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A Diagnostic Approach for Cerebral Palsy in the Genomic Era

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Abstract

An ongoing challenge in children presenting with motor delay/impairment early in life is to identify neurogenetic disorders with a clinical phenotype which can be misdiagnosed as cerebral palsy (CP). To help distinguish patients in these two groups, conventional magnetic resonance imaging (MRI) of the brain has been of great benefit in “unmasking” many of these genetic etiologies and has provided important clues to differential diagnosis in others. Recent advances in molecular genetics such as chromosomal microarray and next generation sequencing have further revolutionized the understanding of etiology by more precisely classifying these disorders with a molecular cause. In this paper, we present a review of neurogenetic disorders masquerading as cerebral palsy evaluated at one institution. We have included representative case examples children presenting with dyskinetic, spastic and ataxic phenotypes, with the intent to highlight the time honored approach of using clinical tools of history and examination to focus the subsequent etiologic search with advanced neuroimaging modalities and molecular genetic tools. A precise diagnosis of these masqueraders and their differentiation from CP is important in terms of therapy, prognosis, and family counseling. In summary, this review serves as a continued call to remain vigilant for current and other to-be-discovered neurogenetic masqueraders of cerebral palsy, thereby optimizing care for patients and their families.

Keywords

Cerebral palsy; masqueraders; spastic; dyskinetic and ataxic phenotypes; neurogenetic

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CONFLICTS OF INTEREST

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INTRODUCTION

Cerebral palsy (CP) represents a group of chronic, non-progressive, but often changing disorders secondary to brain dysgenesis or injury. It is characterized by significant impairment in movement and posture that begins during infancy or early childhood.(The Definition and Classification of Cerebral Palsy 2007) CP affects approximately two to three in 1000 live births in the United States and is the leading cause of motor disability in children.(Accardo 2008; Yeargin-Allsopp et al. 2008; Koman et al. 2004; Prevention 2012) Worldwide, CP has a prevalence of one to five in every 1000 live births.(Stanley 2000; Dolk et al. 2001; Vincer et al. 2006) The incidence of CP increases with lower birth weight and gestational age.(Ancel et al. 2006) The annual economic burden of CP in the United States was five billion dollars in the 1990's, while a separate estimate in 2002 reported an annual cost of 8.2 billion dollars.(Kuban and Leviton 1994; Koman et al. 2004) Since publication of these estimates, CP has been increasingly recognized as a global medical, social and economic concern.

Experienced clinicians recognize that CP, which is generally caused by common external, time-limited etiologic antecedents, including periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH) in premature infants, and hypoxic-ischemic encephalopathy (HIE), can be mimicked by genetically based brain malformations and disorders. However, neurogenetic disorders that clinically resemble CP, but are caused by etiologies with differing natural histories and prognoses, have been termed “masqueraders of CP”. The possibility of a treatable genetic or metabolic etiology of CP emphasizes the importance of being vigilant about the underlying cause. While it is well established that the manifestations of CP are often relatively stable, the motor manifestations may change as a child develops from the neonatal period through childhood and into adulthood.(Smithers-Sheedy et al. 2013) For example, infants with perinatal asphyxia may initially present with hypotonia and years later evolve into dyskinetic forms of CP. It is this fact that may make the identification of “masqueraders” difficult.

In preterm infants with very low birth weight, perinatal white matter injury (PWMI), frequently referred to as PVL, and germinal matrix hemorrhage (GMH), often with hemorrhagic parenchymal venous infarction, represent the most common forms of brain injury.(Papile et al. 1978; Pleacher et al. 2004; Sarkar et al. 2009) Differentiating between early regression caused by genetic diseases affecting brain white matter, also known as leukodystrophies, and delayed motor development in PWMI requires careful clinical history taking. Often there is a period of normalcy preceding a broad range of progressive neurologic symptoms in leukodystrophies.

PWMI typically presents on MRI as hyperintense signal abnormalities on T2- weighted and fluid attenuation inversion recovery (FLAIR) images. While T2- and FLAIR-hyperintense signal abnormalities of the periventricular white matter are a typical finding in PWMI, they are not specific for PWMI and may occur in several additional disorders including some CP masqueraders such as neuronal ceroid lipofuscinosis, metachromatic leukodystrophy or Krabbe disease. In PWMI, however, loss of white matter volume with cortical sulci nearly touching the ventricular walls with widening of the lateral ventricles and irregular borders

are additional neuroimaging findings.(Olsen et al. 1997) Moreover, in PWMI changes occur predominantly in the posterior periventricular regions. Irregular borders of the posterior horns of the lateral ventricles suggest PWMI rather than a neurometabolic CP masquerader.

Magnetic resonance imaging (MRI) findings involving abnormal white matter are found in both PWMI and metabolic white matter diseases. It is important to identify associations between imaging findings and clinical motor phenotypes (spastic, dyskinetic, ataxic and hypotonic). For example, hypomyelination presenting with ataxia is suggestive of disorders such as Pelizaeus-Merzbacher disease and 4H syndrome (see case below). In contrast, patients with hypomyelination and dyskinesia may have MCT8 deficiency (see case below). Diagnostic assessment is available for many metabolic and inherited white matter disorders, with specific testing often focused by characteristic clinical features.

In the term gestation infant, the most common perinatal brain injuries are hypoxic ischemic encephalopathy (HIE) and perinatal stroke.(Nelson and Chang 2008) In HIE, injury is predominantly localized to the basal ganglia (putamen), ventrolateral thalamus, and peri-Rolandic motor strip.(Saint Hilaire et al. 1991; Hoon et al. 2009; Himmelmann et al. 2009; Przekop and Sanger 2011) A careful history and characteristic imaging findings readily separate this group of dyskinetic patients from neurogenetic masqueraders. Oral medications such as baclofen, carbidopa-levodopa and trihexyphenidyl may improve hypertonicity, but complete control is often difficult to obtain.(Mink and Zinner 2010) Intrathecal baclofen can be of benefit when there is severe opisthotonic posturing. Several academic medical centers offer deep brain stimulation, which shows promising results in a select group of patients. (Vidailhet et al. 2009; Apetauerova et al. 2010; Marks et al. 2011; Kim et al. 2011; Kim et al. 2012) Infants with neonatal stroke are at increased risk for neonatal seizures, focal epilepsy, unilateral spastic CP and neurocognitive deficits.(Kirton and deVeber 2009)

Seventy to ninety percent of children with CP have abnormalities on MR imaging, which guide further diagnostic evaluation.(Bax et al. 2006) While the presence of imaging abnormalities often leads to a diagnosis, equally important is the absence of findings. For example, in children with dystonia and/or spasticity without a history of perinatal brain injury, a normal brain MRI points toward testing for a disorder of catecholamine metabolism such as dopa-responsive dystonia.(Friedman et al. 2012)

The diagnostic power of genomic evaluation in children with CP is a growing area of interest as neurogenetic masqueraders can be identified using next generation sequencing technology. The remarkable tools in this evolving era of genomic medicine offer exciting opportunities for clinicians and researchers to participate in the detailed characterization of neurodevelopmental disabilities.

Chromosomal microarray (CMA) is a high-resolution method of chromosome analysis that can detect submicroscopic gains and losses of chromosomal material (copy number variation). Single nucleotide polymorphism (SNP)-based platforms are now the preferred type of CMA, since these can also detect copy neutral loss of heterozygosity due to uniparental disomy or parental consanguinity, whereas the earlier bacterial artificial chromosome (BAC) and oligonucleotide-based platforms can only assess copy number.

CMA is recommended as a first-tier test in the genetic evaluation of patients with global developmental delay, intellectual disability, autism spectrum disorders and/or congenital anomalies, with an expected diagnostic yield of 15–20%. (Manning et al. 2010; Miller et al. 2010) Chromosomal microarray is increasingly being used in the diagnostic evaluation of patients with other neurologic phenotypes such as epilepsy and cerebral palsy when there is suspicion of a genetic etiology.

Newer genome-wide analyses deployed in clinical practice include whole exome sequencing (WES) while whole genome sequencing (WGS) is still mostly used in a research setting. (Bick and Dimmock 2011) WES simultaneously analyzes the protein-coding regions (exons) of >20,000 genes in the human genome. WGS analyzes the non-coding regions as well as coding regions. Both technologies can detect sequence changes such as point mutations and small insertions and deletions. WES and WGS have already proven to be powerful tools in the diagnosis of patients with unknown genetic disorders. (Rabbani et al. 2014)

Early diagnosis of masqueraders of CP represents an advance in medicine that can guide therapy, and provide families with important prognostic and genetic counseling information. It has been our experience that “unmasking” the etiology of disorders that comprise the spectrum of motor disability often improves patient outcome and gives clearer prognostication for affected individuals and their families. As the initial step in this process, an evaluation of motor delay is often made by a general pediatrician, with referral to a neurodevelopmental pediatrician, pediatric neurologist or geneticist. Clinical examination alone is often insufficient for identification of an etiology of CP. Additional studies such as MRI and laboratory testing are frequently required for clarification. In this situation there are a number of clinical and imaging “red flags” that should lead the examiner to consider evaluation for a masquerader (Table 1). While it is impossible to give a comprehensive approach, we suggest a general guideline for evaluation process of the child with cerebral palsy (Figure 1).

It is important to consider the diagnostic yield of a test when evaluating the etiology of cerebral palsy. Shevell et al. (2003) studied 217 individuals with CP and report an overall etiologic yield of 82%. The yield varied according to type of cerebral palsy: 50% dyskinetic, 59% diplegia, 80% monoplegia, 80.9% hemiplegia, 90.9% quadriplegia, 91.7% ataxic hypotonia, and 100% mixed/Woster-Drought. A single etiology was apparent in 144 (66.4%) of the cases, multiple etiologies were believed to be contributory in 34 (15.6%) of the cases. Features of the child’s cerebral palsy, such as microcephaly, neonatal difficulties, prior or coexisting epilepsy, and high-risk source, were found to be predictive of eventual etiologic yield. (Shevell et al., 2003) Metabolic testing in cerebral palsy may have a yield of up to 20%. (Whitehouse, 2011; Heinen, 2011; Leonard et al., 2011) The diagnostic yield of whole exome sequencing (WES) in 78 children in a child neurology practice was reported to be 41%. (Srivastava et al., 2014) Of the 32 patients in the study with pathogenic or likely pathogenic variants 11 exhibited cerebral palsy like encephalopathy. The overall high rate of diagnosis with WES impacted management for all patients with a presumptive diagnosis, triggering reproductive planning, disease monitoring initiation, investigation of systemic involvement of the disorder, alteration of presumed disease inheritance pattern, changing of

prognosis, medication discontinuation or initiation, and clinical trial education. Further studies are needed to strengthen our understanding of the diagnostic yield in this field.

We have chosen select cases from our institution that highlight diagnostic challenges, and discuss them in the context of a classification scheme of dyskinetic, spastic and ataxic neurologic clinical phenotypes based on primary motor impairment. We have chosen to include selected brain malformations as they differ in recurrence risk from acquired etiologies of CP. The list of conditions included as “masqueraders” were based upon clinical examination features of cerebral palsy. The lists are not meant to be exhaustive, rather present the reader a sample of disorders. The etiologies were categorized by cerebral palsy subtype classification.

References for this review were identified through searches of PubMed with the search terms “cerebral palsy”, “neurogenetic”, “masqueraders”, “causes”, “etiology”, “spastic”, “dyskinetic”, and “ataxic” from 1978 until September, 2013. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Overall, this review aims to improve the diagnostic acumen of clinicians by equipping them with a guide to using neuroimaging and molecular genetic techniques as a way to distinguish and identify neurogenetic disorders masquerading as CP, which in turn will improve management for patients and their families.

DYSKINETIC DISORDERS MASQUERADING AS CEREBRAL PALSY

A widely accepted classification of CP is into phenotypes including spastic (bilateral or unilateral), dyskinetic, and ataxic-hypotonic CP (Surveillance of Cerebral Palsy in 2000; Saint Hilaire et al. 1991; Koman et al. 2004), recognizing that many patients have several neurological findings and are best characterized as having a mixed-type CP. Dyskinetic (also called “Extrapyramidal”) CP is characterized by abnormal movements, with fluctuating patterns of tone and posture. Clinical findings include dystonia, chorea, athetosis and/or hemiballismus. We present a few examples of recognizable dyskinetic disorders masquerading as CP, and a list of disorders in Table 2.

Neurotransmitter Disorders: Disorders of Catecholamine Metabolism

Disorders of catecholamine metabolism are important masqueraders of dyskinetic CP that often present with normal or nonspecific imaging findings, for which effective treatment is available. A careful inquiry may elicit the history of worsening symptoms as the day progresses. Several enzyme deficiencies have been described. Evaluation of cerebrospinal fluid allows the detection of the involved metabolites (Table 3). (Hyland 2007) More recently, molecular analysis of the involved genes has become available. There are a number of medications that can improve function in specific disorders. In the patient with dyskinesia of unknown etiology, a trial of L-Dopa points toward this diagnosis and merits further diagnostic assessment.

Case 1. Dopa-Responsive Dystonia (DRD)—A five year-old female born at term presented during late infancy with a diagnosis of “spastic diplegia”. There was a history of progressive dystonia, predominantly during the day. Brain MRI was unremarkable (Figure 1). An empiric trial of carbidopa-levodopa resulted in dramatic improvement in her dystonia and spasticity. Genetic testing subsequently showed a heterozygous mutation in *GCHI* confirming the diagnosis of autosomal dominant DRD.

Tetrahydrobiopterin (BH₄) is as a cofactor for enzymes involved in synthesis of Levodopa, the precursor of dopamine, while *GCHI* encodes the enzyme GTP Cyclohydrolase 1, the initial rate limiting step in BH₄ synthesis. Hence, *GCHI* mutations result in BH₄ deficiency leading to reduced synthesis of dopamine. DRD is a progressive disorder that worsens in the absence of appropriate therapy, but responds well to treatment with carbidopa-levodopa. In this case, a normal MRI in the presence of dystonia increased our suspicion for DRD.

Case 2. Aromatic Acid Decarboxylase (AADC) Deficiency—A six year-old male presented with infantile onset dystonic posturing, and was later on noticed to have oculogyric crises, ptosis and severe dysarthria while cognition appeared to be preserved. Brain MRI showed only minimal prominence of frontal horns (Figure 2). As part of an extensive diagnostic evaluation, CSF neurotransmitters showed an increase in 3-O-methyldopa, while homovanillic acid and 5-hydroxyindolacetic acid were both decreased. This pattern was suggestive of AADC deficiency. Genetic testing confirmed a diagnosis of AADC deficiency with a homozygous p.L222P mutation. Medical therapy with pyridoxol phosphate, folinic acid, and pramipexole resulted in dramatic improvement in speech, gait, hand use and ocular problems.

AADC is responsible for decarboxylation of levodopa and 5-hydroxytryptophan in the synthesis pathways for dopamine and serotonin. Several gene therapy studies for AADC deficiency are in clinical trials addressing safety and efficacy of this approach. (Christine et al. 2009; Muramatsu et al. 2010; Hwu et al. 2012; Zwagerman and Richardson 2012)

Glucose Transporter Type 1 Deficiency Spectrum

Glucose Transporter Type 1 (Glut1) deficiency presents as a spectrum of clinical neurodevelopmental phenotypes from infantile seizures, post-natal microcephaly, developmental delay and movement disorder through childhood epilepsy, intermittent ataxia and alternating hemiplegia. (Sparks SE 2012) The underlying pathophysiology involves impaired glucose transport across the blood-brain barrier. It is almost always the result of a de novo mutation but can rarely be inherited in an autosomal dominant fashion with incomplete penetrance. Low CSF glucose (hypoglycorrachia) in the setting of normal blood glucose reflects the impaired glucose transport into the brain and is essential for diagnosis. A standardized fasting lumbar puncture to account for different glucose fluxes in blood and CSF should be performed to determine hypoglycorrachia. The diagnosis can be confirmed by identification of a heterozygous disruption in the *SLC2A1* gene.

For treatment, the ketogenic diet is effective in reducing dyskinesias and seizures and may lead to subjective improvement in cognition. (Leen et al. 2010) Ketosis is thought to provide the brain with an alternative metabolic fuel. (Klepper et al. 2004)

Case 3. Glucose Transporter Type 1 (Glut1) Deficiency—A four year old female presented with infantile-onset epilepsy, truncal hypotonia, dystonia, spasticity, intellectual disability and intermittent hypoglycemia associated with fatigue. An initial brain MRI at six months of age had shown diffuse T2 hyperintensity in cerebral white matter and mild ventriculomegaly. A repeat MRI at two years showed diffuse bilateral T2 hyperintensity in the subcortical U-fiber regions with temporal predominance. Cerebrospinal fluid glucose was low at 40 mg/dL, compared with blood glucose of 86 mg/dL. A Next Generation Sequencing panel of genes associated with infantile-onset epilepsy was positive for a heterozygous splice-site mutation, IVS7+(1_3)delGTG, in the *SLC2A1* gene, confirming the diagnosis of Glut1 deficiency. Treatment recommendations were for initiation of a ketogenic diet.

Disorders of Neurodegeneration Associated with Brain Iron Accumulation

Another group of diseases that can masquerade as dyskinetic CP are the neurodegeneration associated with brain iron accumulation (NBIA) disorders. (Kruer and Boddaert 2012) NBIA disorders usually present during childhood, and result in periods of clinical deterioration lasting several months, with relatively stable periods in between.

Case 4. Pantothenate Kinase-Associated Neurodegeneration (PKAN)—A 6 year-old male was born at term and developed severe progressive dystonic cerebral palsy in infancy, refractive to treatment with oral baclofen and trihexyphenidyl. A brain MRI at four years of age showed low-signal intensity rings surrounding central hyperintense T2-weighted signal in bilateral globus pallidi, (“eye of the tiger” sign) (Figure 2). *PANK2* gene sequencing showed a homozygous frame-shift mutation, c.215_216insA, confirming the diagnosis of PKAN. While a wide range of treatments have been utilized, the clinical course has been relentlessly progressive.

Currently there is no clinically proven treatment for NBIA disorders. An international consortium has recently initiated a phase 3 clinical trial, Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON), to evaluate the role of iron chelation therapy in this disorder (clinicaltrials.gov/NCT01741532).

Mitochondrial Disorders

Mitochondrial disorders include a large number of diseases due to abnormalities in mitochondrial DNA or nuclear genes responsible for mitochondrial function. This group of diseases has an extremely wide range of clinical phenotypes, often involving but not limited to the central nervous system. (McFarland et al. 2010) On MRI a wide range of brain structures, including the basal ganglia, supra and infratentorial white matter, cortical gray matter and cerebellum can be affected. (Gropman 2013)

As with the variability in underlying genetic cause and imaging findings, the range of neurological findings is extremely wide. Common features including dystonia, choreoathetosis, myoclonic movements, and a Parkinsonian syndrome. Mitochondrial DNA is matrilineally inherited, affecting both males and females. In some cases, a de novo mutation occurs without a family history of a mitochondrial disorder. Mitochondrial

disorders caused by mutations in nuclear-encoded genes can be inherited in autosomal recessive, autosomal dominant or X-linked patterns.

Case 5. Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS)—A 14 year-old boy presented with history of prematurity born at and chylothorax requiring chest tubes and hospitalization in the neonatal intensive care for severe infantile onset dystonic cerebral palsy. The family history was significant for a maternal history of ocular migraine headaches and a maternal aunt with intractable epilepsy. MRI showed bilateral T2 hyperintensity in the globus pallidi. A peripheral blood sample revealed a heteroplasmic mitochondrial DNA mutation, m.3243A>G, consistent with MELAS.

This m.3243A>G mutation in tRNA-Leu (UUR) gene causes respiratory chain dysfunction and accounts for about 80% of cases of MELAS.(Goto et al. 1992) A recent study segregated disease-causing mitochondrial heteroplasmy into pluripotent stem cell clones derived from a patient with MELAS.(Folmes et al. 2013) This model system shows promise for the direct comparison of genotype-phenotype relationships in progenitor cells of bioengineered tissues.(Folmes et al. 2013)

Organic Acid Disorders

Glutaric Aciduria Type 1 (GA1) is an autosomal recessive disorder of amino acid catabolism caused by mutations in glutaryl Co-A dehydrogenase (*GCDH*) that lead to an inability to breakdown lysine, hydroxylysine and tryptophan.(Strauss et al. 2003; Christensen et al. 2004) Excess of these amino acids and their intermediates glutaric acid, glutaryl-CoA, 3-hydroxyglutaric acid, and glutaconic acid accumulate, causing gliosis and neuronal loss particularly in the striatum under stress settings.(Hedlund et al. 2006) There is a high carrier frequency and prevalence among certain groups, including the Lancaster County Old Order Amish population.(Morton et al. 1991)

Case 6. Glutaric Aciduria Type 1—A boy presented to clinic at the age of 13-years with history of infantile onset severe dystonia and chorea involving all extremities with relative sparing of receptive language. He was the product of a term gestation vaginal delivery. Typical development was noted until a febrile illness at seven months of age leading to unilateral ophthalmoplegia, chorea and seizures manifesting on the third day of illness. Cerebrospinal fluid analysis was unremarkable. He was diagnosed with an *E. coli* urinary tract infection. His involuntary movements did not improve and over the course of two years he developed progressive dystonia and choreoathetoid movements. Evaluation at the age of 4 years showed a urine organic acid profile with highly elevated glutaric and 3-hydroxyglutaric acids. A brain MRI revealed bilateral T2 hyperintense signal consistent with striatal necrosis (Figure 2). Molecular testing revealed a homozygous *GCDH* mutation in the patient and also in his younger asymptomatic brother; parents were heterozygote carriers. Therapy was initiated with L-carnitine, tetrabenazine and baclofen which led to a mild improvement in motor function.

Microencephalic macrocephaly at birth is the earliest sign of GA1 and is associated with stretched bridging veins that can be a cause of subdural hematoma and acute retinal

hemorrhage. Acute striatal necrosis during infancy is the principal cause of morbidity and mortality. Injury to the putamen in a symmetric fashion is heralded by abrupt-onset behavioral arrest. Tissue degeneration is stroke-like in pace, radiologic appearance, and irreversibility. It is confined to children under 18 months of age, and occurs almost always during an infectious illness. A secondary carnitine deficiency is often present. Interestingly, striatal necrosis does not occur after two years of age, therefore, patients who were not exposed to any stressors within the first two years are typically asymptomatic like the younger brother in the above-mentioned case.(Strauss et al. 2003) There is, however, recent literature demonstrating that adults with GA1 may still develop headaches and white matter changes.(Bahr et al. 2002) There is no cure but treatment with dietary control, choline, intravenous carnitine, and management of intercurrent illness improves prognosis.

Monocarboxylate Transporter 8 Deficiency

Monocarboxylate Transporter 8 (MCT-8 Deficiency; Allan-Herndon-Dudley syndrome) deficiency is an X-linked recessive disorder caused by mutations in *SLC16A2*, resulting in impaired transport of thyroid hormone T₃. The disorder is believed to account for a significant number of males with neurodevelopmental disability of unknown etiology. (Friesema et al. 2010)

Case 7. Monocarboxylate Transporter 8 Deficiency—A two year-old boy presented with profound global developmental delay, hypotonia, intermittent dystonic posturing, and dysmorphic facial features. Pregnancy and delivery were uncomplicated. Serum thyroid T₃ levels were high at 3.66 ng/mL (0.94 – 2.69 ng/mL), T₄ low at 0.5 ng/dL (4.5 – 12.5 ng/dL), and thyroid stimulating hormone within the normal range at 4.47 µIU/mL (0.5 – 4.70 µIU/mL). MRI revealed T2 hyperintensity of the periventricular white matter, primarily in the posterior and anterior horns of the lateral ventricles. DNA sequence analysis of *MCT8* revealed a hemizygous 8 base-pair deletion at nucleotide c.1696_1703del8 that resulted in an abnormally truncated MCT-8 protein. Follow-up exam at the age of three years demonstrated progressive disability, characterized as mixed spasticity, hypotonia, and dyskinesia. Therapy with thyroid hormone has not been successful.(Zung et al. 2011; Schwartz and Stevenson 2007)

SPASTICITY DISORDERS MASQUERADING AS CEREBRAL PALSY

Spastic cerebral palsy is the most common type of CP and is characterized by abnormally increased muscle tone; often as part of an upper motor neuron syndrome.(Krageloh-Mann and Cans 2009; Barnes 2008) Physiological descriptions are often combined with topographical classification (e.g. diplegia, hemiplegia) when discussing spastic CP. Premature infants with PWMI present with spastic diplegic or quadriplegic CP, depending on the severity of brain injury. Patients with prenatal or perinatal stroke often present with spastic hemiplegic CP. As is the case with dyskinetic CP, there is often mixed neurologic findings. We present examples of disorders masquerading as spastic cerebral palsy (Table 4).

Hereditary Spastic Paraplegias

Hereditary Spastic Paraplegias (HSP), also referred to as spastic paraplegias (SPG), are a heterogeneous group of progressive degenerative disorders presenting with spasticity, usually starting in the lower extremities. More than 50 genes have been identified that can lead to HSP.(Fink 2013) A number have a childhood onset form and are frequently misdiagnosed as CP. The primary distinguishing characteristic is worsening spasticity with age and the lack of a perinatal history that would explain the disability. Complex HSPs are defined as spastic paraplegias with other neurologic impairments including seizures, intellectual disability, dementia or peripheral neuropathy.(Fink 2013) Infantile onset forms of HSP are listed in Table 5.

Case 8. Hereditary Spastic Paraplegias—A male was born at term following an unremarkable pregnancy and delivery. He presented at 25 months of age with infantile-onset spastic diplegia, dysarthria and dystonic posturing. A brain MRI at nine years of age showed mild parenchymal volume loss in the bilateral frontoparietal and cerebellar regions and mild peritrial white matter T2 signal hyperintensity bilaterally. Family history was notable for parental consanguinity. A single nucleotide polymorphism (SNP) chromosomal microarray demonstrated multiple long regions of homozygosity representing eight percent of the genome. Whole exome sequencing was performed and identified a homozygous stop-codon mutation, c.4897C>T (p.Q1633X), in the *ALS2* gene, which is associated with Infantile-Onset Ascending Hereditary Spastic Paraplegia. Follow-up exam at 12 years revealed progressive weakness, worsening scoliosis and excessive drooling. It is anticipated that this patient will worsen over the next few years and become anarthric. Mutations in *ALS2* gene can also lead to two other disorders, Juvenile Amyotrophic Lateral Sclerosis and Juvenile Primary Lateral Sclerosis. Treatment is primarily supportive as there is no effective medical therapy for this disorder. Extended family screening was performed due to several consanguineous marriages within this family, and another younger individual was identified with this disorder.

Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher Disease (PMD) is an X-linked neurodegenerative disorder of myelination, due to gene alterations in the *PLP* gene, with a wide spectrum of clinical findings, ranging from the less involved Spastic Paraplegia Type 2 (SPG2) to the more severe classical PMD.(Hobson and Garbern 2012) Proteolipid-protein (PLP) is a major component of the myelin membrane and plays an integral role in myelin sheath formation. The majority of cases are due to duplication of the gene while point mutations and deletions have also been reported.

Case 9. Pelizaeus-Merzbacher Disease—An 18 month-old male presented with global developmental delay, hypotonia, mixed-type ataxic/dystonic/spastic CP and rotary nystagmus. There were no pregnancy or delivery complications. A brain MRI at eight months of age showed bilateral diffuse T2 hyperintensities involving subcortical and periventricular white matter, corpus callosum, internal capsules and cerebellar white matter, overall suggestive of hypomyelination (Figure 3). Genetic testing showed a mutation

causing a duplication of the proteolipid-protein 1 gene (*PLP1*) consistent with a diagnosis of PMD.

A recent study implementing a cholesterol-enriched diet in PMD mice shows normalization of PLP trafficking, increased myelin content, improved motor function and slowed disease progression when diet was initiated before symptom onset.(Saher et al. 2012) Currently, there is no effective therapy, although very recently neural stem cells were transplanted into the frontal lobe white matter of four male subjects with an early-onset severe form of PMD. Preliminary results showed improved myelination.(Gupta et al. 2012)

Lysosomal Storage Disorders

Several lysosomal storage disorders, including metachromatic or globoid cell Leukodystrophy (Krabbe Disease) can initially present with spasticity and developmental delay. These diseases are degenerative disorders and eventually lead to severe disability and death.

Case 10. Infantile-Onset Krabbe Disease—This boy was born at term following an uncomplicated delivery but was noted to have macrocephaly at birth and appeared hypotonic. A brain ultrasound and MRI showed mild prominence of ventricles without obstruction. At six months of age the patient presented to the emergency department following two weeks of developmental regression characterized as an inability to lift his head, reach for objects or laugh. Clinical exam showed severely increased tone and opisthotonus which would get worse with stimulation. MRI showed global cerebral volume loss, T2 hyperintensity of the periventricular and cerebellar white matter with involvement of the dentate nuclei, ventriculomegaly, bilateral optic nerve hypertrophy, and prominence of extra-axial cerebrospinal fluid spaces (Figure 3). Leukocyte enzyme testing demonstrated abnormally low galactocerebrosidase activity confirming Krabbe disease.

In Krabbe disease, galactocerebrosidase deficiency leads to accumulation of psychosine, a highly toxic lysophospholipid, resulting in oligodendrocyte cell death, demyelination, severe gliosis and neurodegeneration. A clinical trial showed that pre-symptomatic infants with *GALC* deficiency who underwent transplantation of allogeneic umbilical-cord stem cells had a better outcome compared to their untreated affected siblings.(Escolar et al. 2005; Yagasaki et al. 2011)

Disorders of Neuronal Migration

Many individuals with cerebral palsy have a brain malformation as the underlying etiology for the motor disability.(Lequin and Barkovich 1999) A common group are migrational disorders, which are usually non-progressive, commonly genetic, syndromes leading to CP. The genetic defects that cause neuronal migration disorders can recur in other family members. Knowledge about etiology equips families with information about recurrence risk and expectations about prognosis.

The process of neuronal migration along radioglia fibers is a highly orchestrated process involving a number of genes. Pending on the gene involved the phenotype can vary from a migrational defect resulting in lissencephaly, to polymicrogyria, to a primary microcephaly.

Clinical manifestations encompass a wide spectrum of motor and cognitive impairment, seizures and sometimes distinctive dysmorphic features.(Kuzniecky et al. 1989; Hoon and Melhem 2000) While commonly bilateral, brain malformations may predominantly affect a single hemisphere, resulting in hemiplegic or unilateral impairment (Figure 4).

Cortex development is dependent upon pathways that regulate cytoskeletal formation through microtubule and actin function.(Stolp et al. 2012) A number of genes (e.g. *LIS1*, *TUBA1A*, *TUBB3*, *DCX*, *FLNA*, *ARX*) have drawn particular interest.(Spalice et al. 2009; Liu et al. 2012) A better understanding of intrinsic repair mechanisms (e.g. doublecortin) has resulted in progress toward targeted molecular therapy.(Haynes et al. 2011)

Genetic causes of migration disorders have been elucidated through a combination of neuroimaging and genetic techniques.(Liu 2011) A classic case of a migration defect is lissencephaly, a disorder of abnormally smooth appearance of the cortical surface with flattening of sulci and thickened gyri.(Reiner et al. 1993)

Case 11. *LIS1* Lissencephaly—A male was born at term following an unremarkable pregnancy. Ultrasound shortly before delivery showed concern for microcephaly with a simplified gyral pattern. Post-natal day one brain MRI showed microcephaly and a “smooth brain” consistent with lissencephaly (Figure 3). Chromosomal microarray and FISH demonstrated a de novo unbalanced translocation between the long-arm of chromosome 12 at band q24.33 and the short arm of chromosome 17 at band p13, resulting in deletion of *LIS1*, consistent with a diagnosis of Miller-Dieker syndrome. At 4 months of age the patient presented with global developmental delay, hypotonia, extensor hypertonicity, and dysmorphic facial features. The acute onset of rhythmic arching episodes concerning for infantile spasms prompted an electroencephalogram which revealed a modified hypsarrhythmia pattern.

Disorders of Forebrain Cleavage

Holoprosencephaly (HPE) involves incomplete separation of the cerebral hemispheres and deep gray nuclei. The subtypes include alobar, semilobar, lobar and middle interhemispheric variants. In alobar HPE, no hemispheric cleavage of the brain hemispheres occurs and facial malformations are common. Semilobar HPE consists of partial division of brain hemispheres. Lobar HPE is manifested as relatively good separation of hemispheres. In the middle interhemispheric variant, the posterior frontal lobe and the parietal lobe are not properly separated, but the rostromedial forebrain properly separates. In many cases malformations are severe and fetuses die before birth, on the other hand mild variants may be asymptomatic. The severity of neurologic, developmental and medical problems is correlated with the degree of brain malformation. Management is often multifaceted.(Levey et al. 2010)

Chromosomal anomalies account for most identified causes of HPE, but the overall phenotypic spectrum is broad and includes non-syndromic and non-chromosomal forms. (Orioli and Castilla 2010) While numerous environmental risk factors are associated with HPE, there are also monogenic forms caused by mutations in *SHH*, *SIX3*, *TGIF1*, *ZIC2* and other genes.(Rosenfeld et al. 2010) Array-based hybridization and genomic screening has

improved characterization of important loci associated with the disorder. Molecular testing and genetic counseling may be required to further describe prognosis and recurrence risk in patients with HPE.

ATAXIC DISORDERS MASQUERADING AS CEREBRAL PALSY

Ataxic cerebral palsy is one of the least common types of CP, accounting for about 5-10% of cases.(Paneth 1986) It is characterized by impaired coordination of muscle movement and balance originating from the cerebellum and cerebellar pathways. Ataxic CP is frequently associated with hypotonia, tremor, seizures, auditory and speech impairment.(Himmelman et al. 2006; Andersen et al. 2008; Shevell et al. 2009) In 1992, it was estimated that more than 50% of ataxic cerebral palsy is inherited as an autosomal recessive trait.(Hughes and Newton 1992) Subsequently, few studies have investigated the genetic antecedents of ataxic cerebral palsy.(McHale et al. 2000; Lv et al. 2012; Benini et al. 2012; Chen et al. 2013)

There is evidence suggesting ataxic CP has different pathologic mechanisms than spastic and dyskinetic forms of CP. There is high proportion of cerebral anomalies associated with ataxic CP, and these often include the cerebellum and its connections, especially white matter.(Imamura et al. 1992; Rankin et al. 2010) To highlight the differences in etiology between spastic/dyskinetic CP (mostly disruptive/acquired etiologies) and ataxic CP (genetic etiologies), some authors prefer to use the term “non-progressive cerebellar ataxia” instead of ataxic CP.(Steinlin et al. 1999) We present examples of ataxic disorders masquerading as CP (Table 6).

Coenzyme Q10 Deficiency

CoenzymeQ10 (CoQ10) is endogenously synthesized in the mitochondrial inner membrane. Primary CoQ10 deficiency usually manifests with encephalomyopathy and nephropathy. Ataxic CP is the most common neurologic phenotype associated with CoQ10 deficiency.(Lamperti et al. 2003) Some patients with primary CoQ10 deficiency show clinical improvement after initiating oral CoQ10 supplementation.(Montini et al. 2008) Thus, early diagnosis and initiation of therapy may be beneficial for these patients.

Case 12. Coenzyme Q10 Deficiency—A 10 year-old boy presented with ataxia beginning at three years of age. A brain MRI at age six years showed cerebellar atrophy. Whole exome sequencing revealed compound heterozygous mutations in the *ADCK3* gene, c.1015G>A (p.A339T) and c. 1665G>A (p.M555I), consistent with a diagnosis of CoQ10 deficiency. *ADCK3* encodes the rate-limiting enzyme in CoQ10 synthesis and is one of several genes that can cause primary CoQ10 deficiency. Therapy with coenzyme Q10, vitamin C, and vitamin E was initiated.

Congenital Disorders of Glycosylation

Congenital Disorders of Glycosylation (CDG) are characterized by abnormal glycosylation of N-linked and O-linked oligosaccharides caused by deficiency of multiple different enzymes in the synthetic pathway.(Sparks SE 2012) The neuroimaging and natural history is highly variable. The most common reported type is PMM2-CDG (CDG-1a). The screening test for most types of CDG is analysis of serum transferrin glycoforms.

Case 13. Congenital Disorders of Glycosylation—A 17 month-old male was born at term gestation. He presented with dysmorphic facial features, sacral dimple, hypospadias, pes planus, developmental delay, and subacute onset of falls secondary to an unsteady gait in the setting of otitis media. SNP chromosome microarray, amino acids, organic acids, and MRI of the brain and spine were unremarkable. Transferrin affinity chromatography by mass spectrometry showed an unusual glycoform variant (hexasialo transferrin) suggestive of a CDG. Over the course of 5 years he worsened with his neurologic status and became nonverbal, quadriplegic, and g-tube dependent and suffers from seizures.

***MECP2* Duplication Syndrome**

MECP2 duplication syndrome is an X-linked neurodevelopmental disorder.(Neul et al. 2010) The majority of females are unaffected due to X-inactivation. Almost all affected males inherited the duplication from their mother, rarely have de novo cases been reported. In contrast to whole-gene duplications of methyl CpG binding protein 2 gene (*MECP2*), mutations or deletions of this gene cause Rett syndrome in females and severe encephalopathy in males.

Case 14. *MECP2* Duplication syndrome—A 34 year-old male presented to clinic with global developmental delay since infancy. He was born at term, sat unassisted at 15 months, walked at 30 months and never gained any language. During his teenage years his gait began to worsen and he became increasingly more ataxic with frequent falls. Physical exam revealed facial hypotonia, spasticity, ataxia, autistic traits and severe intellectual disability. A brain MRI at age 30 years showed vermian atrophy and bilateral T2 hyperintensities in parietal and occipital periventricular white matter. SNP array detected a 502 kb duplication on the X chromosome within band q28. The duplication encompassed several genes including the *MECP2* gene, which is the major cause of intellectual disability in Xq28 duplication males.

Joubert Syndrome

Joubert syndrome (JS) is characterized by hypoplasia and dysplasia of the cerebellar vermis. Mutations in genes that play a role in formation and function of primary, non-motile cilia are responsible for the manifestations of Joubert syndrome. Cilia are important for cell function in the brain, eye, kidney and liver.(Romani et al. 2013) Mutation in the 23 JS genes discovered so far account for about 50% of the patients. The most common form of inheritance is autosomal recessive, although there is one gene that is X-linked.

Case 15. Joubert Syndrome—A 20 month-old female born at term presenting with hypotonia with prominent head lag, and bilateral esotropia. An ultrasound at 20 weeks gestation revealed concern for a posterior fossa malformation. Fetal brain MRI at 32 weeks gestation showed increased retro-/infracerebellar cerebrospinal fluid. Postnatal MRI revealed hypoplastic vermis with midline contact of the cerebellar hemispheres, elongated, horizontally orientated and thickened superior cerebellar peduncles in a “molar tooth” configuration, a “batwing” configuration of the fourth ventricle, and thinning of the pontomesencephalic junction as a result of dysgenesis of the isthmus with deepening of the

interpeduncular cistern (Figure 5). These findings were consistent with Joubert syndrome. Recommendations for renal, ophthalmologic, and hepatic monitoring were made.

Angelman Syndrome

Angelman syndrome is caused by mutations on chromosome 15 within band q11.2 and is a classic example of genomic imprinting in that it is caused by deletion or inactivation of genes on the maternally inherited chromosome 15 while the paternal copy, which may be of normal sequence, is imprinted and therefore silenced.(Williams et al. 2010) The most common mechanism is a deletion of this region, which can be diagnosed by FISH or microarray; the remainder of cases can be detected by methylation analysis and/or *UBE3A* gene sequencing.

Case 16. Angelman Syndrome—A 30 year-old man presented with epilepsy, scoliosis, infantile onset spasticity in lower extremities, truncal ataxia and intellectual disability. He was born at term without complications. In infancy he fed poorly and developed global developmental delay. At one year of age he was diagnosed with ataxic CP. Language impairment was profound, but he was reported to have a happy temperament. He did not walk independently until the age of 14 years. At the age of 16 years, he was diagnosed with Angelman syndrome by FISH testing that showed a deletion on chromosome 15q11.2. There was no pertinent family history. Physical exam revealed dysmorphic facial features, microcephaly, short stature, happy demeanor, short attention span, restlessness, lower extremity spasticity, clonus, truncal ataxia, dysmetria, and an ataxic wide-based gait.

CONCLUSIONS

This paper highlights the well-established approach to diagnosis in medicine- start with a comprehensive history, including family history, and in combination with a careful physical/neurological examination establish a CP phenotype and formulate a differential diagnosis. The advent of neuroimaging and advanced molecular genetic techniques have provided valuable tools to sharpen diagnosis. As this report illustrates, this approach promotes the diagnosis of individual rare but clinically important, neurogenetic masqueraders of cerebral palsy.

Neuroimaging, particularly conventional brain MRI, is a powerful tool in the evaluation of the child with suspected CP. MRI may elucidate the timing of injury and contribute to an understanding of the etiology and pathogenesis underlying CP.(Hoon et al. 2003; Krageloh-Mann and Horber 2007; Himmelmann and Uvebrant 2011) In 2004 the American Academy of Neurology and Practice Committee of the Child Neurology Society have recommended neuroimaging be part of the diagnostic assessment.(Ashwal et al. 2004; Msall et al. 2009) The pattern of neuroimaging findings in children with CP has been shown to be associated with the CP phenotype.(Krageloh-Mann and Horber 2007; Towsley et al. 2011) Spastic diplegia is often associated with PWMI; spastic quadriplegia with severe PVL or bilateral cortical and deep gray matter injury; unilateral spastic CP with sequelae of cerebrovascular events; and dyskinetic CP with deep gray matter injury. Rigidity is not a common feature following prematurity, but may be seen in cases involving anoxia. Rigidity occurs more commonly in patients with basal ganglia dysfunction, such as in Parkinson's disease. While

many patients present with a mixed-type CP, several disorders comprising this category, including neurotransmitter disorders and mitochondrial disorders, may present a primarily hypotonic phenotype.

In a study of 273 children with CP born after 35 weeks gestation, one-third of infants had normal conventional neuroimaging studies.(Wu et al. 2006; Benini et al. 2013) In these patients it is often beneficial to look closely for neurotransmitter disorders, with an empiric trial of levodopa and consideration of spinal tap for neurotransmitter analysis, as this group of disorders is often medically treatable.

The benefits of identifying an etiologic diagnosis are clear and include helping affected patients and their families understand the cause of disease (“including it is not my fault”), prognostication, locating appropriate support groups, medical management and surveillance for associated complications or other organ system involvement; and in some conditions, disease-modifying therapy. In addition, an etiologic diagnosis will establish the inheritance pattern, enabling genetic counseling regarding recurrence risk and reproductive options.

Obtaining a pertinent family health history is an essential part of the diagnostic evaluation. A three-generation pedigree should be constructed for each patient using standardized pedigree nomenclature.(Bennett et al. 2008) In addition to inquiring about the general health of each relative, the clinician should ask targeted questions about whether there are any family members with developmental disabilities, neurologic conditions (e.g. seizures, movement disorders), early-onset hearing or vision loss, psychiatric illness, recurrent pregnancy loss, fetal/infant death, or congenital abnormalities. The clinician should also ask about parental consanguinity and ethnicity/ancestry.

Genetic counselors are valuable in the process of helping patients and families understand and adapt to the medical, psychological and genetic contributions to disease.(National Society of Genetic Counselors’ Definition Task et al. 2006) Genomic testing is becoming increasingly accessible, yet families often lack an understanding of the implications of testing and diagnosis. Ideally the genetic counselor should be involved from the beginning of the diagnostic process, in order to provide ongoing support and education and to ensure informed consent.

At our institute, we have established a collaborative effort between the Division of Neurogenetics, the Phelps Center for Cerebral Palsy, and the Genetic Counseling Program to improve the diagnostic process of patients with motor impairment. This network of specialists has significantly enhanced evaluation and management, and demonstrated better outcomes for patients and their families.

Individually rare but collectively common, neurogenetic disorders often masquerade as CP. Identification of these disorders has become increasingly important when discussing treatment, prognosis, and family planning with patients and their families. In an era of dazzling neuroimaging modalities and molecular genetic tools, it is worth remembering that diagnosis begins with a comprehensive history and meticulous examination to initially channel the evaluation. In many situations a conventional brain MRI can further focus testing for specific disorders, which are often confirmed utilizing chromosomal microarray,

targeted gene sequencing, whole exome and/or whole genome sequencing. On the horizon are targeted signaling pathway treatments which show promise to improve outcome for individuals with neurogenetic masqueraders of CP.

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Fig. 1.
Diagnostic Evaluation of the Child with Cerebral Palsy.

Fig. 2.

Masqueraders of dyskinetic CP. a, Axial T2-weighted image of a 5-year-old child with panthothenate kinase associated neurodegeneration and severe, generalized dystonia shows a bilateral, symmetric hyperintense signal abnormalities within the globus pallidi surrounded by rings of low signal intensity; b, Midsagittal T1- and c, Coronal T2-weighted images of a 12-month-old infant with pontocerebellar hypoplasia type 2 due to *TSEN54* mutation, progressive microcephaly and dyskinetic movement disorders demonstrates a small cerebellum with enlarged intrafoliar spaces (the cerebellar hemispheres are more affected compared to the cerebellar vermis), a reduction in size of the pons, a delayed myelination and a cerebral atrophy; d, Axial T2-weighted image of a 10-years-old child with Wilson disease, severe dystonia and a bilateral Kayser-Fleischer ring reveals a bilateral, symmetric hyperintense signal within the putamina and caudate nuclei; e, Axial T2-weighted image of a 6-year-old boy with aromatic acid decarboxylase deficiency, dystonia, oculogyric crisis and global developmental delay shows a normal brain anatomy; f, Axial T2-weighted image of a 7-month-old girl with glutaric aciduria type 1, macrocephaly and severe dystonia demonstrates a bilateral, symmetric hyperintense signal in and atrophy of the putamina and caudate nuclei; g, Axial T2-weighted image of a 4-year-old girl with Segawa disease and progressive dystonia with diurnal fluctuations presents normal brain anatomy

Fig. 3.

Masqueraders of bilateral spastic CP. a, Axial T2-weighted image of a 1-day-old newborn with Miller-Dieker syndrome due to *LIS1* mutation shows a lissencephalic brain with a smooth and abnormally thick cerebral cortex; the child developed severe epileptic seizures, bilateral spasticity and microcephaly and did not achieve almost any developmental milestones; b, Axial T2-weighted image of a 12-month-old infant with Alexander disease, progressive macrocephaly, regression and bilateral spasticity reveals symmetrical hyperintense signal abnormalities in the bilateral frontal white matter and arcuate fibers, caudate nuclei and putamina; c, Axial T2-weighted image of a 3-year-old girl with a “double cortex”, severe epileptic seizures and mild, bilateral spasticity demonstrates bilateral, subcortical heterotopic bands and ventriculomegaly; d, Axial T2-weighted image of a 3-month-old male infant with Pelizaeus-Merzbacher disease, bilateral nystagmus and progressive, bilateral spasticity shows complete absence of myelinated white matter (all the white matter appears T2-hyperintense); e, Axial T2-weighted image of a 6-month-old infant with Krabbe disease, irritability, progressive bilateral spasticity and regression reveals hyperintense signal abnormalities within the lateral/dorsal extension of the middle cerebellar peduncles (white arrows), dentate nuclei (white arrow heads) and periventricular white matter with predominant involvement of the posterior regions (not shown); f, Axial T2-weighted image of a 4-year-old child with bilateral open-lip schizencephaly, seizures and bilateral spasticity demonstrates bilateral clefts communicating with the lateral ventricles and outlined by dysplastic gray matter

Fig. 4.

Masqueraders of unilateral spastic CP. a, Axial T2-weighted image of a 4-year-old child with isolated left hemimegalencephaly, seizures and right spastic hemiparesis shows enlargement of the left cerebral hemisphere with dilatation of the left lateral ventricle and hyperintense signal abnormality of the left periventricular white matter; b, Axial T2-weighted image of a 3-year-old child with right sided open-lip schizencephaly, focal epileptic seizures and left sided spastic hemiparesis reveals a cleft within the right parietal lobe communicating with the lateral ventricle and outlined by dysplastic gray matter

Fig. 5.

Masqueraders of ataxic CP. a, Midsagittal T1-weighted image of a 2-year-old child with Dandy-Walker malformation and cerebellar ataxia shows hypoplasia of the cerebellar vermis, which is elevated and upward rotated (white arrows), and cystic dilatation of the fourth ventricle; b, Axial and c, Coronal T2-weighted images of a 3 year-old-girl with 4H syndrome (Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism) and ataxia reveals only few areas of low signal in the white matter (posterior limb of the internal capsule and optic radiation) compatible with hypomyelination and cerebellar atrophy; d, Midsagittal T1- and e, Axial T2-weighted images of a 3-year-old child with Salla disease and ataxia demonstrates severe vermian atrophy, a thin corpus callosum and diffuse hyperintensity of the white matter as a sign of hypomyelination; f, Axial T2-weighted image at the level of the pontomesencephalic junction of a 2-year-old child with Joubert syndrome, ataxia, ocular motor apraxia and global developmental delay shows the pathognomonic 'molar tooth sign' characterized by a deepened interpeduncular fossa, elongated, thickened and horizontally orientated superior cerebellar peduncles (white arrows) and vermian hypodysplasia; g, Axial T2-weighted image of a 8-year-old child with rhombencephalosynapsis and ataxia reveals fused cerebellar hemispheres without intervening vermis, abnormal, transverse orientation of cerebellar folia and mild dilatation of the temporal horns of the lateral ventricles; h, Coronal and i, Axial T2-weighted images of a 3.5-year-old child with late-infantile neuronal ceroid lipofuscinoses, ataxia and myoclonic seizures demonstrates moderate global cerebellar atrophy, mild cerebral atrophy and symmetric hyperintensity of

the periventricular white matter (images d, e, h and i are reprinted with permission from Poretti A et al., Differential diagnosis of cerebellar atrophy in childhood, Eur J Paediatr Neurol, 2008)

Table 1

Clinical and Imaging Red Flags in Patients with Suspected Cerebral Palsy

1	Normal MRI findings
2	Imaging abnormalities isolated to the globus pallidus
3	Severe symptoms in the absence of a history of perinatal injury
4	A pattern of disease inheritance, or consanguinity
5	Neurodevelopmental regression, or progressively worsening symptomatology
6	Isolated muscular hypotonia
7	Rigidity (as opposed to spasticity) on physician examination
8	Paraplegia

Neurogenetic Disorders Masquerading as Dyskinetic Cerebral Palsy

Table 2

Dyskinetic Disorders	<i>a</i> Gene(s)	<i>b</i> Distinctive Characteristics	<i>c</i> Neuroimaging Findings	Diagnostic Tests	<i>d</i> Treatment
Aromatic Acid Decarboxylase Deficiency	DDC	Oculogyric crises, autonomic dysfunction, ptosis, athetosis	None	CSF study (Table 3), blood enzyme assay, genetic analysis	Pyridoxal phosphate, folinic acid, pramipexole
Dopa-Responsive Dystonia	GCH1	Progressive dystonia, low CSF bipterin and neopterin	None	CSF study, genetic analysis	Levodopa
Pantothenate Kinase-Associated Neurodegeneration	PKAN2	Progressive dystonia	Bilateral globus pallidus hyperintensity with hypointensity in the anterior/lateral region (eye of the tiger)	Neuroimaging, genetic analysis	None
Monocarboxylate Transporter 8 (MCT-8) Deficiency	MCT8	GDD/ID, hypotonia, dystonia, high T3, low T4, normal TSH	White matter hyperintensity	High T3, rT3 levels, genetic analysis	None
Glutaric Aciduria Type 1	GCDH	Macrocephaly, dystonia	Frontotemporal atrophy, caudate and putamen hyperintensity and atrophy, temporal cysts	Organic acid analysis, enzymatic analysis, genetic analysis	Carnitine and choline; lysine restriction
Succinic Semialdehyde Dehydrogenase Deficiency	ALDH5A1	Progressive dystonia, seizures, GDD/ID	Bilateral globus pallidus, dentate, subthalamic nuclei, and subcortical white matter hyperintensity	Organic acid analysis, enzymatic analysis, genetic analysis	None
Lesch-Nyhan Syndrome	HPRT1	Cognitive delay, self-mutilation, hyperuricemia, dystonia	None	Serum uric acid, enzymatic analysis, genetic analysis	None
Wilson's Disease	ATP7B	Hepatic disease, psychosis, Kayser-Fleischer rings, dystonia	Putamen, thalami, substantia nigra hyperintensity (panda sign), cerebellar atrophy	Low ceruloplasmin in serum, increased urinary excretion of copper, genetic analysis	Penicillamine, trientine hydrochloride
Glucose Transporter 1 Deficiency	SLC2A1	GDD/ID, seizures, ataxia, microcephaly, chorea, dystonia	None	Low CSF Glucose, genetic analysis	Ketogenic diet
Non-Ketotic Hyperglycinemia	GLDC	Developmental regression, seizures, apnea, lethargy	White matter hyperintensity, agenesis corpus callosum	High CSF Glycine, genetic analysis	None; consider ketamine
Propionic Acidemia	PCCA, PCCB	Encephalopathy, GDD/ID, hyperammonemia, seizures	Globus pallidus hyperintensity	Urine organic acid or acylcarnitines analysis, enzymatic analysis, genetic analysis	Caline, isoleucine, methionine, and threonine restriction
Leigh Syndrome	SURF1 and many more	Progressive dystonia, relapsing encephalopathy, vision and hearing loss, vomiting, seizures	Basal ganglia, cerebellum (dentate nuclei) and brainstem hyperintensity	Neuroimaging, genetic analysis	None
Pontocerebellar Hypoplasia Type 2	TSEN54	Chorea, dystonia, progressive microcephaly	Cerebellar atrophy (hemispheres>vermis), flat pons, thin corpus callosum, delayed myelination	Neuroimaging, genetic analysis	None
Maple Syrup Urine Disease	BCKDHA-B, DBT, DLD	Myelinated white matter, basal ganglia, and thalamic hyperintensity	GDD/ID, dystonia, hypotonia, sweet smelling urine	Plasma amino acids analysis, enzymatic analysis	Avoid branched chain amino acids

^aGene(s) most commonly associated with disease.

^bSalient disease characteristics. GDD/ID: Global developmental disability/Intellectual disability.

^c Magnetic resonance imaging findings that may assist in characterization of disease. Intensity is discussed with respect to T2-weighted image sequences.

^d Potentially disease modifying or curative treatment, not including supportive therapy.

Table 3

Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids

	Phe	BH ₄	BH ₂	Neop	Sep	Prim	HVA	5HIAA	3OMD
GTPCH (Recessive)	↑ ^p	↓ ^{u,c}	N	↓ ^{u,c}	N	N	↓ ^c	↓ ^c	N
GTPCH (Dominant)	N	↓ ^c	N	↓ ^c	N	N	↓ ^c	±↓ ^c	N
6TPS	↑ ^p	↓ ^{u,c}	N	↑ ^{u,c}	N	N	↓ ^c	↓ ^c	N
6TPS (Mild)	↑ ^p	↓ ^u	N	↑ ^u	N	N	N	N	N
SR	N	↓ ^c	↑ ^c	N	↑ ^c	N	↓ ^c	↓ ^c	N
PCD	↑ ^p	↓ ^u	N	N	N	↑ ^u	N	N	N
DHPR	↑ ^p	↓ ^{u,c}	↑ ^{u,c}	N	N	N	↓ ^c	↓ ^c	N
TH	N	N	N	N	N	N	↓ ^c	N	N
AADC	N	N	N	N	N	N	↓ ^c	↓ ^c	↑ ^{p,c,u}

GTPCH, GTP cyclohydrolase; 6TPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PCD, pterin α-carbinolamine dehydratase; DHPR, dihydropteridine reductase; TH, tyrosine hydroxylase; Phe, phenylalanine; BH₂, 7, 8-dihydrobiopterin; neop, neopterin; Sep, sepiapterin; Prim, primapterin; 3OMD, 3-O-methyldopa; N, normal; ↓, decreased; ↑, elevated; P, plasma; U, urine; C, CSF. Adapted for use with permission from Hyland K J. Nutr. 2007; 137:1568S-1572S.

Neurogenetic Disorders Masquerading as Spastic Cerebral Palsy

Table 4

Spastic Disorders	a Gene(s)	b Distinctive Characteristics	c Neuroimaging Findings	Diagnostic Tests	d Treatment
Holoprosencephaly	SHH, TGIF1, SIX3, ZIC2	Midline anomalies, GDD/ID, seizures, endocrine problems	Varied degrees of incomplete hemispheric separation	Neuroimaging, genetic analysis	None
Schizencephaly	COL4A1	GDD, seizures, hemi- or quadriparesis, microcephaly	Hemispheric cleft lined by heterotopic grey matter	Neuroimaging	None
Lissencephaly	LIS1	GDD/ID, seizures	Smooth gyral-sulcal pattern, 4 cortical layers instead of 6, cerebellar and pontine hypoplasia in some (TUBA1A, RELN)	Neuroimaging, genetic analysis	None
Hemimegalencephaly	PIK3CA, AKT3, MTOR	Macrocephaly, seizures, GDD/ID, hemiparesis	Unilateral enlarged cerebral hemisphere with ipsilateral cortical dysplasia, white matter signal abnormality, ventriculomegaly	Neuroimaging, genetic analysis	Hemispherectomy
Septo-optic Dysplasia Spectrum	HESX1	Vision, cognitive, and pituitary problems, seizures, nystagmus	Optic nerve hypoplasia, absent septum pellucidum	Neuroimaging	None
Polymicrogyria	WDR62	GDD/ID, seizures, hemi- or quadriparesis	Shallow sulci, thick cortex, many small cortical folds packed tightly together	Neuroimaging, genetic analysis	None
Alcardi Goutières Syndrome	TREX1, RNASEH2A-C, SAMHD1	Developmental regression, sterile pyrexia, chilblains, microcephaly, hepatomegaly	Basal ganglia and white matter calcification, periventricular white matter hyperintensity, cerebral atrophy	Neuroimaging, CSF interferon study, genetic analysis	None
X-linked Hydrocephalus with Aqueductal Stenosis	L1CAM	GDD/ID, upward gaze palsy, adducted thumbs, spastic paraparesis	Stenotic aqueduct of Sylvius, hydrocephalus, tectum dysplasia	Neuroimaging, genetic analysis	Endoscopic third ventriculostomy
Agenesis of the Corpus Callosum	None	GDD/ID, midline dysmorphology	Agenesis corpus callosum, lipoma and interhemispheric cysts occasionally	Neuroimaging	None
Pelizaeus-Merzbacher Disease (and PMD-Like Disease)	PLP1, GJA12	GDD/ID, dystonia, seizures, nystagmus, spasticity, stridor	Hypomyelination	Neuroimaging, genetic analysis	None
Krabbe Disease	GALC	Hypotonia, macrocephaly, developmental regression, progressive spasticity	Demyelination (posterior predominance and cerebellar white matter), thalamic hyperintensity	Enzymatic analysis, genetic analysis	None
Alexander Disease	GFAP	Developmental regression, seizures, spasticity, macrocephaly	Demyelination with frontal and brainstem predominance, thalamic and basal ganglia hyperintensity, rim of periventricular hypointensity	Neuroimaging, genetic analysis	None
Hereditary Spastic Paraplegias	SPG, L1CAM, ATL1	Progressive spastic paraplegia, GDD/ID, cataracts, ataxia	In some types thin corpus callosum (e.g. SPG11) or cerebellar atrophy (e.g. SPG7)	Genetic analysis	None
Arginase Deficiency	ARG1	Spastic diplegia, GDD/ID, hyperammonemia	None; occasional cerebral atrophy	Plasma arginine level, genetic analysis	None
RNASET2-Deficiency	RNASET2	Microcephaly, GDD/ID, seizures, hearing impairment	Multifocal cystic and calcified white matter lesions, temporal cysts	Genetic analysis	None
Mitochondrial DNA Depletion Syndrome	MT-TK2, POLG1	Seizures, hepatorenal failure	Basal ganglia, dentate hyperintensity, cerebellar atrophy	Genetic analysis	Folate
Hyperekplexia	GLRA1, SLC6A5	Exaggerated startle, truncal hypertonia	None	Clinical findings, genetic analysis	Clonazepam, Levetiracetam

Spastic Disorders	<i>a</i> Gene(s)	<i>b</i> Distinctive Characteristics	<i>c</i> Neuroimaging Findings	Diagnostic Tests	<i>d</i> Treatment
Purine Nucleoside Phosphorylase Deficiency	PNP	Immune deficiency, autoimmune disorders, GDD/ID	Multifocal leukoencephalopathy, stroke	Genetic analysis	Bone marrow transplant
Sjogren-Larsson Syndrome	ALDH3A2	Ichthyosis, spastic diplegia, GDD/ID, myopia	Non-progressive white matter T2 hyperintensity	Abnormal leukotriene metabolites in urine, genetic analysis	None
Homocystinuria	CBS, MTHFR	GDD/ID, tall stature, seizures, myopia, ectopia lentis	Stroke, basal ganglia and white matter hyperintensity	Plasma total homocysteine level, genetic analysis	Vitamin B6
Pseudo-TORCH Syndrome	None	Microcephaly, GDD/ID, seizures, spasticity	Periventricular calcifications, atrophy, polymicrogyria, simplified gyration	Neuroimaging	None
Sulfite Oxidase Deficiency/ Molybdenum Cofactor Deficiency	SUOX	GDD/ID, seizures, axial hypotonia with peripheral hypertonia	White matter and basal ganglia hyperintensity, cerebellar hypoplasia, cystic encephalomalacia	Urine sulfites, Plasma and urine amino acids and urine organic acids study, genetic analysis	None

^aGene(s) most commonly associated with disease.

^bSalient disease characteristics. GDD/ID: Global developmental disability/Intellectual disability.

^cMagnetic resonance imaging findings that may assist in characterization of disease. Intensity is discussed with respect to T2-weighted image sequences.

^dPotentially disease modifying or curative treatment, not including supportive therapy.

Table 5

Clinical and neuroimaging findings in hereditary spastic paraplegias (HSP) with pediatric onset^a

HSP form	HSP type	Inheritance	Gene	Childhood onset	Disease characteristics ^b	Neuroimaging findings (brain)
Pure	SPG3A	aut. dom	<i>ATL1</i>	+++	None	Normal
Pure	SPG4	aut. dom	<i>SPAST</i>	++	None	Leukoencephalopathy, thin corpus callosum
Pure	SPG6	aut. dom	<i>NIPA1</i>	+	None	Normal
Pure	SPG10	aut. dom	<i>KIF5A</i>	+++	Neuropathy	Normal
Pure	SPG12	aut. dom	<i>RTN2</i>	+++	None	Normal
Pure	SPG31	aut. dom	<i>REEP1</i>	++	None	Normal
Complicated	SPG1	X-linked	<i>L1CAM</i>	++	Intellectual disability, adducted thumb	Thin corpus callosum
Complicated	SPG2	X-linked	<i>PLP1</i>	+++	Intellectual disability, epilepsy	Normal
Complicated	SPG7	aut. rec.	<i>SPG7</i>	+	Optic atrophy, neuropathy, cerebellar ataxia	Cerebellar atrophy
Complicated	SPG11	aut. rec.	<i>KIAA1840</i>	+++	Intellectual disability, neuropathy	Leukoencephalopathy, thin corpus callosum
Complicated	SPG15	aut. rec.	<i>ZFYVE26</i>	+++	Intellectual disability, retinopathy, cerebellar ataxia	Leukoencephalopathy, thin corpus callosum
Complicated	SPG17	aut. rec.	<i>BSCL2</i>	+	Neuropathy	Normal

^a Onset before 18 years of age;

^b other than the classic HSP symptoms including spastic paraparesis, atrophy of the distal lower extremities and neurogenic bladder dysfunction; aut. dom., autosomal dominant; +, occasional; ++, common; +++, characteristic

Table 6

Neurogenetic Disorders Masquerading as Ataxic/Hypotonic Cerebral Palsy

Disorder	<i>a</i> Gene(s)	<i>b</i> Distinctive Characteristics	<i>c</i> Neuroimaging Findings	Diagnostic Tests	<i>d</i> Treatment
Ataxia-Telangiectasia	ATM	Immune deficiency, ocular motor apraxia, telangiectasia, ataxia	Pure cerebellar atrophy	Serum alpha-feto protein, intracellular ATM protein	None
Congenital Vitamin E Deficiency	TTPA	Ataxia, sensory neuropathy	None	Vitamin E level, genetic analysis	Vitamin E
Dandy-Walker Malformation	FOXC1, ZIC1, ZIC4, FGF17	Hydrocephalus, ataxia, GDD/ID	Cystic dilatation of the fourth ventricle, hypoplasia of the cerebellar vermis	Neuroimaging	Neurosurgical shunting
Joubert Syndrome	NPHP1, AHI1, CEP290	Ataxia, ocular motor apraxia, GDD/ID	Molar tooth sign, hypoplasia and dysplasia of the cerebellar vermis	Neuroimaging	None
Niemann Pick Disease Type C	NPC1, NPC2	Ataxia, vertical gaze palsy, regression, hepatosplenomegaly, psychiatric problems	Periventricular white matter hyperintensity, cerebral and cerebellar atrophy	Filipin test, genetic analysis	None
MELAS Syndrome	MT-TL1, MT-ND5, MT-TH	Seizures, ataxia, cognitive delay, lactic acidosis, strokes	Stroke (primarily occipital), cerebellar atrophy	Genetic analysis	None; consider CoQ10, riboflavin
Coenzyme Q10 Deficiency	ADCK3	Ataxia, encephalomyopathy, nephropathy	Cerebellar atrophy	CoQ10 level, genetic analysis	Coenzyme Q10
MECP2 Duplication Syndrome	MECP2	Ataxia, epilepsy, spasticity, intellectual disability, recurrent infections, hand wringing, breathing problems	Cerebellar hypoplasia, periventricular white matter hyperintensity	Genetic analysis	None
Infantile Neuroaxonal Dystrophy	PLA2G6	Developmental regression, hypotonia, nystagmus, neuropathy	Bilateral globus pallidus and dentate hypointensity, cerebellar atrophy, hyperintensity of cerebellar cortex	Genetic analysis	None
Thiamine Transporter Deficiency	SLC19A3	Ataxia, opthalmoplegia, nystagmus, seizures	Bilateral medial thalamus and periaqueductal hyperintensity, cortical-subcortical white matter lesions	Neuroimaging, genetic analysis	Thiamine
Biotinidase Deficiency	BTD	Alopecia, skin rash, seizures, hearing loss, optic atrophy, ataxia	Myelopathy, basal ganglia hyperintensity	Serum biotinidase activity	Biotin
Pyruvate Dehydrogenase Deficiency	PDHA1	Developmental regression, seizures, acidosis, ataxia, weakness	Cortical atrophy, agenesis corpus callosum, dilated ventricles, germinolytic cysts	Plasma and CSF lactate and pyruvate, genetic analysis	Ketogenic diet, citrate, dichloroacetate
Fumarase Deficiency	FH	GDD/ID, microcephaly, seizures, leucopenia, dysmorphic features, hypotonia	Cerebral atrophy, agenesis corpus callosum, polymicrogyria	Urine organic acid analysis, enzymatic analysis, genetic analysis	None
Galactosemia	GALT	Hepatomegaly, E.coli sepsis, cataracts, GDD/ID, hypotonia	White matter hyperintensity, cerebellar atrophy	Enzymatic analysis, genetic analysis	Eliminate lactose and galactose from diet
Creatine Metabolism Disorders	AGAT, GAMT	GDD/ID, seizures, hypotonia, behavioral changes	Globus pallidus hyperintensity, absent creatine peak on MRS	Neuroimaging, genetic analysis	Creatine, ornithine, restrict arginine
GM1 & GM2 Gangliosidoses	GLB1, GM2A	Hepatosplenomegaly, seizures, blindness, regression, hypotonia	Hypomyelination, basal ganglia hyperintensity	Enzymatic analysis, genetic analysis	None
Neuronal Ceroid Lipofuscinosis	PPT1, CLN1, CLN2, CLN3	Developmental regression, seizures, myoclonus, retinitis pigmentosa, ataxia	Periventricular white matter hyperintensity, cerebral and cerebellar atrophy, thalamic hypointensity	Genetic analysis	None
Late-onset GM2 Gangliosidosis	HEXA	Developmental regression, ataxia, seizures	Pure cerebellar atrophy	Enzymatic analysis, genetic analysis	None
Angelman Syndrome	UBE3A	GDD/ID, seizures, autism, absent speech, gait ataxia	White matter hyperintensity (periventricular, inconsistent)	Genetic analysis	None

Disorder	<i>a</i> Gene(s)	<i>b</i> Distinctive Characteristics	<i>c</i> Neuroimaging Findings	Diagnostic Tests	<i>d</i> Treatment
Vanishing white matter disease	EIF2B	Ataxia, spasticity, seizures, encephalopathic crises after head trauma/infections	White matter hyperintensity, cysts relatively sparing the temporal lobe and cerebellar white matter	Neuroimaging, genetic analysis	None
Hypomyelination with Congenital Cataract	FAM126A	Cataracts, GDD, spasticity, ataxia	Hypomyelination	Genetic analysis	None
L-2-Hydroxyglutaric Aciduria	L2HGDH	Ataxia, microcephaly, seizures, regression	Subcortical white matter hyperintensity sparing deep white matter, dentate nuclei hyperintensity	Urinary organic acids analysis, genetic analysis	None
Rhombencephalosynapsis	None	Ataxia, head nodding, often intellectual disability	Agensis cerebellar vermis, fused cerebellar hemispheres, hydrocephalus	Neuroimaging	
4H Syndrome	POLR3A	Ataxia, delayed dentition, growth failure	Hypomyelination, cerebellar atrophy	Genetic analysis	None
Infantile Sialic Acid Storage Disease (Salla disease)	SLC17A5	GDD/ID, seizures, cardiomegaly, hepatomegaly, ataxia, hypotonia, transient nystagmus	Hypomyelination, cerebellar atrophy	Urine sialic acid analysis, genetic analysis	None
Metachromatic Leukodystrophy	ARSA	Developmental regression, seizures, ataxia, neuropathy	Demyelination in supratentorial deep white matter with sparing of U-fibers, tigroid pattern	Enzymatic analysis, genetic analysis	None
Peroxisome Biogenesis Disorders	PEX	GDD/ID, distinct facial features, hepatic disease, hearing loss, seizures, hypotonia	White matter hyperintensity (supratentorial and cerebellar), polymicrogyria, germinolytic cysts	VLCFA analysis, genetic analysis	None
Canavan Disease	ASPA	Hypotonia, developmental regression, macrocephaly	Demyelination (subcortical earlier than deep white matter), thalamic hyperintensity, NAA peak on MRS	Urine NAA analysis, enzymatic analysis, genetic analysis	None
Merosin-deficient Muscular Dystrophy	LAMA2	Hypotonia, profound weakness, increased creatine kinase	Diffuse white matter hyperintensity	Muscle biopsy, genetic analysis	None
Abetalipoproteinemia	MTTP	Fat soluble vitamin deficiency, ataxia, sensory neuropathy, retinitis pigmentosa, steatorrhea	None	Serum cholesterol, genetic analysis	Vitamin E; triglyceride restriction
Phenylketonuria	PAH	GDD/ID, seizures, autism, hypotonia	Parieto-occipital white matter hyperintensity	Newborn screening, plasma phenylalanine level, genetic analysis	Low phenylalanine diet; BH ₄
Methylmalonic Acidemia	MMA	GDD/ID, hyperammonemia, seizures, hypotonia	Globus pallidus hyperintensity	Urinary organic acids or acylcarnitines analysis, enzymatic analysis, genetic analysis	Low protein diet; carnitine and cobalamin
Gaucher Disease, Type II and III	GBA	Hepatosplenomegaly, eye movement disorders, GDD/ID, myoclonic seizures, ataxia	None	Enzymatic analysis, genetic analysis	IV glucocerebrosidase enzyme replacement
Congenital Disorders of Glycosylation	PMM2	GDD/ID, multiorgan involvement, ataxia, hypotonia	Stroke, white matter cysts, cerebellar hypoplasia with superimposed atrophy, pontine hypoplasia	Transferrin isoform analysis, genetic analysis	None
Duchenne Muscular Dystrophy	DMD	Weakness, pseudohypertrophy, cognitive delay, cardiomyopathy	None	CK, Genetic analysis	None
Rett Syndrome	MECP2, CDKL5, FOXP1	Developmental regression, seizures, hand wringing, microcephaly, apnea, hyperpnea, gait dyspraxia	Cerebral atrophy with predominance in parietal grey matter	Genetic analysis	None

^aGene(s) most commonly associated with disease.

^bSalient disease characteristics. GDD/ID: Global developmental disability/Intellectual disability.

^cMagnetic resonance imaging findings that may assist in characterization of disease. Intensity is discussed with respect to T2-weighted image sequences.

^dPotentially disease modifying or curative treatment, not including supportive therapy.