caused by genetic mutations, both suspected and proven. The rate of DSMV diagnosis in the proven genetic group was 54.2% and within the suspected genetic group the rate of DSMV diagnoses was 50.0%. The specific psychiatric disorders across both the proven and suspected genetic disorders were similar, with anxiety disorders the most commonly reported, as well as disruptive disorders and ODD also found.

The group least affected by psychiatric comorbidities in this cohort were patients with neurotransmitter disorders, although the prevalence in this group remained above expected norms, with a rate of 23.1%. The patients who had psychiatric comorbidities in the neurotransmitter subgroup had anxiety disorders, as well as one patient who had conduct disorder.

DSMV diagnoses occurred in 22 patients (27.3%) with dyskinetic cerebral palsy. Within the multifactorial cerebral palsy subgroup, the psychiatric comorbidities included anxiety and disruptive disorders.

Psychiatric comorbidities were detected in 36.4% of the immune subgroup and the specific diagnoses were quite varied, including social phobia, major depression, bipolar/ mania, ADHD combined and ODD.

The rates and types of psychiatric comorbidity found across the aetiological entities are shown in table 4.5.

Table 4.5 Rate of psychiatry and specific psychiatric diagnoses by movement disorder aetiology

Aetiology	n =	Patients with psychiatry (%)	Specific diagnoses present
All neurotransmitter	**13**	**3 (23.1%)**	**Generalised anxiety disorder (2), separation anxiety (1), conduct disorder (1)**
Dopa responsive dystonia (GTP cyclohydrolase deficiency)	4	0	
Dopa responsive dystonia (gene negative)	3	2	Generalised anxiety (2), conduct disorder (1)
Tyrosine hydroxylase deficiency	3	1	Separation anxiety (1)
6 PTPS deficiency	3	0	-
All proven genetic	**24**	**13 (54.2%)**	**Separation anxiety (4), ADHD inattentive (3), ODD (3), other anxiety (2), social phobia (1), specific phobia (1), major depression (1), ADHD combined (1), ODD (1)**
KMT2B dystonia	2	2	Separation anxiety (1), social phobia (1), ADHD combined (1), ADHD inattentive (1)
TBC1D24 dystonia	1	0	-
Myoclonus dystonia (SCGE)	7	3	Specific phobia (1), other anxiety (1), ADHD inattentive (1)
GNB1 dystonia	1	0	
Glutaric acidura type 1	2	1	Separation anxiety (1)
Paroxysmal kinesiogenic dystonia (PRRT2)	4	2	Major depression (1), ODD (1)
Benign hereditary chorea	5	4	Separation anxiety, (1) other anxiety (1), ADHD inattentive (1), ODD (2)
Wilson's disease	1		
Juvenile Huntington's disease	1	1	Separation anxiety (1)

All suspected genetic	**18**	**9(50%)**	**Separation anxiety (2), generalised anxiety (2), social phobia, (1), specific phobia (1), major depression (1), panic disorder (1), ADHD combined (2), ADHD hyperactive (1), ODD (1)**
Dystonia - gene negative	11	6	Separation anxiety (2), generalised anxiety (1), social phobia, (1), generalised anxiety (1), specific phobia (1), ADHD combined (1), ADHD hyperactive (1), ODD (1)
Chorea - gene negative	1	0	
Myoclonus - gene negative	2	1	ADHD combined (1)
Tremor gene negative	4	2	Generalised anxiety (1) panic disorder (1), major depression (1)
All immune	**11**	**4(36.4%)**	**Social phobia (2), major depression (2), Bipolar/mania (1) ADHD combined (1), ODD (1)**
Sydenham's chorea	2	2	Bipolar/mania (1), major depression (2)
Antiphospholipid chorea	1	0	
Basal ganglia encephalitis (Dopamine 2 Receptor Antibody positive)	4	2	Social phobia (2) ADHD combined (1), ODD (1)
Rasmussen encephalitis with hemidystonia	1	0	-
Opsoclonus myoclonus syndrome	2	0	-
Acute immune akinetc psychotic syndrome	1	0	-
All multifactorial (dyskinetic CP group)	**22**	**6 (27.3%)**	**ADHD inattentive (2), specific phobia (2), separation anxiety (1), generalised anxiety (1), social phobia (1)**
Prematurity defined as cause	7	4	Separation anxiety (1), social phobia (1), specific phobia (1), ADHD inattentive (2)
Vascular event (in utero or neonatal)	4	0	
Kernicterus	3	1	Generalised anxiety (1)

Hypoxic ischaemic encephalopathy or traumatic delivery	4	1	ADHD inattentive (1), specific phobia (1)
Unknown	4	0	-
Stereotypy (All developmental)	**11**	**4(36.4%)**	**Generalised anxiety (1), ADHD, inattentive (2) ODD (1), PDD/autism (2)**
Psychogenic movement disorder	**3**	**1(33.3%)**	**Generalised anxiety (1), PTSD, (1), major depression (1), ADHD inattentive (1), conduct disorder (1)**
	102	**40 (39.2%)**	

4.2.4 Secondary outcome 5: Correlation between diagnosis made by clinician and DAWBA diagnoses

For those patients recruited at CHW, Australia (n=180), (inclusive of both Tic MD and Non-tic MD patients), DAWBA psychiatric diagnoses were compared to clinical diagnoses attributed by the patient's treating Neurologist. Overall, the Neurologist had diagnosed a DSMV diagnosis in 48.3% of patients with movement disorders, compared to 46.1% diagnosed by the DAWBA.

Table 4.6 below demonstrates the number of patients with and without clinician diagnosis that received positive or negative for DAWBA psychiatric diagnosis.

Table 4.6 Clinician versus DAWBA diagnosis in all Australian movement disorder patients

Clinician findings for all movement disorder patients	DAWBA positive for DSMV	DAWBA negative for DMSV
Clinician diagnosis (n=87)	56	31
No clinician diagnosis (n=93)	27	66
All Australian cohort (n=180)	83	97

Of the 180 MD patients recruited at CHW, Australia, 87 were diagnosed with a DSMV diagnosis by their treating Neurologist. Of those 87, 56 (64.3%) were also diagnosed with a psychiatric diagnosis by the DAWBA. Presented alternatively, of the 180 MD patients recruited at CHW, Australia, the DAWBA diagnosed a psychiatric comorbidity in 83. Of those 83 DAWBA positive patients, the treating Neurologist had diagnosed a psychiatric disorder in 56 (67.5%). Within the 180 MD patients recruited at CHW, the DAWBA was negative for psychiatry disorder in 97. Of those 97, the treating Neurologist had been in agreement that no psychiatric diagnosis applied in 66 cases (68.0%).

4.2.5   Secondary outcome 6: Relationship between clinical and DAWBA OCD findings

Special consideration was allocated to diagnosis of OCD as the prevalence rates found in this study were lower than anticipated. Across both Tic and Non-tic patients the Neurologist had diagnosed 36 cases with OCD. The DAWBA also diagnosed OCD in 12 (33.3%) of these cases, however an additional 11 (31.4%) of clinician rated OCD patients, the DAWBA diagnosed an alternative anxiety diagnosis such as separation anxiety or specific phobia. In 13 (36.0%) of cases of clinician diagnosed OCD patients, the DAWBA did not attribute any psychiatric diagnosis. Rates of positive and negative DAWBA vs clinician diagnose are outlined in table 4.7.

Table 4.7 Clinician versus DAWBA OCD diagnosis in all Australian movement disorder patients

Clinician findings for all movement disorder patients	DAWBA positive for OCD	DAWBA negative for OCD
Clinician diagnosis (n=36)	12	24
No clinician diagnosis (n=144)	4	140
All Australian cohort (n=180)	16	164

Of the 180 MD patients recruited at CHW, Australia, the DAWBA diagnosed OCD in 16 patients. The treating Neurologist had also diagnosed OCD in 12 of those 16 patients (75.0%). Within the same Australian 180 MD patients, the treating Neurologist had diagnosed OCD in 36, and the DAWBA agreed in 12 (33.3%) of cases. Interestingly however, of the remaining 24 who were clinician positive and DAWBA negative for OCD, 9 were diagnosed with a different anxiety disorder by the DAWBA.

4.3   Secondary outcome 7: Description of therapeutic interventions

With respect to all MD patients, both with and without DSMV diagnoses, pharmacological therapies for psychiatric symptoms had been prescribed for 40.5% of the Tic MD cohort and 15.7% of the Non-tic MD cohort. Medications included fluoxetine, fluvoxamine, risperidone, quetiapine, clonidine, methylphenidate and atomoxetine. Psychological therapy had been recommended for 37.3% of all Tic MD patients and only 14.7% of Non-tic MD patients. Interestingly, for patients with a DAWBA DSMV diagnosis, 45.5% of patients in the Tic MD cohort had taken psychiatric medications compared to only 22.5% of Non-tic patients. In terms of psychological therapy in the DAWBA DSMV positive subgroup, 43.9% of the Tic patients had accessed therapy, compared to only 15.0% of Non-tic patients with a psychiatric diagnosis.

4.4   Associations

4.4.1   Impact of parental tertiary education

I analysed whether parental tertiary education could be a confounder and influence the rate of psychiatric diagnoses in offspring. There was no clear difference in parental tertiary education in the different cohorts. In the children with movement disorders (both Tic and Non-tic movement disorder), of the patients with a DAWBA rated DSMV diagnosis, 40.0% of parents had tertiary education, whereas in patients without a DAWBA rated DSMV diagnosis, 25.9% of parents had tertiary education. The difference was not statically significant (p= 3.871).

4.4.2   Impact of neurological comorbidities in the Non-tic cohort

A further factor which may have influenced the DSMV psychiatric diagnosis was the presence or absence of neurological comorbidity. As outlined in table 4.8 below, neurological comorbidities were noted in 45.1% of patients with Non-tic MD patients and included

hypertonia or hypotonia, bulbar or cranial nerve dysfunction, ataxia and epilepsy. In the Tic MD cohort neurological comorbidities were only reported in 1.9%. Overall, neurological comorbidities were not associated with increased rates of psychiatric comorbidities, however the smaller subsets of these study cohorts with neurological are not ideal for allowing extensive extrapolations regarding these associations.

Table 4.8 Neurological in each cohort and rate psychiatric diagnosis

	Neurological comorbidities	Patients (n=)	Rates of DSMV diagnoses in patients with specific comorbidities
Tic MD (n=158)	**All neurological comorbidities**	**3**	**30.0%**
	Epilepsy	3	30.0%
Non-tic MD (n=102)	**All neurological comorbidities**	**46**	**34.8%**
	Hypertonia	28	27.5%
	Bulbar/crania nerve dysfunction	8	7.8%
	Ataxia	4	3.9%
	Epilepsy	4	3.9%
	Hypotonia	4	3.9%

5 Discussion

5.1 Important novel finding of psychiatric prevalence

This study demonstrates that children with movement disorders are four times as likely to have a psychiatric diagnosis than children in the general community. More importantly, this is the first large study that specifically examines children with Non-tic movement disorders, including dystonia and chorea, and describes that whilst there has long been concern about elevated rates of psychiatric comorbidities with tics and TS, children with other movement disorders such as dystonia and chorea have almost the same rate of psychiatric comorbidities as children with tics (39.2% in the Non-tic MD cohort: 41.8% in the Tic MD cohort). Of the 102 Non-tic patients in this study, greater that 1/3 (39.2%) satisfied criteria for a DSMV diagnosis. This is the largest study of psychiatry in paediatric dystonia performed to date, comprising of 66 patients with dystonia secondary to primary and secondary aetiologies. One third of these children (33.3%) had a psychiatric comorbidity. These comorbidities represent a burdensome aspect of the patient's neurological disorder. The psychiatric diagnoses may often be unrecognised, and therefore untreated. These new insights into the high rates of psychiatric comorbidities provide an important contribution to our understanding of paediatric movement disorders, and opportunities to improve patient care.

5.2 Psychiatry in the Non-tic cohort

This study included 102 patients with Non-tic movement disorders, and 39.2% had a psychiatric diagnosis. This rate was not statistically significant to the tic movement disorder cohort.

The rates of psychiatric comorbidities in dystonia patients (33.3%), our largest Non-tic movement disorder subgroup, were in keeping with anecdotal reports of troubling anxiety disorders in this population. Children with chorea had rates of psychiatry (66.7%) elevated

above the other movement disorder types, although the chorea subgroup was small (n=11). The high rates of psychiatric problems were expected within the Sydenham's chorea patients, however the elevated rate of psychiatry in patients with genetic chorea had not been anticipated.

In terms of aetiology, patients with suspected genetic disorders had similar rates of psychiatric conditions to those with proven genetic conditions. Interestingly, patients with strictly neurotransmitter diagnosis were lower than those in the broader genetic subgroup. It is possible that larger multicentre studies may be needed to evaluate psychiatric comorbidities of the rare neurotransmitter disorders with greater accuracy.

Psychiatric comorbidities were less frequent in the dyskinetic cerebral palsy sub-group. Anecdotal discussions with treating clinicians of these patients had led to a suspicion that psychiatric problems were a very common problem for children with dyskinetic cerebral palsy. The method of this study, however, was not purpose built for evaluating children with cerebral palsy, many of whom have communication or intellectual disabilities. As children who were non-verbal were excluded from this study, the patients with cerebral palsy represent a particularly high functioning subgroup and this is likely to have impacted on the psychiatric profile. Moving forward, a study of psychiatric comorbidities for children with dyskinetic cerebral palsy by way of a tool not relying on verbal responses would be a valuable contribution to our understanding of psychiatry in dyskinetic cerebral palsy.

5.3   Differences in treatment patterns between the Tic and Non-tic cohort

One of the most pertinent and surprising findings in this study related to therapies provided to patients in the Tic and Non-tic cohorts. Whilst the rates of DSMV diagnosis were similar in both MD cohorts, the rate of treatment was very different. Essentially, patients with tics and psychiatric diagnoses were far more likely to have received therapy than patients with Non-tic movement disorders and psychiatric diagnosis. Of all the patients with tics who had a

psychiatric comorbidity, 45.5% were either receiving or had received psychiatric medications, and 43.9% had received psychological therapy. These numbers are far greater than the Non-tic cohort, where only 22.5% had taken psychiatric medications and 15.0% had undergone psychological therapy. Of course, these are crude comparisons that do not take in to account the severity of each patient's comorbidity, or other factors affecting treatment such as treatment adherence or parental insight, however it is likely that these numbers are influenced by the difference in our understandings of these movement disorders. Tic disorders and TS have been well researched with respect to psychiatric comorbidities and screening for these comorbidities is generally considered best practice for these patients. However, Non-tic movement disorders have remained largely unexplored in terms of psychiatric comorbidity until now, suggesting many patients have gone undiagnosed and untreated in terms of their psychiatry.

5.4   Prevalence of psychiatry in the various tic disorders

It was interesting to note that the rate of psychiatry in chronic motor tics (40.0%) was elevated above those with definite Tourette (36.7%). One possible reason for this was that children with motor tics are primarily looked after by general paediatricians. The patients recruited for this study with chronic motor tics were all being managed at a specialised tic clinic at a quaternary paediatric hospital. They had all been reviewed by paediatricians and referred on for specialised care, mostly in view of their severe tics or other complexities (therefore representing referral bias). With that in mind it is not surprising that this most severe subgroup of patients with a chronic tic would have an elevated rate of comorbidities. It was not surprising to find 100% rates of comorbidities in PANDAS and PANS, as these conditions both have emotional symptoms as part of their diagnostic criteria.

5.5   Specific psychiatric comorbidities detected

The most common comorbidities across all groups were anxiety disorders, with ADHD also commonly observed. ODD was seen frequently in the Tourette group and oppositional and conduct problems have been observed in other studies of patients with TS (Khalifa and von Knorring, 2006). Our rates of ADHD (13.7% in the Non-tic MD and 8.8% in the tic MD cohort) were lower than previously published rates of 21-90% (Mol Debes, 2013) and it is expected that the absence of school teacher responses in our study lowered the reported symptoms and impact. The option of seeking teacher responses, was considered during the study design however it was considered that this would be logistically difficult and potentially reduce the level of uptake of parents who may not want to draw school-based attention to their child's psychiatric profile. Another comorbidity that was lower than anticipated in the tic cohort was OCD, with other studies showing rates of obsessive compulsive symptoms in approximately 40% (Como et al., 2005, Lebowitz et al., 2012). During the comparison between DAWBA and clinician diagnosis it became evident that of the 36 patients that had been diagnosed with OCD by their treating Neurologist, 9 (25.0%) were attributed an alternative anxiety diagnosis by the DAWBA, but not OCD. This occurred most commonly with patients being diagnosed with separation anxiety by the DAWBA. When I spoke to parents of children who experienced OCD it was often the case that the family had so effectively adjusted to the OCD conditions, that the impact was negligible within the family unit (negating the significant impact required for the DAWBA diagnosis) but that the child avoided being away from their main carer as a result, and was therefore allocated a diagnosis of separation anxiety.

The DAWBA determines diagnosis by impact or 'burden' and does not count prevalence on the basis of symptoms only. During the DAWBA interviews many parents seemed to respond to the questions about impacts and burden by replying with a variation of "He/She will never be a burden. We have just needed to adjust to it." This observation was made during the paper that reported UK Mental Health Survey in which the DAWBA was initially utilized and several

studies have shown that tools relying on impact for diagnosis produce lower prevalence rates (Anderson et al., 1987, Ford et al., 2003, Shaffer et al., 1996). Furthermore several psychiatric comorbidities such as obsessive-compulsive disorder and depression tend to increase in later adolescence and the mean age of the population (10 years) would likely lead to a lower rate of psychiatric comorbidities captured (Ford et al., 2003).

5.6   The DAWBA as a screening tool

Overall the rates of psychiatric comorbidities in children with tic movement disorders children were lower than other studies where comorbidities have been described in up to 90% (Cavanna and Termine, 2012). The DAWBA has been described as more conservative than other psychiatric screening tools such as the DISC and CAPA; in one study the DAWBA detected 1 or more diagnoses in 17.7% of patients in paediatric care clinics, whilst the DISC and CAPA diagnosed disorders in 47.1% and 32.4% respectively (Angold et al., 2012). Several papers have confirmed that the DAWBA tends to under diagnose emotional disorders. In the study by Groth that examined comorbidities in Tourette, the DAWBA was used along with several other tools and compared to clinical assessment. The rates of OCD were significantly lower in the DAWBA assessments than the clinical assessments (6% vs 24%). (Groth et al., 2017b) Another paper looking at the clinical utility of the DAWBA against clinical assessment in patients with suspected ADHD (n=86) found there was a high rate of false negatives of emotional disorders when using DAWBA (13 false negatives) and suggested emotional disorders were conservatively diagnosed by the DAWBA. (Foreman et al., 2009) For my study, it was felt than a tendency to under-diagnose, rather than over-diagnose, would lend to a study of greater validity. In this context it was important to use the Tic MD cohort as a positive control, and this study showed similar rates of psychiatric comorbidity between tic MD and Non-tic MD patients.

In this study, assessment of the Australian subgroup of movement disorder patients revealed that the DAWBA was slightly more conservative than the treating clinician, attributing a DSMV diagnosis to 45.9% of patients compared to the treating Neurologist who had diagnosed 48.1% of patients with psychiatry.

5.7   The control cohorts

The hospital control groups both consisted of patients recruited in a quaternary hospital and both hospital control groups were elevated in their rate of psychiatry when compared to the community control. The Emergency control group was comprised of children between 5 and 16 years who presented to the Emergency Department at CHW for an acute medical condition. The prevalence of psychiatry in this cohort (18.0%) was within the range of 18-21% found in previous studies that utlised the DAWBA in a tertiary hospital outpatient (Jesmin et al., 2016, Machnes-Maayan et al., 2014).

Whilst patients with significant chronic illness were excluded from the study, there were several factors that led to suspicion that psychiatric prevalence in these patients would be greater than the community prevalence. First of all, these patients were being recruited at a time of illness and therefore family stress, which may have influenced their view of recent behaviour and resulted in recall bias. Secondly, the study excluded children who were critically unwell or in pain for obvious ethical reasons. This exclusion criteria meant that patients who remained eligible had been brought to a quaternary Emergency department for non-critical acute medical concerns including fevers, rashes, upper respiratory tract infections and abdominal pain. Whilst several patients in this control cohort required hospital interventions such as plastering fractured limbs or nebulized treatment for asthma, many patients attended hospital with medical issues that could have been seen by general practitioner or outpatient clinic. There are numerous reasons why families may chose care from an Emergency department as opposed to a local primary care setting, and some of these include parental

anxiety, previous negative experiences in accessing local health services, socio-economic barriers to seeking outpatient care (including difficulties in making or attending appointments or being unable to afford services and medications) and factors relating to the child themselves including the child's own level of anxiety about their symptoms or pre-existing developmental issues. Therefore, it is not unreasonable to suggest that psychiatric conditions may be elevated in this cohort. Another reason that parents reported bringing their child to Emergency throughout the recruitment process was that relatively benign complaints had occurred for a concerning amount of time. This was specifically the case with headaches and abdominal pain. It is well understood in the paediatric discipline that chronic headaches and chronic abdominal pain frequently co-exist with mood and anxiety problems, which may explain the elevated psychiatric diagnoses in the emergency cohort when compared to the community control.

The 27% rate of psychiatry in the Neurology control is likely explained by the incorporation of epilepsy where rates of psychiatric comorbidity have been reported to be at least 40% (Grabowska-Grzyb et al., 2006, Verrotti et al., 2014). In addition, patients in the neurology cohort have been dealing with chronic illness that may potentially contribute to psychiatric vulnerabilities not found in healthy populations. I attempted to avoid recruitment bias in this cohort by recruiting all patients who fulfilled the inclusion criteria, rather than those who were recognised as having psychiatric problems. The Neurology control group represented the most challenging aspects of recruitment for this study, due to the small number of patients affected by peripheral neuropathies in the hospital, and the high rate of moderate to severe intellectual disability in the epilepsy group making them ineligible. A limitation of the study was the small size of this Neurology cohort, and the subsequent difficulty in statistically comparing rates from this group (due to the small cohort size). The difference between the rates of psychiatry in the Non-tic cohort and the Neurology cohort was not statistically significant for all comparisons, which may be a reflection of the prevalence of psychiatry in

those groups being similar, however it may also reflect the fact that larger numbers are needed, particularly in the Neurology cohort, to interrogate any differences more completely.

5.8   Limitations

Obviously, a larger study cohort, especially of the Neurology control group, would have been advantageous to the study. In actuality the initial study method included plans for 100 neurology control patients with CMT. As the study unfolded it became evident there were not enough CMT patients eligible in the age range to recruit. The study was then amended to aim for 50 patients with CMT. It was disappointing to find that even 50 patients became unattainable; patients with peripheral neuropathies are generally managed out of hospital and contact with them was limited as they attend one appointment every one or two years. As such the study was amended to include epilepsy patients in the neurology cohort. However, despite epilepsy being a relatively common condition, recruiting patients with epilepsy also proved more difficult than initially anticipated. Children with epilepsy who frequently attended the hospital, generally had significant intellectual impairment which rendered them ineligible for the study. Those patients with mild epilepsy were not often attending a tertiary hospital and therefore not available for recruitment.

A further limitation is that this study examined a heterogenous group of movement disorders and within the Non-tic cohort there are multiple small subgroups. Each of these individual diagnoses provide interesting questions as to the relationship between neurology and psychiatry, and larger cohorts of each genetic and neurotransmitter subtype would be useful to better understand these disorders. Equally, as our genetic diagnoses of movement disorders continues to improve, detection of the genes responsible for suspected genetic conditions in this cohort will allow for meaningful comparisons and phenotyping of these disorders with respect to their neuropsychiatric profiles.

Throughout the study there was a definite attempt to avoid recruitment bias, with an effort made to recruit every eligible patient with a movement disorder, as opposed to targeting only those suspected to have a psychiatric comorbidity. However, in real life clinical practice there are some consultations that are harder than others, with occasional opportunities for recruitment being missed due to factors beyond this study. Despite these theoretical recruitment biases, it is anticipated that in a study with >100 patients in both the tic and Non-tic cohorts respectively, a relatively accurate picture of these patient groups has been obtained. During the recruitment process, there were 70 patients from all groups (who had initially agreed to participate in the DAWBA who did not complete the questionnaire (n=467, including participants and non-participants). This rendered the completion rate to be 85.0%. It is possible that the patients who did not complete the DAWBA may have had different psychiatric profiles to the patients included, and this may have impacted on the findings.

The study is also limited by the use of only one psychiatric screening tool and every tool has its limitations. In this case it is likely the DAWBA has under diagnosed some disorders, especially given that the teacher questionnaire was not included. A best-case study would have used several tools and a clinical screening process to ensure diagnostic accuracy, but this would have not been practical with the cohorts of these sizes. A local, out of hospital community control would also have been advantageous in supplementing the UK community control however this was not logistically possible.

This study examined the rate of psychiatric comorbidities in children with movement disorders, however it has not interrogated the aetiology of these disorders or their prognosis over time. Equally, further research into the treatment options for psychiatric comorbidities in this specific group as well as analysis of the protective factors that prevents some patients from experiencing these comorbidities provide opportunities for further research.

6 Conclusion

Children with Tourette Syndrome are well known to have elevated rates of psychiatric comorbidities, well above community cohorts. This study contributes new information by demonstrating that children with other movement disorders such as dystonia and chorea have almost the same rates of psychiatric comorbidities as those with tics and Tourette Syndrome. These findings may modify the clinical approach to children with movement disorders by suggesting that psychiatry is prevalent and impactful in all patients with movement disorders. Screening for, and managing psychiatric comorbidities, as recommended in TS patients should therefore be considered for patients with other movement disorders.

This study includes a total of 260 patients affected by movement disorders, and for more than a third of these patients, their difficult movements are compounded by additional psychiatric disease. It is hoped that this study contributes to the field in a way that informs future directions and enhances the current care of families who took hope from this research.

7   Bibliography

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8　Appendices