Movement Disorders Presenting in Childhood: An Overview and Update

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[AU: Continuum uses a structured abstract with the following sections (one of which you've included below, and can make part of your current abstract): Purpose of Review, Recent Findings, and Summary. Please rework your abstract to include all three of these sections. Thank you!]

Abstract

Movement disorders in childhood comprise a wide spectrum of both genetic and acquired diseases, ranging from benign self-limiting conditions to more progressive phenotypes associated with significant morbidity and mortality. Elucidation of the underlying cause is achieved through accurate history, detailed clinical examination and, where appropriate, neuroimaging and laboratory investigations. In this review, the key clinical features of diseases that present in childhood will be discussed, including benign, genetic, acquired and psychogenic movement disorders. Early accurate diagnosis will facilitate the instigation of appropriate management strategies.

Purpose of Review

The aim of this review is to provide an overview of movement disorders that present in childhood. Key clinical features will be discussed, as well as a brief guide to management strategies. There is also a focus on recent advances in the field of pediatric movement disorders.

Learning Objective

To understand the broad spectrum of movement disorders that may present in childhood and have awareness of latest advances in the field.

Introduction

Movement disorders in childhood comprise a heterogeneous group of conditions that lead to impairment of voluntary movement, abnormal postures or inserted involuntary movements. Movement disorders in children are often classified into two main categories, namely hyperkinetic/dyskinetic movement disorders (including stereotypies, tics, tremor, dystonia and chorea)[1] and hypokinetic movement disorders, encompassing parkinsonian phenotypes[2]. A number of other classification systems are also recognized, subgrouping disorders according to temporal and spatial patterns, clinical features, motor semiology and underlying aetiology (molecular genetic features and/or neuropathology).

A wide range of movement disorders are described in childhood, from benign, self-limiting transient phenomena to more progressive disorders associated with significant morbidity and mortality. Movement disorders in childhood may present acutely, sub-acutely or in a more chronic manner. The underlying aetiologies for childhood movement disorders are diverse, and include both acquired and genetic conditions. In recent times, significant advances in genetic technologies have facilitated the discovery of a number of novel disease-causing genes and movement disorder syndromes in childhood.

Accurate diagnosis of childhood onset movement disorders requires careful ascertainment of clinical history, detailed neurological examination (for recognition of phenomenology and associated features) and a broad knowledge of potential differential diagnoses. In this review, an updated overview of movement disorders in childhood will be provided, with particular focus on newly recognized conditions.

(1) Benign Movement Disorders of Childhood

A number of relatively benign movement disorders of childhood are described, relating to specific stages of normal development (**Table 1**)[3]. The underlying basis of such movement disorders is not fully understood, but some are thought to be a manifestation of the developing brain, reflecting central nervous system immaturity. The majority of these conditions occur early in life, during the neonatal period, infancy and early childhood, with resolution of symptoms over time. Furthermore, other neurological symptoms are rarely present, and most children are found to have a normal neurological examination. Accurate recognition is crucial to avoid unnecessary neurological investigations and provide families with reassurance regarding long-term prognosis, where appropriate.

[AU: Thank you for providing Key Points for your article; however, we like to have about one key point per manuscript page, so please provide an addition 10 to 15 key points for your article and put them after the paragraph in which they should appear.]

Key Point 1:

A number of benign movement disorders of childhood are recognized, which are transient in nature, and usually have a good long-term prognosis

(2) Tics, Tourette Syndrome and Stereotypies

Tics are the most common movement disorder in childhood, and can be separated into motor tics or vocal tics. Motor tics typically involve the face, head and

shoulders, although can affect any body part. The characteristic features of tics are their repetitive, stereotypical nature, the fluctuating nature (wax and wane), suppressibility, and suggestibility. Despite being common (transient tics affect ~5-10% of children at some time, and Tourette syndrome affects 0.5% of children), these disorders remain poorly understood and recognized by clinicians and lay people. Patients are often referred to opticians (blinking, eye movements), ENT clinicians (throat clearing) and respiratory physicians (repetitive cough) before a diagnosis is made. Tics are often mis-labelled as 'habits'. The first priority is a confident diagnosis, and education of the child, family and school that tics/Tourette is a neurobiological 'brain' condition, and tolerance and acceptance is required. The fact that tics peak between 10-12 years and typically reduce in severity thereafter is comfort to families, and an important component of counseling. The second priority is to define how impairing the tics are on the child's function and psychological well-being. When the tics are affecting the child's function significantly, therapeutic intervention can be considered including tic reversal therapy delivered by psychologists, or medical therapies such as alpha-agonists (guanfacine, clonidine) and when severe and impairing function, neuroleptics such as risperidone. The third priority is to determine whether co-morbidities such as attention deficit disorder, anxiety, obsessive-compulsive disorder are present, as these can be more impairing than the tics, and are arguably more treatable than tics with psychological or medical interventions. Neurodevelopmental disorders are also over-represented in patients with Tourette syndrome, and a significant minority of patients may have autistic spectrum disorder, sensory processing disorder, or other dysexecutive problems, which can affect school and general functioning. Tourette syndrome is not a

disease, but instead a 'symptom syndrome' and the aetiology is likely multi-factorial with genetic vulnerability factors plus environmental factors[4] (Ganos and Martino, 2015).

Stereotypy is a common movement phenotype, and is a normal feature of infant development, but when stereotypy continues beyond this period the episodes can become concerning to parents (less for the child) because of the unusual nature of the episodes and the potential for social stigmatization. Stereotypies are repetitive movements and classic examples include rocking, flapping and 'body-tensing', however some stereotypies are extremely complex including twisting, grimacing and posturing. The most important characteristics are the stereotypical nature of the movements (the episodes are similar), are partially distractible (although the child may subsequently need to complete the movement after being distracted), and the fact that episodes are often more likely to occur with certain stimuli such as excitement or anticipation (waiting in a queue), a favourite activity (watching TV), or sometimes boredom (sitting in back of car). Parental videos are essential for diagnosis, and are highly informative. Stereotypy is more common in children with developmental disorders such as language delay and autistic spectrum disorder, but complex motor stereotypy can also occur in normally developed children[5]. Detailed assessment for subtle neurodevelopmental disorders is important as this may present therapeutic options, although the treatment of stereotypy itself is challenging and drugs are ineffective, although psychological approaches may be useful in well motivated, cognitively able individuals. Many normally developed older children with stereotypy have associated neuropsychiatric conditions such as ADHD, anxiety or tics[5]. Some children with

complex stereotypy describe complex, sometimes imaginary thoughts during the movements[6].

Key Point 2:

Tics and stereotypy are the most common movement disorders of childhood. Diagnosis is dependent on careful history, observation and parental videos. Education of the family, and searching for neurodevelopmental and neuropsychiatric comorbidty is paramount, as associated comorbidities such as anxiety and OCD can exacerbate the movements, and are arguably more amenable to psychological or medical treatments.

(3) Acquired Movement Disorders

(i) Cerebral palsy (hypoxic ischaemic)

The classic movement disorder cerebral palsy phenotype is 'dystonic CP' although other terms such as 'dyskinetic CP' or 'choreoathetoid CP' are sometimes used dependent on the movement phenomenology. Classic teaching is that dystonic CP occurs as a consequence of hypoxic ischaemic injury predominantly to the subcortical structures during early brain development. Although a clear history of brain injury is present in a proportion of cases, there is no history in a significant proportion, and many patients with dystonia CP have a normal MRI. It is increasingly likely that some patients labeled as 'dystonic CP' in fact have a genetic movement disorder, or instead have other disease mechanisms. A positive family history of neurological disease, a fluctuating course, apparent initial normal early development, a normal MRI and clinical features such as progressive dystonia,

exercise induced dystonia, or oculogyric crises are some features that should alert the clinician to the possibility this is not 'typical' dystonic CP.

(ii) Infectious

Direct CNS infection resulting in encephalitis does not commonly result in movement disorders, but would be more typically observed in autoimmune encephalitis (discussed below). However there are a number of infections that can affect subcortical structures resulting in movement disorders. The most important worldwide cause is Japanese encephalitis, which remains endemic in certain parts of the world, especially Asia, and commonly results in a severe dystonic-akinetic phenotype[7]. Other infections that can affect subcortical structures and result in movement disorders include Epstein-Barr virus, enterovirus, Group A Streptococcus, Influenza and mycoplasma pneumoniae, amongst others. Whether these encephlitides are due to direct invasion of the CNS by the microorganism, or are post-infectious or immune-mediated is not always clear, and both mechanisms appear to be possible and may overlap. One of the most important examples of this overlap between infection and autoimmunity is the post-herpes simplex encephalitis relapse syndrome. In the weeks after presentation with typical herpes simplex encephalitis, 20% of patients will relapse with encephalopathy and movement disorders (typically chorea). During the relapse, the CSF no longer demonstrates positive herpes simplex PCR, but instead the CSF harbors autoantibodies against the NMDA- receptor[8,9]. These patients benefit from immune suppression. This syndrome therefore represents a prototypic example of infection-triggered autoimmunity[10].

(iii) Post-infectious/ Autoimmune

The presence of movement disorders in the context of encephalitis is strongly predictive of an autoimmune encephalitis, particularly anti-NMDAR encephalitis[11]. Almost all children with anti-NMDAR encephalitis have movement disorders, and young children often have generalized chorea and dystonia which is often impairing, whereas older children and adults are more likely to have more localized movements of the face, such as oro-buccal dyskinesia. In children, almost any movement disorder is possible in the course of disease, and the movements typically evolve over the course of disease with chorea, dystonia, stereotypy, akinesia and tremor all observed. Arguably the most characteristic movement disorders of anti-NMDAR encephalitis are the repetitive, stereotypical clonic or tonic posturing that result in purposeless, repetitive and sometimes violent agitated movements[12]. Some of the postures can be reminiscent of the syndrome catatonia. The movements rarely occur in isolation, but instead are part of a complex evolving encephalopathy syndrome with aphasia, psychosis, agitation, dysautonomia, as well as non-specific encephalitis features such as seizures and confusion. The syndrome is now very recognizable, and if suspected, immune suppressive therapy should be started whilst awaiting CSF and serum NMDAR antibodies. Early treatment and the willingness to use second line immune therapy (rituximab and/or cyclophosphamide) improve outcomes and reduce relapses[13].

Other autoimmune encephalopathies include 'basal ganglia encephalitis' which is a rare pure basal ganglia inflammatory encephalitis with restricted inflammation of the basal ganglia, typically presenting in young children with dystonia and akinesia, or sometimes chorea, plus change in behaviour[14]. Early use of steroids,

immunoglobulin and plasma exchange can improve outcomes and reduce the chance of residual atrophy and gliosis of the basal ganglia. These patients may harbor autoantibodies against dopamine-2 receptor.

Sydenham chorea is still endemic in the world, and remains one of the more common causes of acute chorea. Triggered by beta-haemolytic strepotoccus as part of rheumatic fever, Sydenham chorea is a neuropsychiatric syndrome with acute behavioural change in addition to chorea. Although the disease is usually monophasic and self-resolving, a significant proportion of patients are left with minor chorea or residual neuropsychiatric disease, and for this reason it can be argued that patients should be treated with acute immune therapy, as there is some evidence that this can improve short term outcomes[15], although long term data is lacking.

Infection mediated tics and emotional lability, either as a post-streptococcal phenomenon (PANDAS) or post-infectious phenomenon (Pediatric acute neuropsychiatric syndrome, PANS) is an uncommon entity, and although tics are part of the syndrome, the acute anxiety, separation anxiety and obsessive-compulsive symptoms with repetitive urination are more characteristic features of PANS[16]. Although these entities are clearly infection-associated and may benefit from antibiotics or immune modulation, the evidence that these disorders are definitely autoimmune is lacking at this time.

Progressive encephalopathy with rigidity and myoclonus (PERM) is a rare syndrome considered part of the 'stiff-person syndrome' spectrum and is associated with glycine receptor antibodies[17]. More common in adults, this

syndrome has been described in young children who present with mild encephalopathy, irritability, rigidity and stimulus induced startle, which is distressing. The syndrome is an autoimmune version of genetic hyperekplexia and given the immune therapy responsiveness of PERM, it is important to recognize. Autoantibodies against DPPX (a subunit of potassium channel) can be associated with an autoimmune encephalitis associated with diarrhoea, weight loss, encephalopathy and movement disorders such as myoclonus, rigidity and startle[18]. And finally, autoantibodies against GABA-A receptor can sometimes be associated with autoimmune encephalitis and movement disorders, although status epilepticus appears to be the dominant phenotypic association of this autoantibody[19].

Opsoclonus myoclonus ataxia syndrome is a recognizable entity that can be infection-triggered, paraneoplastic (neural crest tumours) or 'idiopathic'. The diagnosis is clinical and there is no defining autoantibody. Suspicion should result in screening for neural crest tumours, and giving immune therapy. Some patients appear to respond quickly to steroids and IVIG, whereas others require rituximab or more chronic immune suppression. General principles of treatment include early intervention, induction of complete remission avoid residual symptoms as this may infer ongoing inflammation and risk of permanent neurocognitive disability[20]. More aggressive intervention appears to have changed the natural history of this condition, with better outcomes now described[21].

In conclusion, although rare, the emergence of such autoimmune encephalopathies have radically changed the clinical approach to the child with acute autoimmune movement disorders. Rather than observation and

symptomatic therapy, there is increasing willingness to use immune therapies as early recognition and intervention appears to improve outcomes.

Insert Clinical Vignette Case 1

(iv) Stroke and other space-occupying lesions

Any patient presenting with an acute movement disorder requires neuroimaging, and MRI is the optimal modality. Hemi-movement disorders can be caused by acute vascular events such as stroke or vasculitis, and MRI with diffusion weighted imaging is part of the diagnostic pathway. Moyamoya and other vasculopathies may present with chorea and surgical interventions can improve the movement disorders and reduce risk of ongoing stroke[22]. Likewise, tumours or other space occupying lesions involving the subcortical structures may present with acute or subacute onset of movement disorders, and imaging is diagnostic.

(v) Toxic/iatrogenic

Iatrogenic or toxic mechanisms are important causes of movement disorders, but are usually moderately straightforward to diagnose as there is usually a clear temporal association of drug usage and onset of movement disorder. Direct questioning regarding potential drug ingestion would therefore be an important part of the clinical history in children who acutely present with involuntary movements or postures. More common associations include neuroleptic induced dystonia/neuroleptic malignant syndrome, anti-epileptic induced dyskinesias in (often genetic) epilepsies, amphetamine or other stimulant use or misuse, withdrawal movement disorders such as with midazolam infusion withdrawal, and cancer-drug use resulting in movement disorders often with leukoencephalopathies[23].

(vi) Treatment strategies for acquired movement disorders

The primary approach to the child with acquired movement disorders is defining the aetiology and then treating the underlying cause. Defining and treating the cause of disease in a timely fashion provides the best chance of a good outcome and reduces the potential destructive nature of disease. Symptomatic treatment of acquired movement disorders is generally unsatisfactory, and patients with autoimmune movement disorders appear to be vulnerable to drug adverse events, for example neuroleptics can induce akinesia and neuroleptic malignant syndrome in Sydenham chorea and anti-NMDAR encephalitis, respectively[24]. Agents such as benzodiazepines, alpha-agonists may be safer treatments of acquired movement disorders, but the evidence base is limited.

Key Point 3:

Acquired movement disorders have multiple potential causes. Although investigations such as MRI, CSF and autoantibody testing are important, it cannot be over-estimated that a careful clinical history and examination for specific movement disorder phenomenology is essential. Focus should be on defining the aetiology and providing specific targeted intervention. The concept of early recognition and intervention is increasingly emphasised.

(4) Genetic Movement Disorders

Advances in molecular genetic techniques such as chromosomal microarray studies, targeted next generation multiple gene panels and whole exome/genome sequencing strategies have led to significant increase in the diagnosis of genetic

movement disorders of childhood. Furthermore, a large number of new genetic disorders have been identified and clinically characterized.

(i) Primary Genetic Dystonia

Traditionally genetic dystonias have been classified according to a DYT number assigned to each disease locus. Paroxysmal disorders have also been assigned DYT numbers, and are discussed below [**Section 4(iii)**]. The most common forms presenting early in life, are DYT1, DYT5 and DYT11 dystonia, but DYT12, DYT23 and DYT26 may also present in childhood (**Table 2**). DYT1-early onset primary generalized torsion dystonia is inherited in an autosomal dominant manner with incomplete penetrance (30-40%)[25]. It is due to mutations in *TOR1A* encoding torsinA, postulated to have a role in the regulation of subcellular compartments such as the nuclear envelope and endoplasmic reticulum. The vast majority of patients harbor the common GAG deletion. Symptom onset is usually in childhood or early adolescence, with dystonia usually beginning in one limb. In many patients, generalised dystonia usually ensues within 5 years of presentation.

DYT5 represents disorders of neurotransmission secondary to inherited dopa-responsive defects in the dopamine synthesis pathway. GTP cyclohydrolase deficiency, also known as Segawa's disease, is due to heterozygous mutations in *GCH1,* with incomplete penetrance[26]. Affected patients present from early childhood with limb dystonia, which can often mimic the symptoms and signs of diplegic cerebral palsy. Atypical disease presentations, including writer's cramp, dystonic tremor and exercise-induced dystonia have all been described[27]. More recently there have been reported associations of GCH1 carriers manifesting early onset Parkinson's disease[28]. DYT5b, tyrosine hydroxylase deficiency represents

another form of dopa-responsive dystonia, but is more complex, often with concurrent features of parkinsonism, other motor semiology and neurodevelopmental delay[29] [**Section 4(iv)** Though response to L-dopa can lead to significant clinical benefit in Type B (hypokinetic rigid phenotype), the earlier onset Type A subtype, associated with neonatal encephalopathy, is more drug resistant. TH deficiency is likely a phenotypic spectrum with a number of intermediate forms. Patients with TH deficiency often require much higher doses of L-dopa than in autosomal dominant GCH1 deficiency for a therapeutic response.

DYT11, or myoclonus dystonia syndrome has clinical onset in childhood (median age 5 years), and frequently presents with early myoclonus affecting the upper limbs and neck with predominantly upper (but also lower) limb dystonia[30]. More pronounced truncal involvement is evident later in childhood and adolescence. Alcohol responsiveness is sometimes reported in older patients. Comorbid neuropsychiatric features are commonly reported. Affected patients have hetererozygous mutations in *SGCE,* encoding the ε-sarcoglycan protein. Disease mechanisms are not yet fully elucidated but mutations are postulated to impair targeting of ε-sarcoglycan to the plasma membrane, affecting proteosomal degradation, protein glycosylation and ectodomain shedding.

DYT12 is a rarer cause of genetic dystonia-parkinsonism due to autosomal dominant mutations in *ATP1A3,* encoding the α3 subunit of the Na+/K+-ATPase pump. Affected patients usually present acutely or sub-acutely (from over a few minutes–months) with rostrocaudal progression of dystonia-parkinsonism and significant bulbar dysfunction. More recently it has become clear that the clinical spectrum of *ATP1A3*-related disease is broad, encompassing a number of other

overlapping phenotypes including alternating hemiplegia of childhood as well as Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS) syndrome[31]. The reasons for this phenotypic pleiotropy may be mutation dependent, but are yet to be fully elucidated.

Heterozygous mutations of *CACNA1B* and *KCTD17* have recently been described in extended kindreds with childhood-onset myoclonus dystonia[32,33]. Cardiac arrhythmias are additionally reported in those with *CACNA1B* variant p.R1389H. CaV2.2 channels carried less current when compared with WT channels and it is postulated that such altered channel properties could affect neurotransmitter release at excitatory and inhibitory channels. Screening of another myoclonus dystonia patient cohort for this missense change has not identified further cases, with observation of this rare variant in control populations. The significance of this mutation remains yet to be fully determined[34]. KCTD17 is postulated to show significant putaminal expression, and mutations thought to impair endoplasmic reticulum-dependent calcium signaling.

(ii) Genetic Chorea

A number of genes causing primarily choreiform dyskinesia are now reported. Often children with such conditions manifest chorea as part of a complex neurological disorder, as exemplified by FOXG1 syndrome.[35]

Benign hereditary chorea (BHC) is a childhood onset hyperkinetic movement disorder due to mutations in *NKX2.1*[36]*.* Hypotonia is commonly described in infancy, with onset of chorea from 2.5-3 years of age. Chorea is usually generalized and may be exacerbated by excitement or stress. Patients often frequently

manifest neonatal/infantile respiratory symptoms (including respiratory distress syndrome, obstructive airways disease and chronic interstitial lung disease) and thyroid abnormalities (congenital hypothyroidism). NKX2.1, from the natural killer (NK) gene family of highly conserved homeodomain-containing transcription factors is postulated to have a role in embryonic development of the brain, lung and thyroid gland. The combination of chorea with thyroid abnormalities are also described in Allan Herndon Dudley Syndrome (AHDS), an X-linked disorder associated with mutations in *SLC16A2* encoding the monocarboxylate transporter 8 (MCT8)[37]. Mutations lead to loss-of-function of this thyroid transporter, thereby impairing triiodothyronine transport capacity. Triiodothyronine has an important role in oligodendrocytes, inducing differentiation of the precursor, as well as acting as a survival factor in these cells, and influencing the distribution of myelin-related proteins. Affected individuals with AHDS present with profound hypotonia and early limb spasticity. A complex movement disorder evolves over time, with prominent chorea, but also dystonia.

In 2014, mutations in *MICU1* were identified in patients with cognitive impairment, proximal myopathy and a progressive choreiform movement disorder[38]. MICU1 is a regulator of MCU, a Ca(2+)-selective ion channel located within the inner mitochondrial membrane Ca(2+) uniporter complex, and mutations disrupt mitochondrial Ca (2+) signaling.

Mutations in *ADCY5* are the most recently recognized significant cause of progressive chorea in children. Originally reported in patients presenting with familial dyskinesia with facial myokymia[39]. *ADCY5*-related disease comprise a wide clinical spectrum of disorders including those mimicking dyskinetic cerebral

palsy (CP) and conditions resembling *TITF1*-BHC[40]. A relapsing-remitting disease course is often evident, and severe sleep-disrupting movements are frequently reported. Unlike *TITF1*-BHC, motor symptoms are typically progressive. Eliciting a history of sleep disturbance and disease progression can thus aid clinical differentiation from BHC and CP. ADCY5 is a membrane-bound adenylyl cyclase that generates cyclic adenosine-3',5'-monophosphate (cAMP) from an adenosine triphosphate (ATP). ADCY5 shows high expression in the brain striatum, and in the nucleus accumbens, where it is responsible for 80% of adenylate cyclase activation. β-adrenergic agonists stimulate ADCY5 through a G-protein-coupled receptor, which leads to a conformational change in the protein, facilitating formation of a catalytic pocket into which ATP binds. Pathogenic variants are predicted to lead to gain-of-function, increasing ADCY5 enzyme activity, either through β-adrenergic stimulation of the signal transduction pathway or by the interaction of the protein with other regulatory molecules.

Insert Clinical Vignette Case 2

(iii) Genetic Paroxysmal Movement Disorders

A number of genetic movement disorders may present episodically (**Table 3**). Such paroxysmal dyskinesias typically present in childhood, often in children with normal neurodevelopment and behavior. Paroxysmal movements may be dystonic, choreiform, or ataxic and are often associated with specific triggers[41]. Detailed clinical history with direct questioning for precipitants of the movement disorder should be undertaken to aid diagnosis (**Table 3**). Many episodic movement disorders are caused by mutations in genes encoding channels, and therefore it is not surprising that such genes also account for other paroxysmal

disorders such as epilepsy and migraine (**Table 3**). Recognition of such syndromes is of significant clinical importance as many are amenable to treatment strategies (**Table 3**).

(iv) Genetic Myoclonus

Non-epileptic myoclonus is reported in a number of genetic conditions, often in association with other movement phenotypes. It is a prominent feature of myoclonus-dystonia syndrome [**Section 4(i)**] but also reported in a number of inherited inborn errors of metabolism [**Section 4(vii)**]

(v) Genetic Ataxia

A number of predominantly ataxic disorders of genetic origin are described in childhood (**Table 4**), and many are complex progressive neurological disorders. Friedreich's ataxia (FA) is the most commonly reported, with clinical features of a progressive, mainly sensory cerebellar ataxia, with speech difficulties, absent reflexes, pyramidal tract signs with weakness, hypertrophic cardiomyopathy, diabetes and sensorineuroal deafness[42]. Expanded GAA repeats within intron 1 of frataxin (FRDA) are thought to impair exon splicing with reduced protein expression. Frataxin is postulated to have a role in mitochondrial iron metabolism and dyshomeostasis is thought to lead to increased free radical damage and oxidative stress. Ataxia with Vitamin E deficiency can mimic many of the features seen in FA, and is characterized by a progressive ataxia, with other cerebellar features of tremor, head titubation and nystagmus, as well as myoclonus, dystonia, hyporeflexia, and retinitis pigmentosa[43] Disease is caused by mutations in the alpha-tocopherol transfer protein, with impaired incorporation of Vitamin E into

very low density lipoproteins, and subsequent excess loss of Vitamin E. Low Vitamin E levels are detectable on blood testing.

Ataxia telangiectasia presents with gait disturbance and truncal instability in early childhood but choreiform movements and dystonia are also described[44]. Often subtle abnormalities in ambulation can precede the onset of ocular and cutaneous telangiectasia. Patients are at risk of immunodeficiency (secondary to low immunoglobulins) and lymphoreticular neoplasia. A raised alpha-fetoprotein can be a useful disease marker. Disease is due to mutations in *ATM,* encoding a DNA repair protein. Clinically similar to AT are two forms of autosomal recessive ataxia with oculomotor apraxia (AOA) due to mutations in *ÂPTX* (AOA1) and *SCAR1* (AOA2)[45,46]*.* Both types present with a distinctive eye movement disorder in context of ataxia, chorea, distal sensory axonal neuropathy and progressive cerebellar atrophy on MR brain imaging.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a recently described condition originally in individuals originating from Quebec, Canada. ARSACS is caused by mutations in *SACS,* with over 100 reported mutations to date in patients if different ethnicities[47]. Ataxia, dysarthria, spasticity, weakness, distal sensorimotor neuropathy and nystagmus are commonly reported clinical symptoms. Distinctive neuroradiological features include atrophy of the superior vermis and cerebellum, with pontine linear hypointensities.

A number of both dominant and recessive spinocerebellar ataxia disorders may also present in childhood with prominent ataxia and gait instability, as well as other movement phenotypes (dystonia, chorea), speech disturbance and

progressive motor dysfunction (**Table 4**). The increasing availability of targeted multiple gene panel testing for the ever-expanding list of SCA and other ataxia genes has improved the overall diagnostic rate for these childhood-onset ataxias,[48] though detection of certain mutations (trinucelotide repeats, intronic variants) can still be challenging.

(vi) Genetic Parkinsonism

Rarely, genetic disorders presenting predominantly with infantile or juvenile parkinsonism are reported[2]. Typically symptoms resemble those seen in idiopathic Parkinson's disease, with bradykinesia, resting tremor, rigidity and hypomimia. Pure parkinsonism is rarely reported, with most patients manifesting other movement disorders, most commonly dystonia (parkinsonism-dystonia) but also chorea and myoclonus. Cognitive impairment may also be a co-morbid feature. A number of aetiologies are reported, including disorders of monoamine synthesis, metabolism and transport, as well as other inborn errors of metabolism (including mitochondrial disorders), disorders of brain metal ion accumulation and juvenile onset genetic parkinsonism due to mutations in the PARK genes (**Table 3**). Recognition of clinical features can be key to diagnosis, but adjunct tests, such as CSF neurotransmitter analysis, CSF and blood lactate, muscle biopsy, DaTSCAN nuclear imaging and molecular genetic studies will often be needed to confirm the diagnosis.

(vii) Complex Inherited Neurometabolic Syndromes

Movement disorders are often a prominent clinical feature in a number of inborn errors of metabolism that present in childhood. Many of these conditions are complex, and patients often manifest a number of different movement

phenotypes. Frequently there is multisystem disease involvement, with cognitive and motor delay.

Dystonia, chorea, athetosis, ballismus, tremor, myoclonus and parkinsonism are all described in disorders of monoamine synthesis and transport[27] (**Table 5**). The presence of eye movement disorders (oculogyric crises, ocular flutter, saccade initiation failure) as well as autonomic features (sweating, nasal congestion, temperature instability, ptosis) can be additional clinical features that raise clinical suspicion for these diseases, which can usually be diagnosed on CSF neurotransmitter analysis and confirmatory genetic studies. Patients with cerebral folate deficiency, for example, secondary to recessive mutations in the gene encoding the folate transporter *FOLR1*, can present with a number of non-specific features including gait instability, hypotonia, seizures and acquired microcephaly[49]. Ataxia, chorea and ballsimus are also reported in a proportion of these patients.

Inherited mineral deposition disorders, including Wilson's disease, Neurodegeneration with Brain Iron Accumulation (NBIA) and SLC30A10 Deficiency can all present with progressive neurological phenotypes[50-52] and prominent extrapyramidal features including dystonia, chorea, tremor, parkinsonism and spasticity. Characteristic MR brain findings and molecular genetic testing can aid diagnosis of these disorders of metal ion accumulation (**Table 5**).

A number of inborn errors of metabolism can present with movement disorders, including lysosomal disorders, mitochondrial diseases, amino acidopathies,

organic acidurias, disorders of purine and creatine metabolism and glucose transporter deficiency. Detailed metabolic screening is therefore often warranted in patients with complex progressive neurological syndromes associated with motor phenotypes (**Table 5**).

More recently, a number of genes have been reported in infantile and childhood-onset bilateral striatal necrosis (BSN) (**Table 5**). Mitochondriocytopathies are frequently associated with BSN. *ADAR1* has emerged as an important cause, accounting for a significant proportion of patients with BSN presenting with severe, progressive, medically intractable generalized dystonia[53]. An interferon signature, measuring upregulation of interferon-stimulated genes can aid diagnosis of this BSN subtype. The finding of BSN should prompt a clinician to look for treatable causes including thiamine transporter deficiency due to mutations in *SLC19A3*, where instigation of biotin and thiamine supplementation can lead to marked improvement or even reversal of clinical symptoms in tandem with radiological improvement of the striatal features[54].

Structural abnormalities of the basal ganglia may also be seen in some genetic hypomyelinating disorders. In 2013, *TUBB4A* was identified as the genetic cause of hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)[55]. Mutations are postulated to disrupt tubulin dimerization, microtubule polymerization, or microtubule stability. Extra-pyramidal features, namely dystonia, rigidity and rarely choreoathetosis are reported in affected patients. A number of patients also manifest ataxia and gait instability. *TUBB4A*-related diseases encompass a broad spectrum from H-ABC, to other hypomyelinating

disorders and also whispering dysphonia (**Table 5**). The reasons for this phenotypic pleiotropy remain to be fully elucidated[56].

(viii) Treatment Strategies for Genetic Childhood Movement Disorders

Treatment strategies for children with genetic movement disorders are usually dictated by disease aetiology and movement disorder semiology. Children with dystonia of undetermined cause will often have an early trial of L-dopa to rule out a treatable dopa responsive dystonia[27]. Symptomatic treatment of dystonia is managed with a number of different agents including baclofen, trihexyphenidyl, the benzodiazepines[57] and more recently clonidine and gabapentin. More invasive therapies such as intrathecal baclofen and deep brain stimulation (DBS) are also used. DBS is particularly effective for children with primary dystonia due to DYT1[58], but has also been used as palliation in a number of other genetic disorders such as pantothenate kinase associated neurodegeneration (PKAN). Chorea can often be difficult to manage from a therapeutic perspective but tetrabenazine, benzodiazepines and anti-epileptic drugs (levetiracetam, sodium valproate, carbamazepine) can be used[59]. The paroxysmal disorders have specific treatments, which can often be very effective (**Table 4**). Genetic parkinsonian disorders are treated with either L-dopa therapy or dopaminergic drugs such as pramipexole, ropinirole and rotigotine. Neurotransmitter disorders and other complex neurometabolic syndromes will require specific disease-targeted treatments, often necessitating consultation with a specialist in the field. All children with complex genetic syndromes should be under the care of a multidisciplinary team including a neurologist with expertise in movement disorders with close links to physiotherapy, occupational therapy and speech and

language therapists. Regular input from a general paediatrician to monitor general health issues, vision and hearing, and surveillance for orthopaedic and secondary gastrointestinal complications is also an integral part of routine care. Genetic counseling to discuss risk for future pregnancies should also be offered to affected families.

Key Point 4:

Genetic movement disorders are increasingly recognized and diagnosed in children. Often chromosomal microarray is an early investigation in such children, looking to identify copy number variants accounting for disease phenotypes. Further genetic testing is guided by clinical history, features on examination and radiological or metabolic biomarkers. The evolution of multiple gene panels and whole exome sequencing technologies has further improved diagnostic approaches for this group of patients.

Insert Clinical Vignette Case 3

(5) Psychogenic Movement Disorders in Children

Psychogenic presentations represent a significant proportion of acute presentations to neurology services, and are important as they often represent a significant and complex issue for the child. Early recognition and treatment is considered important to provide the best chance of a good outcome. The issue of whether these problems should be termed 'psychogenic' or 'functional' is under debate but not discussed here, and there is little doubt that our understanding of these disorders is changing. Careful clinical history and observation is essential- sometimes the diagnosis is straightforward, however sometimes prolonged observation in difficult cases can be informative diagnostically. Psychogenic

movement disorders (PMD) occur more commonly in adolescents, and in females, and a diagnosis in a young child under 10 should be made with caution (although they do occur). The hallmarks of PMD are an acute often 'explosive' onset with a short time to maximum severity (often hours or day), incongruous characteristic (atypical or 'odd'), inconsistent findings, inconsistent performance relative to the severity of movements (able to use mobile phone despite violent movements). 'Pseudo-myoclonus' or 'pseudo-tremor' are the most common PMD movements, and pseudo-'dystonia', akinesia and chorea are uncommon although occasionally observed[23]. The classic patient may have a history of high performance in academic or sporting activity, a predisposition to anxiety, some preceding psychosocial stressors, and sometimes an acute, often minor, stress such as a dental procedure or infection.

It is essential to approach the problem with care, empathy and perform necessary investigations to reassure the patient and family that there is no serious brain pathology such as a tumour. Neuroimaging is almost always necessary to progress. Explanation of the problem is important to the child and family, and this may require repeated consultations and discussions before the clinician and family accept the likely explanation. Arguably the most useful test can be a second opinion from an experienced colleague, although polymyography can be useful[60].

Key point 5:

Early recognition and intervention of PMD, and involving a multi-disciplinary team to rehabilitate the patient physically and psychologically is essential. Treating PMD can be rewarding to child, family and health practitioners.

[AU: Please provide a brief conclusion for your article that summarizes the points made in your article.]

Insert Clinical Vignette Case 4

(6) Clinical Vignettes

Case 1:

Clinical case: A previously well 7 year old Australian girl of Chinese descent presented with change in behaviour and restlessness. Over the following week, the illness progressed with increasing agitation, apparent delusional thoughts with repeated statements of 'I'm going to die'. Examination revealed a generalized movement disorder with repetitive restless movements, scratching her face and cycling movements of her legs. In the second week she had 3 focal seizures and she became mute. MRI brain was normal, CSF showed 20 monocytes/mm3, and EEG showed non-specific slowing. A clinical diagnosis of anti-NMDAR encephalitis was made and intravenous methylprednisolone was started for 5 days in addition to intravenous immunoglobulin. Ten days later there was no apparent improvement, she remained mute, unresponsive to her parents and environment despite being apparently awake, she only slept for 2 hours a night, and had ongoing purposeless, stereotypical repetitive movements of her limbs and face. 14 days after commencing immune therapy, the CSF NMDAR antibodies returned positive, and given the lack of improvements, rituximab was started 375mg/m^2 weekly for 4 weeks. 10 days after starting rituximab she started to make improvements, her movement disorder evolved to dystonic posturing, but she became more interactive and less agitated. After a 2-month admission, she was discharged on a 6 month total oral prednisolone taper. She remained B cell

depleted for 6 months, and continued to improve. At 12 months all of her symptoms had resolved, although her school performance was slightly behind.

Comment: The case exemplifies the movement phenomenology in anti-NMDAR encephalitis with restless stereotypical movements, later followed by dystonia. The case also exemplifies the fact that the movement disorder rarely occurs in isolation, and is almost always accompanied by other changes in neurological function- in this case cognitive changes, loss of speech, seizures and agitated psychosis. The case also demonstrates it is possible to make a clinical diagnosis and start treatment before getting confirmatory diagnostic results. A positive antibody result empowers the clinician to use rituximab or other immune suppression if the patient does not adequately respond to first line therapy.

Case 2:

Clinical case: A male infant was born to fit and healthy parents, with no significant family history of note. Following an unremarkable pregnancy, he was delivered by emergency Caesarian section for fetal bradycardia/decelerations. He was born in good condition, with excellent APGAR scores (9^1, 10^5) and had an uneventful early neonatal course, not requiring admission to the Special Care Baby Unit. Abnormal involuntary movements were noted from mid-infancy, which were initially paroxysmal in nature, occurring in clusters often several times a day, with periods of relapse and remission. Choreiform limb movements were reported, with orolingual dyskinesia and mild truncal athetosis. Over time through early childhood, the movement disorder progressed, eventually becoming nonparoxysmal and continuous in nature. Furthermore, involuntary movements began to disrupt his sleeping pattern. He did not show clinical response to a number medications, including carbamazepine, levetiracetam and tetrabenazine.

Detailed neurological investigation revealed normal MR brain and spinal imaging, as well as normal blood, urine and CSF screening for metabolic disorders. Routine diagnostic testing for *NKX.2.1*, *SLC2A1* and *SGCE* were negative. Whole exome sequencing undertaken on a research basis identified a previously reported mutation in *ADCY5*, which was confirmed to be de novo.

Comment: *This clinical case clearly exemplifies the typical disease pattern of ADCY5-related disease. Although dyskinetic cerebral palsy may be one of the differential diagnosis here, a number of features in his history should prompt investigation of an alternative cause, including (i) the relatively uneventful antenatal/ postnatal course (ii) evidence of normal neuroimaging (iii) clear disease progression with worsening of symptoms. Testing for BHC is reasonable, but negative sequencing for NKX2.1 should alert the clinician to look for other causes of BHC mimics, and instigate ADCY5 testing. Further clinical clues towards this diagnosis include the disruption of sleep and progressive nature of disease.*

Case 3:

Clinical Case: A female infant was born to fit and healthy consanguineous parents. She was born in good condition and did not require any resuscitation, nor was she admitted to the Neonatal Intensive Care Unit. She was discharged on Day 2 of life. From the early neonatal period, she was irritable, with difficulty in feeding and a disrupted sleep pattern. The parents described that often she would look as if she was "half asleep", with her eyes half-closed. She was profoundly hypotonic and had delay in her motor milestones. By 2-3 months of age, abnormal eye movements were noted, and the family described periods lasting from seconds to several hours, when her eyes would deviate to the right and fixate in upward gaze. Often during these periods her body would be arched and hands fisted. The

parents also noted that she always seems to have a cold, with nasal congestion and even during the winter, her hands and the back of her head were sweaty. During infancy she developed a complex movement disorder, with dystonic posturing of her limbs, truncal athetosis, tremulous hand movements and occasional myoclonic jerks. A diagnostic lumber puncture was undertaken and CSF neurotransmitter analysis revealed a low homovanillic, low 5-hydroxyindoleacetic acid and normal pterin profile. CSF 3-O-methyl dopa and 5-hydroxytryptophan were markedly elevated. Further testing revealed low AADC plasma enzyme activity. Molecular testing revealed that she was a compound heterozygote for two mutations in the *DDC* gene, one reported in association with AADC deficiency and the other a novel 2 base pair deletion.

Comment: *This case illustrates a child with a very early-onset neurological disorder, characterized by severe motor delay, hypotonia and mixed movement semiology. The ptosis and severe hypotonia could indeed be presenting features of neuromuscular disease, though the complex movement disorder and presence of autonomic features (sweating, nasal congestion, ptosis) should prompt CSF neurotransmitter analysis to look for disorders of monoamine metabolism. CSF findings are indeed classical for AADC deficiency, later confirmed by enzyme assay and molecular genetic testing. The first mutation is already reported in the literature associated with AADC deficienct. The second mutation, though novel, as a 2 base pair deletion, will lead to a frameshift with significant alteration to the protein and likely premature stop.*

Case 4:

A 12 year old girl with no significant medical problems presented with shaking movements of the arms. She had attended school normally the day before, but had

onset of shaking movements the preceding evening, which had deteriorated dramatically over the course of the next day. There was no other change in function. Examination revealed dramatic coarse shaking of the upper limbs but no abnormal movements of the legs, head or trunk. Her walking revealed unsteadiness with significant wobbling during walking but without falls. During observation on the ward, it was noted that her symptoms fluctuated significantly, and she was observed to use her mobile phone normally without shaking, and her shake varied according to the people around her. Her behaviour, thinking and memory was normal, and formal neurological examination was also normal. On subsequent history, it became apparent that she had been the victim of significant bullying at school. The school described her as a kind diligent and sensitive girl who was training 5 nights at week at state-level netball. MRI brain and EEG were normal.

Comment: The incongruous and inconsistent nature of the movement disorder lead to a diagnosis of psychogenic movement disorder, presumably secondary to the significant stressors. Psychological input uncovered some baseline anxiety and fears of failure with perfectionism and some obsessive-compulsive behaviour. A confident diagnosis, acceptance of the diagnosis by the family followed by a multi-disciplinary rehabilitation with physiotherapy and psychological inputs resulted in a rapid improvement and return to normal function.

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Table 1: Benign Movement Disorders of Childhood

Condition	Symptom onset	Average Age at Symptom Resolution	Clinical Features	Associated Aetiology
Jitteriness	Neonatal period	Mid-infancy	Generalised rhythmic oscillation	• Hypoxic ischaemic encephalopathy • Hypoglycaemia • Hypocalcaemia • Drug withdrawal
Benign Neonatal Sleep Myoclonus	Neonatal period	Mid-infancy	Repeated myoclonic jerks in sleep	
Benign Myoclonus of Early Infancy	Infancy	Usually by 2 years	Myoclonic spasms neck, trunk and limbs, like infantile spasms	
Spasmus Nutans	Infancy	Within few months, nystagmus can persist	Horizontal/ vertical head tremor with pendular nystagmus	• Rarely cerebellar abnormalities on neuroimaging
Infantile Masturbation	Infancy		Limb posturing, rocking, thigh adduction with genital manipulation/pressure over pubic area	
Shuddering	Infancy – end of the first decade	Usually get better with age	Shivering movements of head, shoulders and upper limbs often with facial grimace	
Benign Idiopathic Dystonia of Infancy	Infancy	Usually by 1 year	Segmental dystonia, usually upper limb	
Benign Paroxysmal Torticollis of Infancy	Infancy	Mid-childhood	Paroxysmal head tilt, often with vomiting irritability, pallor, s	• Mutations in *CACNA1A* • Mutation in *PRRT2*
Paroxysmal Tonic Upgaze of Infancy	Infancy	Mid-childhood	Paroxysmal deviation of eyes upward/downward	• Mutations in *CACNA1A* • Hypomyelination • Periventricular leukomalacia • Vein of Galen malformation • Pinealoma
Head nodding	Usually by early childhood	Normally resolve in a few months, but may last through childhood	Horizontal, vertical and oblique head movements	• Onchocerca volvulus infection (sub Saharan Africa)

Table 2: DYT classification of primary genetic dystonia in childhood

DYT Number	Clinical presentation	Pattern of Inheritance	Causative Gene
DYT1	**Early onset primary generalized idiopathic torsion dystonia**	**Autosomal dominant**	***TOR1A***
DYT5a	**Dopa responsive dystonia**	**Autosomal dominant**	***GCH1***
DYT5b	**Tyrosine hydroxylase deficiency**	**Autosomal recessive**	***TH***
DYT8	**Paroxysmal non-kinesogenic dyskinesia**	**Autosomal dominant**	***MR-1***
DYT10	**Paroxysmal kinesogenic dyskinesia**	**Autosomal dominant**	***PRRT2***
DYT11	**Myoclonus-dystonia**	**Autosomal dominant**	***SGCE***
DYT12	**Rapid onset childhood dystonia-parkinsonism**	**Autosomal dominant**	***ATP1A3***
DYT18	**Paroxysmal exercise induced dyskinesia**	**Autosomal dominant**	***SLC2A1***
DYT23	**Myoclonus dystonia**	**Autosomal dominant**	***CACNA1B***
DYT26	**Myoclonus dystonia**	**Autosomal dominant**	***KCTD17***

Non-paroxysmal dystonias that may present in childhood are highlighted in red
Paroxysmal Disorders that may present in childhood are highlighted in blue

Table 3: Clinical Features of Commoner Genetic Paroxysmal Disorders

Disorder	Age of onset	Reported triggers	Duration of episode	Medication	Causative Gene	Allelic disorders
Paroxysmal kinesogenic dyskinesia	Infancy – 4th decade	Sudden movement	Short – seconds to minutes	Carbamazepine Phenytoin	*PRRT2*	• ICCA infantile convulsions, choreoathetosis • Benign paroxysmal torticollis of infancy • Familial migraine
Paroxysmal non-kinesogenic dyskinesia	Infancy – 4th decade	Caffeine Alcohol Stress/anxiety Sleep deprivation	Longer – minutes to hours	Benzodiazepines	*MR-1*	
Paroxysmal exercise induced dyskinesia	Infancy – adulthood	Exercise Stress Fasting	Longer – minutes to hours	Ketogenic diet	*SLC2A1*	• Glucose transporter deficiency phenotypes: • Absence epilepsy • Myoclonic-atonic epilepsy • Generalised epilepsy • Early infantile epileptic encephalopathy
Alternating Hemiplegia of Childhood	Infancy – early childhood	Unclear	Minutes	Flunarizine	*ATP1A3*	• Rapid onset dystonia parkinsonism • CAPOS
Episodic Ataxia Type 1	Childhood	Sudden movement Stress Exertion Fatigue Illness	Short – seconds to minutes	Acetazolamide Carbamazepine	*KCNA1*	
Episodic Ataxia Type 2	Childhood – adolescence	Sudden movement Stress Exertion,exercise Fatigue Caffeine Alcohol Cigarettes	Very long – hours to days	Flunarazine Acetazolamide	*CACNA1A*	• Spinocerebellar ataxia 6 • Familial hemiplegic migrane

Table 4: Childhood Onset Genetic Disorders with Prominent Ataxia

Condition	Inheritance	Gene(s)	Age of Presentation	Movement semiology
Friedreich's Ataxia	AR	*FRDA*	Childhood 2-15years	Ataxia
Ataxia with Isolated Vitamin E deficiency	AR	*Alpha tocopherol transfer protein*	Childhood	Ataxia Other cerebellar features: tremor, nystagmus
Ataxia Telangectasia	AR		Early Childhood <5 years	Ataxia Chorea Athetosis Dystonia Eye movement abnormalities
Ataxia Oculomotor Apraxia (AOA)	AR	*ÂPTX (AOA1)* *SCAR1 (AOA2)*	Mid-, later Childhood	Ataxia Oculomotor apraxia Chorea, athetosis
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay	AR	*SACS*	Childhood – adulthood	Ataxia
Spinocerebellar Ataxia (SCA)	AD and AR	Many genes including *SCA1 Ataxin* *SCA2 Ataxin* *SCA3 MJD1* *SCA7*	Childhood-adulthood	Ataxia Dystonia and chorea also sometimes present Parkinsonism

Table 5: Pediatric Parkinsonism and Complex Neurometabolic Syndromes

Group of Disorders	Typical Age of Onset	Syndrome/Condition	Reported motor phenotypes	Useful diagnostic tests/disease biomarkers	Causative Genes (molecular confirmation)
Monogenic early onset parkinsonism (PARK loci)	Childhood/ adolescence/early adulthood	Juvenile parkinsonism	Parkinsonism Dystonia	DaTSCAN Prolactin	*PARK2* *DNAJC6* *PINK1* *DJ1* *SNCA* *LRRK2* *VPS35* *EIFG41* *SYNJ1* *PD8B*
Monoamine neurotransmitter disorders	Infancy/ childhood/adulthood	Autosomal dominant GTP cyclohydrolase deficiency	Dystonia Parkinsonism Tremor	CSF neurotransmitters Phenylalanine loading Trial of L-dopa	*GCH1*
	Infancy/ early childhood	Autosomal recessive GTP cyclohydrolase deficiency	Dystonia Hypotonia	CSF Neurotransmitters	*GCH1*
	Infancy	6 Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency	Parkinsonism Dystonia Chorea Oculogyric crises	CSF Neurotransmitters	*PTS*
	Infancy	Sepiapterin reducase deficiency	Dystonia Oculogyric crises Dyskinesia “CP mimic”	CSF neurotransmitters Phenylalanine loading Serum Prolactin	*SPR*
	Infancy	Dihydropteridine reductase (DHPR) deficiency	Dyskinesia Choreoathetosis	CSF neurotransmitters	*QDPR*

			Dystonia Tremor		
	Infancy	Aromatic L-amino acid decarboxylase (AADC) deficiency	Hypotonia Dystonia Dyskinesia Hypokinesia Oculogyric crises	CSF neurotransmitters AADC plasma activity Serum prolactin Urine organic acids	*DDC*
	Infancy	Dopamine Transporter Deficiency Syndrome	Dystonia Chorea Orolingual dyskinesia Axial hypotonia Later parkinsonism Oculogyric crises and eye movement disorder "CP mimic"	CSF Neurotransmitters DaTSCAN	*SLC6A3*
	Infancy	Brain Dopamine Serotonin Transport Disease	Dystonia Parkinsonism Axial hypotonia Dyskinesia Oculogyric crisis		*VMAT2*
Other inborn errors of metabolism	Infancy	**Lysosomal disorders** GM1 Gangliosidosis GM2 Gangliosidosis Niemann Pick C (NPC) Gaucher Disease Neuronal Ceroid lipofucinosis	Ataxia Dystonia Chorea Parkinsonism Supranuclear gaze palsy (NPC) Gaucher carrier –Parkinson disease risk	Lysosomal enzyme assay	*GLB1* *GM2A* *NPC1, NPC2* *GBA1* *CLN1-11*
	Infancy	**Organic acidurias** Glutaric Acidura Type 1	Hyperkinesia Dystonia	OA: glutaric acid, 3-hydroxyglutaric acid	*GCDH*

			Choreoathetosis	Fibrobast assay: reduced glutaryl-CoA dehydrogenase activity Acylcarnitines: glutyrylcarnitine MRI scan – enlarged subdural spaces, frontotemporal atrophy, bat-winged dilatation of Sylvian fissures	
		Methylmalonic aciduria	Dystonia, hypotonia	OA: elevated MMA Hyperammonaemia Hypoglycaemia Metabolic acidosis	*MUT*
		Proprionic acidemia	Dystonia Choreoathetosis Spasticity	OA: elevated PA Metabolic acidosis Hyperammonaemia Hyperglycinaemia	*PCCB, PCCA*
	Infancy	**Aminoacidopathies** Homocystinuria	Dystonia	Abnormal plasma and urine homocysteine	*CBS, MTRR, MTRMMACHC, MTHFR etc*
		Harntnup disease	Ataxia, spasticity, dystonia		*SLC6A19*
	Infancy	**Disorders of purine metabolism** Lesch-Nyhan disease	Choreoathetosis, dystonia, hypotonia, spasticity	Hyperuricaemia	*HPRT*

	Infancy	**Disorders of creatine metabolism** Guanidinoacetate methyltransferase (GAMT) deficiency	Dystonia, choreoathetosis	MRS: low creatine peak Urine: low creatine, high guanidinoacetate	*GAMT*
	Infancy/ childhood/ adulthood	**Glucose transporter deficiency**	Dystonia Choreoathetosis Ataxia Often paroxysmal symptoms	Low CSF glucose Low CSF:plasma glucose ratio	*SLC2A1*
	Infancy	**Cerebral folate deficiency**	Ataxia Dystonia Chorea	Low 5-methyltetrahydrofolate on CSF analysis	*FOLR1* *DHFR* *MTHFR* *GJA12*
	Infancy/ childhood/ adulthood	**Mitochondrial Disorders** Numerous, including Leigh syndrome *POLG1*-related disease Pyruvate carboxylase deficiency Lebers Hereditary Optic Neuropathy plus Dystonia	Dystonia Myoclonus Choreoathetosis Parkinsonism Tremor Ataxia	Lactate, organic acids Muscle biopsy respiratory chain enzyme analysis	*Numerous mitochondrial DNA point mutations and autosomal genes*
Striatal disorders	Infancy	Bilateral striatal necrosis	Progressive dystonia	MRI: bilateral striatal necrosis ADAR1: Interferon signature	*ADAR1* *ATP6,5* *ND1, ND6* *NDUFV1* *NUP62* *SLC19A3,* *SLC25A19* *ADAR1*

Disorders of Metal Ion Accumulation					
Iron	Childhood	Pantothenate Kinase Associated Neurodegeneration (PKAN)	Early gait disturbance Progressive dystonia Spasticity	MRI: Eye-of –the –tiger in GP Blood film -acanthocytes Retinal pigmentation	*PANK2*
	Infancy/ childhood/ adulthood	Phospholipase A2-associated Neurodegeneration (PLAN)	Infantile neuroaxonal dystrophy (INAD) – dystonia, spasticity Atypical neuroaxonal dystrophy (NAD) – dystonia, spasticity *PLA2G6*-related dystonia-parkinsonism -subacute onset of dystonia-parkinsonism, spasticity	MRI: Brain iron (NAD, INAD) in GP and SN Cerebellar atrophy/gliosis Optic atrophy EEG: (INAD) – fast rhythms EMG/NCS: distal sensory axonal neuropathy	*PLA2G6*
	Childhood	Mitochondrial Membrane Protein Associated Neurodegeneration (MPAN)	Dystonia Spasticity	MRI: Brain iron in GP and SN Linear streaking of medial medullary lamina between globus pallidus externa and interna	*C19orf12*
	Infancy/ Childhood	Beta propeller protein Associated Neurodegeneration (BPAN)	Early delay, stereotypies Later development of dystonia-parkinsonism	MRI Brain iron in SN and GP T1 “halo” in SN	*WDR45*
	Childhood	Fatty acid hydroxylase-associated Neurodegeneration (FAHN)	Focal dystonia Spasticity with gait disturbance Later ataxia	MRI: Brai iron in SN and GP Cerebellar and brainstem atrophy White matter changes	*FA2H*

		COASY protein associated Neurodegeneration (CoPAN)	Dystonia Spasticity Parkinsonism	MRI: Brain iron in GP and SN	*COASY*
Manganese	Childhood/ adulthood	Manganese Transporter Defect	Dystonia Parkinsonism	MRI: T1-weighted hyperintensity of basal ganglia, midbrain and cerebellum Raised blood manganese levels	*SLC30A10*
Copper	Childhood/ adulthood	Wilson's Disease	Dystonia Parkinsonism Tremor Choreoathetosis Ataxia	MRI: T2-weighted hyperintensity in putamen and thalami, midbrain face of the giant panda sign Kaiser Flesicher rings on slit lamp eye examination Copper, caeruloplasmin, urinary copper profile	*ATB7B*
Other	Infancy/ childhood	Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	Dystonia Choreoathetosis	MRI: hypomyelination, basal ganglia and cerebellar atrophy	*TUBB4A*

CSF: Cerebrospinal fluid
MMA: Methylmalonic acid
MRS: Magnetic resonance spectroscopy
OA: Organic acids

PA: Propionic acid