

REVIEW ARTICLE**Differential diagnosis of Mendelian and mitochondrial disorders in patients with suspected multiple sclerosis****James D. Weisfeld-Adams,^{1,2,3} Ilana B. Katz Sand,⁴ Justin M. Honce⁵ and Fred D. Lublin⁴**

Several single gene disorders share clinical and radiologic characteristics with multiple sclerosis and have the potential to be overlooked in the differential diagnostic evaluation of both adult and paediatric patients with multiple sclerosis. This group includes lysosomal storage disorders, various mitochondrial diseases, other neurometabolic disorders, and several other miscellaneous disorders. Recognition of a single-gene disorder as causal for a patient's 'multiple sclerosis-like' phenotype is critically important for accurate direction of patient management, and evokes broader genetic counselling implications for affected families. Here we review single gene disorders that have the potential to mimic multiple sclerosis, provide an overview of clinical and investigational characteristics of each disorder, and present guidelines for when clinicians should suspect an underlying heritable disorder that requires diagnostic confirmation in a patient with a definite or probable diagnosis of multiple sclerosis.

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Keywords: multiple sclerosis; misdiagnosis; inherited disease; mitochondrial disease

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LHON = Leber's hereditary optic neuropathy; MELAS = myoclonic epilepsy with lactic acidosis

Introduction

Multiple sclerosis is a common, chronic demyelinating neurological disease primarily affecting young adults, with a prevalence of ~0.1% in the Caucasian population (Miller and Leary, 2007). Early, accurate diagnosis is critical to effective patient management and counselling, but assignment of an incorrect diagnosis of multiple sclerosis remains a frequent concern.

Patients with multiple sclerosis are classified according to their clinical phenotype, with ~85% following a relapsing-remitting course (relapsing-remitting multiple sclerosis) characterized by recurrent, acute neurological deficits punctuating periods of latency or remission (Lublin and Reingold, 1996). Typical symptoms of relapses may be referable to demyelinating pathology involving the optic nerves (e.g. optic neuritis), brainstem (e.g. internuclear ophthalmoplegia) or spinal cord (e.g. partial myelitis), although

non-specific symptoms referable to the cerebral hemispheres or other brain regions can also occur (Katz Sand and Lublin, 2013). Approximately 15% of patients follow a primary progressive or progressive relapsing course from disease onset, usually characterized by symptoms of progressive myelopathy (gait instability, spasticity, bladder symptoms) and cognitive impairment. Approximately half of relapsing-remitting patients develop a secondary progressive course within 20 years of disease onset (secondary progressive multiple sclerosis; Tremlett *et al.*, 2008).

McDonald Criteria (Polman *et al.*, 2011) for multiple sclerosis integrate data from neurological history, physical examination, and MRI appearances of the brain and cord. Diagnostic criteria and classification of multiple sclerosis subtypes have evolved in recent decades, and, although successive versions have differed in emphasis, all have required dissemination of disease in space (requiring involvement of multiple areas of the CNS) and in time (requiring ongoing disease activity over time). Unmatched oligoclonal bands are observed in the CSF of >80% of patients with multiple sclerosis and may be considered as supporting evidence, but are neither completely sensitive nor specific for multiple sclerosis. In the absence of pathognomonic clinical findings or a definitive laboratory test, the diagnosis of multiple sclerosis remains challenging in many patients, and diagnostic criteria emphasize the caveat of ‘no better explanation’ for a patient’s clinical presentation and MRI findings. If the presentation is atypical, alternative diagnoses should be explored and investigated, and patients subjected to a diligent search for clinical, imaging or laboratory ‘red flags’; in 2008, a scheme and ‘red flag’ scoring instrument was presented as a tool to be used in the differential diagnosis of multiple sclerosis (Miller *et al.*, 2008). Patients with adolescent or adult-onset inherited disorders, as well as those with non-multiple sclerosis idiopathic inflammatory demyelinating disease entities such as neuromyelitis optica and acute disseminated encephalomyelitis, or infectious, neoplastic, or vascular disorders, can all present similarly to multiple sclerosis, resulting in misdiagnoses (Miller *et al.*, 2008; Rudick and Miller, 2012).

The spectrum of disorders mistaken for multiple sclerosis have likely changed over time as a result of evolution of diagnostic criteria for multiple sclerosis (Solomon *et al.*, 2012). These disorders share characteristics with multiple sclerosis but have quite different clinical courses and prognostic implications. The incidence of multiple sclerosis misdiagnosis probably varies between individual clinicians and institutions, and depends upon efforts used to investigate for other disorders in patients with ‘multiple sclerosis-like’ presentations (Engell, 1988; Solomon and Weinschenker, 2013). In a recent editorial concerned with multiple sclerosis misdiagnosis, the authors suggested that multiple sclerosis diagnosis is based on symptoms, signs and MRI findings, clinical judgement, experience, and, crucially, the capacity needed to identify an alternative diagnosis (Rudick and Miller, 2012). They also discussed over-reliance on MRI appearances in multiple sclerosis diagnosis, as well

as the phenomenon of ‘cessation of critical thinking about alternative diagnoses once the multiple sclerosis diagnosis has been made’.

Multiple historical case reports describe clinical and diagnostic confusion between multiple sclerosis and various single gene disorders. Diagnosis of some of these rare disorders is likely to be subject to ascertainment bias, with classic presentations occurring during early childhood, and later-onset variants going unrecognized and conferring more subtle presentations. Several such disorders can present in adolescence or adulthood with progressive spastic paraparesis and accompanying white matter lesions on MRI, mimicking primary progressive multiple sclerosis. Less commonly patients with such disorders can display relapsing-remitting or insidiously progressive neurological symptoms. The overlap may at times result in misdiagnosis of multiple sclerosis, ultimately leading to inappropriate treatment with immunomodulatory therapies and, in certain disorders, a missed opportunity for other potentially helpful management interventions.

No comprehensive review of single-gene aetiologies of ‘multiple sclerosis-like’ presentations has been written since that by Natowicz and Bejjani (1994), 20 years ago. Since then, neuroimaging technologies have evolved unrecognizably, and have brought an abundance of knowledge regarding MRI characteristics in multiple sclerosis and other conditions. In the same period, the molecular genetic and/or biochemical basis of many ‘multiple sclerosis mimics’ has been elucidated, and much has been learned about the phenotypic spectrum of these disorders. Most inherited mimics of multiple sclerosis are now amenable to molecular genetic testing of specific genes, or interrogation of multiple genes using next-generation, whole exome, or whole genome sequencing. The current article, based on an extensive review of the literature of cases of Mendelian diseases misdiagnosed as multiple sclerosis, and the authors’ own clinical experiences, presents a scheme for neurologists and medical geneticists to follow for differential diagnosis of several single-gene disorders that may mimic multiple sclerosis and seem to meet McDonald criteria, and outlines strategies for evaluation of such patients.

Disorders of lysosomal storage and peroxisomal function

Lysosomal storage diseases are inherited metabolic disorders characterized by defective catabolism of complex molecules, including lipids, glycoproteins, and oligosaccharides, and by resultant toxic accumulation of cellular debris. Several lysosomal disorders have CNS white matter involvement in patterns that may overlap with those observed in multiple sclerosis, and attenuated forms of Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, Niemann-Pick disease type C (a disorder of cholesterol trafficking), Fabry disease, and variant forms

of X-linked adrenoleukodystrophy and adrenomyeloneuropathy, also have the potential to show clinical overlap with multiple sclerosis in adult patients, and are probably underdiagnosed. Several published single cases or case series in the literature report individuals with confirmed lysosomal storage disease or peroxisomal disease who were originally diagnosed with ‘suspected multiple sclerosis’ or clinically definite multiple sclerosis (Zwetsloot *et al.*, 1992; Stöckler *et al.*, 1993; Kazibutowska *et al.* 2002; Chebel *et al.*, 2009; Godeiro-Junior *et al.*, 2009; Carra-Dalliere *et al.*, 2013; Weisfeld-Adams *et al.*, 2013). The biochemical defects underlying specific lysosomal disorders and peroxisomal disorders that can potentially mimic multiple sclerosis, together with corresponding clinical and radiologic features and guidelines for diagnostic testing, are summarized in Table 1.

Various newborn screening initiatives for several lysosomal and peroxisomal disorders are now underway (Matern *et al.*, 2013) and may help answer several unsolved questions relating to their natural histories and phenotypic spectra. Over 7 years of experience with newborn screening for Krabbe disease in New York State suggests that late-onset Krabbe disease is significantly more common than previously recognized. This is indicated by large numbers of asymptomatic infants with low galactosylceramidase (GALC) activity and biallelic, pathogenic GALC mutations. Specific GALC missense alleles (p.G57S, p.W115R and p.G286D) are associated with late-onset Krabbe disease (Lissens *et al.*, 2007). Many infants with very low GALC activity on newborn screening have remained asymptomatic over several years (Wang *et al.*, 2011) and at what age, if ever, these individuals will develop symptomatic Krabbe disease is unclear. Late-onset Krabbe disease typically presents in adolescence or adulthood with insidiously progressive paraparesis and gait disturbance which can appear similar to progressive multiple sclerosis. MRI ‘red flags’ to suggest the diagnosis of Krabbe disease over multiple sclerosis include prominent involvement of the pyramidal tracts and/or symmetric or confluent involvement of the posterior white matter, splenium of the corpus callosum, and corticospinal tracts (Fig. 1A–C; Farina *et al.*, 2000; Sedel *et al.*, 2008).

Based on their extensive clinical overlap with each other and with acquired neurologic conditions, it is probably reasonable to extrapolate the under-ascertainment phenomenon suggested by early experiences with newborn screening for Krabbe and Fabry diseases to other disorders including metachromatic leukodystrophy and X-linked adrenoleukodystrophy/adrenomyeloneuropathy (X-ALD/AMN). Among European patients with adult-onset metachromatic leukodystrophy, the p.I179S allele (associated with a predominant psychiatric phenotype) and p.P426L, account for the majority of ARSA alleles (Ługowska *et al.*, 2005). Non-pathogenic pseudodeficiency alleles occur at relatively high frequencies in ARSA, and may complicate interpretation of ARSA enzymology for metachromatic leukodystrophy; the best overall initial screening test for

metachromatic leukodystrophy is therefore urinary sulphatides. A complex ARSA pseudodeficiency allele (c.[1049A>G; *96A>G]) has been recognized at higher frequency among patients with multiple sclerosis compared to matched controls (Kappler *et al.*, 1991; Baronica *et al.*, 2011). Genotype–phenotype correlations have also been observed in adult-onset forms of Chédiak-Higashi disease, a disorder of lysosomal trafficking with associated pigmentary abnormalities, progressive spastic paraplegia and progressive spinocerebellar degeneration and leukoencephalopathy on MRI, with most cases occurring in the setting of biallelic missense mutations or in-frame deletions in *LYST* (Karim *et al.*, 2002; Weisfeld-Adams *et al.*, 2013).

Patients with the adrenomyeloneuropathy phenotype of X-linked adrenoleukodystrophy can be confused with primary progressive multiple sclerosis, and classically present with progressive spastic paraparesis and bladder disturbance in early or middle adulthood. Families with *ABCD1* mutations exhibit extreme intra and interfamilial heterogeneity, and very long chain fatty acid profiles are poorly predictive of clinical phenotypes. More than 80% of female heterozygotes harbouring pathogenic mutations in *ABCD1* develop adult-onset spastic paraparesis, mild myeloneuropathy, and/or peripheral neuropathy usually after 40 years of age, and have a high incidence of bladder spasticity and faecal incontinence. Prevalence of symptoms in female heterozygotes seems to correlate strongly with advancing age (Engelen *et al.*, 2014). Cerebral disease is highly unusual in females. Most hemizygous males develop adult-onset adrenomyeloneuropathy (accounting for 40–45% of males) or childhood-onset cerebral adrenoleukodystrophy (30–35% of males), whereas a much smaller proportion of adult males develop clinical and radiological features of cerebral disease without preceding myeloneuropathy symptoms (Engelen *et al.*, 2012). Although the prevalence of cerebral disease in males with adrenomyeloneuropathy was previously estimated at 20% within 10 years of onset (van Geel *et al.*, 2001), a more recent Dutch study evaluating 27 males with adrenomyeloneuropathy with mean symptomatic onset at 35.3 years of age showed that >60% of patients developed evidence of cerebral demyelination a mean of 10.2 years after onset of adrenomyeloneuropathy (de Beer *et al.*, 2014). Furthermore, survival after onset of cerebral demyelinating symptoms in these patients was limited to a mean of 3.4 ± 2.9 years, suggesting that cerebral disease in adult males, once underway, may be as devastating and as rapidly progressive as is the case for childhood-onset cerebral X-linked adrenoleukodystrophy. Head trauma and stroke may precipitate the onset of cerebral disease (Raymond *et al.*, 2010). Several different MRI patterns have been described in adults and children; these patterns have utility in predicting clinical course and, together with extent of disease and age of onset, may be helpful in determining candidacy for haematopoietic stem cell transplantation. The classic pattern seen in childhood-onset cerebral X-linked adrenoleukodystrophy encompasses

Table 1 Lysosomal and peroxisomal disorders with potential to mimic multiple sclerosis

Disorder	Gene(s); biochemical defect	Inheritance mechanism	Neurologic presentations in adult-onset disease	'Typical' MRI appearances	Recommended diagnostic testing
Globoid cell leukodystrophy (Krabbe disease)	GALC Galactocerebrosidase (GALC) deficiency; lysosomal accumulation of incompletely metabolized galacto-cerebroside and galacto-sylsphingosine (psychosine)	AR	SP and gait dysfunction, cognitive deterioration, clumsiness; lower extremity paraesthesia and visual loss reported rarely	T ₂ /FLAIR hyperintensities involving CS or pyramidal tracts are characteristic. Symmetric periventricular, T ₂ /FLAIR WM hyperintensity, predominantly posterior (parieto-occipital) with common involvement of the splenium of the CC; U-fibres generally spared	GALC activity, lymphocytes (decreased) Molecular testing of GALC^a <i>Also consider:</i> Nerve conduction studies (demyelinating or axonal neuropathy with delayed NCV) Protein analysis, CSF (normal or increased) Sulfatide analysis, urine (increased sulfatides) ARSA activity, lymphocytes (decreased) ^b Molecular testing of ARSA <i>Also consider:</i> Nerve conduction studies (acute/subacute demyelinating polyneuropathy with delayed NCV) Sural nerve/brain biopsy (metachromatic deposits)
Metachromatic leukodystrophy	ARSA Arylsulphatase A (ARSA) deficiency; lysosomal accumulation of sulphatides	AR	Neuropsychiatric symptoms with cognitive deterioration progressing to dementia; spasticity and incoordination; visual failure; dystonia; peripheral neuropathy	Symmetrical 'sheet-like' areas of abnormal T ₂ /FLAIR WM periventricular hyperintensity, typically with frontal predominance, progressing to involve subcortical WM while sparing the U-fibres; variable involvement of cerebellar, thalamic or projection fibre WM in advanced disease; typically no enhancement	Fundal examination/retinal photography (perifoveal white patches) Protein analysis, CSF (increased) VLCFA analysis, plasma (increased C26 and C26:C22 ratio; normal phytanic/pristanic acid) ^b Molecular testing of ABCD1 Adrenocortical function^c <i>Also consider:</i> Nerve conduction studies (demyelinating or axonal polyneuropathy) Protein analysis, CSF (increased)
X-linked adrenoleukodystrophy/adrenomyeloneuropathy	ABCD1 Defect of peroxisomal β -oxidation of VLCFA	X-linked	<i>Male hemizygotes:</i> SP with progressive gait, spastic paraparesis and bladder dysfunction; erectile dysfunction; abnormalities of proprioception and vibration sense; headache, hemiparesis and ataxia also reported; primary adrenocortical insufficiency with/without neurologic symptoms; <i>Female heterozygotes:</i> 20–50% eventually develop SP or mild myelopathy, often after middle age; adrenocortical insufficiency rare	In AMN, primary involvement of frontopontine or corticospinal projection fibres; many AMN patients develop cerebral involvement limited to long tracts (posterior limbs internal capsules, brain stem) or with lobar involvement similar in appearance to childhood X-ALD (frontal or parieto-occipital); peripheral enhancement common	α-gal A activity, plasma and leucocytes (decreased) ^e Molecular testing of GLA <i>Also consider:</i> Slit lamp ophthalmologic exam (corneal haziness or opacity/whorled streaking; lenticular opacities in 30% of affected males) Skin exam (angiokeratoma) Urinalysis (proteinuria) Protein analysis, CSF (increased)
Fabry disease	GLA Deficiency of α -galactosidase A (α -gal A); accumulation of globotriaosylceramide (gb3) in vascular endothelial cells, cardiomyocytes, and renal podocytes	X-linked	Temperature-sensitive acroparesthesias usually signal clinical onset of disease; anhidrosis; recurrent/chronic abdominal pain; transient TIA/stroke episodes include hemiparesis or vertigo; chronic fatigue, anxiety and depression common ^d	Non-specific, multifocal, asymmetric T ₂ /FLAIR hyperintense lesions in deep and subcortical WM; progressive WM lesion load over time due to cerebral vasculopathy; T ₁ hyperintensities of thalamic pulvinar are characteristic but only present in 25% of patients	

(continued)

Table 1 Continued

Disorder	Gene(s); biochemical defect	Inheritance mechanism	Neurologic presentations in adult-onset disease	'Typical' MRI appearances	Recommended diagnostic testing
Niemann-Pick disease, type C	NPC1, NPC2 Excessive LDL uptake with deficient dysregulated cholesterol biosynthesis/ esterification and trafficking; endosomal accumulation of cholesterol	AR	Partial/generalized seizure disorder with gelastic cataplexy and vertical supranuclear gaze palsy are characteristic; also neuropsychiatric symptoms with cognitive deterioration and dementia; dystonia, dysarthria; peripheral neuropathy reported rarely	Thinning of CC with increased signal in peritriaxial WM; widespread GM/WM abnormalities; reduced pons:midbrain ratio; cerebellar vermian atrophy (late)	Cholesterol esterification studies/filipin staining, fibroblasts (abnormal intracellular cholesterol esterification and homeostasis) Molecular testing of NPC1 ± NPC2 <i>Also consider:</i> Oxysterol quantification, plasma Abdominal ultrasound study Peripheral blood smear (abnormal PMNs with enlarged granules) Natural killer cell function (decreased/absent) Molecular testing of LYST <i>Also consider:</i> Skin biopsy (cutaneous amyloid deposition; abnormal pigmentation) Light microscopy of hair shaft (abnormal pigmentary clumping) Nerve conduction studies
Chédiak-Higashi disease	LYST Regulatory defect of lysosomal trafficking; defective membrane targeting of secretory lysosomes	AR	Late-onset disease characterized by SP, spinocerebellar degeneration, parkinsonism, dystonia, cognitive deterioration ^g	T ₂ -FLAIR hyperintensity in periventricular WM becoming more prominent with time; global atrophy, especially spinocerebellar atrophy	

AMN = adrenomyeloneuropathy; AR = autosomal recessive; CC = corpus callosum; CS = corticospinal; GM = grey matter; LDL = low-density lipoprotein; NCV = nerve conduction velocities; SP = spastic paraparesis; TIA = transient ischaemic attack; VLCFA = very long chain fatty acids; WM = white matter; X-ALD = X-linked adrenoleukodystrophy.

^a High prevalence of 30 kb deletion allele in Caucasian population.

^b VLCFA analysis normal in 10–20% of female heterozygotes (Moser *et al.*, 1999); VLCFA abnormalities generally correlate poorly with clinical phenotypes.

^c Males only; 70% of adult males with adrenomyeloneuropathy phenotype have adrenal insufficiency.

^d Concurrent evidence of cardiovascular, cerebrovascular, or renal disease common; female heterozygotes can be asymptomatic with normal life expectancy or present similarly to hemizygous males with classic disease, depending on pattern of X-inactivation.

^e Full diagnostic algorithm provided in Gal *et al.* (2011); both plasma and leucocytes should be assayed as some mutations specifically affect trafficking of enzyme; measure of α -gal A is insufficient for detection of carrier status in females.

^f Limited availability outside of research laboratories at time of submission.

^g Adult-onset patients with mild or subclinical immunodeficiency, pigmentary abnormalities of skin, hair and retina common but less apparent than in infantile onset disease.

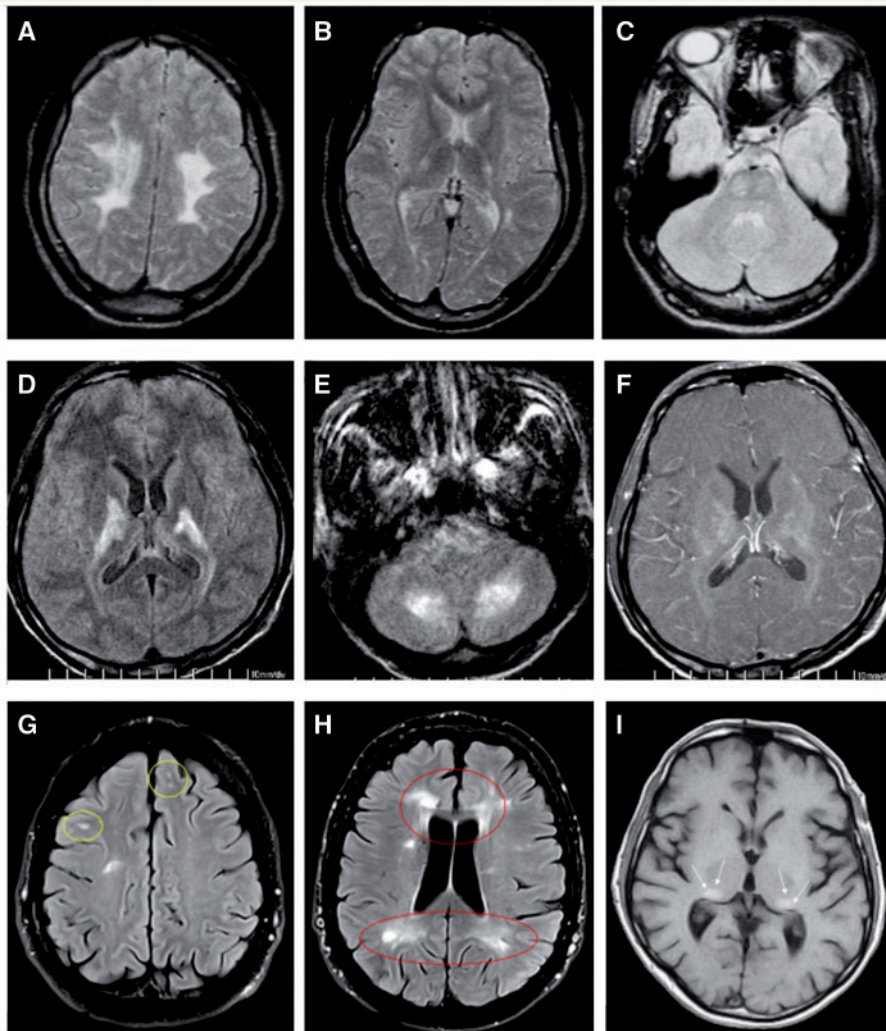


Figure 1 Selected magnetic resonance images from patients with adult-onset lysosomal and peroxisomal disorders. (A) Axial T₂-weighted image of a 24-year-old female with Krabbe disease (globoid cell leukodystrophy) demonstrating confluent T₂ hyperintensity in the bilateral centrum semiovale, centred in the fronto-parietal lobes and involving the corticospinal tracts. The patient presented with a 2-year history of worsening spastic paraparesis and symmetrical lower extremity sensory disturbance. (B and C) Axial T₂ and proton-density weighted images of the same patient showing symmetric hyperintensity in the posterior limbs of the internal capsule and pons, corresponding to the corticospinal tracts. (D and E) Axial FLAIR images from a 35-year-old Taiwanese male with an 18-year history of progressive spastic paraplegia, diagnosed with adrenomyeloneuropathy. Images demonstrate asymmetric T₂ hyperintensity within the internal capsules with corticospinal tract involvement, and asymmetric T₂ hyperintensity in cerebellar white matter and dentate nuclei. (F) Post-contrast T₁-weighted image of the same patient demonstrating patchy contrast enhancement in and around corresponding regions of signal hyperintensity (reproduced with permission, Mo *et al.*, 2004). (G and H) Axial FLAIR images of a 64-year-old female with a confirmed diagnosis of Fabry disease and with a 40-year history of ataxia and intermittent right-sided hemiparesis and hemisensory disturbance. There is focal and confluent T₂ hyperintensity in the periventricular, subcortical and deep white matter, in a pattern mimicking multiple sclerosis (reproduced with permission, Böttcher *et al.* 2013). Although the patient met McDonald criteria for multiple sclerosis, oligoclonal bands were absent from CSF. (I) Axial T₁-weighted image of a 46-year-old male with Fabry disease demonstrating classic, intrinsic T₁ hyperintensities in the pulvinar nuclei bilaterally, a classic imaging feature of Fabry disease (reproduced with permission, Burlina *et al.*, 2008).

symmetric T₂ hyperintensity of parieto-occipital white matter, classically periaxially (so-called ‘Pattern 1’ disease); most cases are of early-onset and are characterized by rapid progression (Loes *et al.*, 2003). Males with the adrenomyeloneuropathy phenotype can have normal brain MRI, changes that appear in advance of clinical disease, or changes that appear several years or decades later (Loes

et al., 2003; de Beer *et al.*, 2014). Abnormalities restricted to the pyramidal tracts, or diffuse MRI abnormalities involving the cerebral hemispheres, posterior limbs of the internal capsules, brainstem and cerebellum can also occur (Fig. 1D–F; Kumar *et al.*, 1995).

Pilot newborn screening studies for Fabry disease, which frequently presents with intermittent acroparaesthesias and

abnormal white matter appearances on MRI, have also revealed an unexpectedly high incidence among male newborns (Spada *et al.*, 2006; Inoue *et al.*, 2013). Relapsing-remitting symptoms sharing characteristics with relapsing-remitting multiple sclerosis have been observed in Fabry disease. In a retrospective study of 187 confirmed patients with Fabry disease, 11 patients had concomitant diagnoses of clinically definite multiple sclerosis or possible multiple sclerosis; Fabry disease was diagnosed a mean of 8.2 years after the multiple sclerosis diagnosis was assigned (Böttcher *et al.*, 2013) and some patients with ‘true’ Fabry disease had unmatched oligoclonal bands in CSF. ‘Red flag’ characteristics suggesting an alternative diagnosis of Fabry disease were suggested and included patients with asymmetric, confluent white matter T₂ hyperintensity on MRI (Fig. 1G and H), normal spinal MRI, ectatic vertebrobasilar arteries, proteinuria and absence of unmatched CSF oligoclonal bands (Böttcher *et al.*, 2013). Additionally, T₁ hyperintensity in the pulvinar nuclei of the thalami, seen in 25% of patients with Fabry disease, are a specific feature of the condition (Fig. 1I; Moore *et al.*, 2003; Burlina *et al.*, 2008).

Further complicating the differentiation of these disorders from multiple sclerosis, unmatched oligoclonal bands have been reported in confirmed cases of Fabry disease, X-linked adrenoleukodystrophy and adrenomyeloneuropathy, metachromatic leukodystrophy, and Niemann-Pick disease type C (Böttcher *et al.*, 2013). Clinical clues to lysosomal or peroxisomal disease in patients with ‘multiple sclerosis-like’ presentations include peripheral neuropathy (frequently observed in Krabbe disease, metachromatic leukodystrophy, and X-linked adrenoleukodystrophy spectrum disorders), extra-neurological manifestations, such as cardiac, renal and dermatological manifestations of Fabry disease, splenomegaly in Niemann-Pick disease type C and more rarely in Fabry disease, and immunodeficiency and pigmentary abnormalities in Chédiak-Higashi disease. Phenotypic heterogeneity is a well-known feature of Niemann-Pick disease type C, and data from an international patient registry demonstrated that 27% of participants experienced symptomatic onset in late adolescence or adulthood, and that a majority presented with ataxia, dysarthria, and cognitive impairment, features often seen in progressive multiple sclerosis. Many patients also had clinical features more specific to Niemann-Pick disease type C and less typical of multiple sclerosis, such as vertical supranuclear gaze palsy and gelastic cataplexy (Patterson *et al.*, 2013).

Of all the groups of heritable disorders that have the potential to mimic multiple sclerosis, lysosomal storage disorders are likely to be among the most amenable to pharmacotherapeutic interventions that can effectively modify disease outcomes, illustrating the importance of accurate and timely diagnosis of these conditions. Available treatments for Krabbe disease, metachromatic leukodystrophy, and childhood cerebral X-linked adrenoleukodystrophy are currently limited to haematopoietic stem cell transplantation, and are generally reserved for pre- or early

symptomatic disease, and outcomes have only been reported in any detail in paediatric patients (Escobar *et al.*, 2005; Biffi *et al.*, 2013). There are currently limited data to support the efficacy of haematopoietic stem cell transplantation in adults with cerebral X-linked adrenoleukodystrophy (Engelen *et al.*, 2012) and other adult-onset leukodystrophies. Trials of gene therapies, stem cell therapies, or intrathecal enzyme replacement therapy are underway or in development for Krabbe disease, metachromatic leukodystrophy, and X-linked adrenoleukodystrophy, and are showing promise in animal subjects as well as in small-scale human studies (Cartier *et al.*, 2009; Stroobants *et al.*, 2011; Rafi *et al.*, 2012; Patil *et al.*, 2013).

The efficacy of systemic enzyme replacement therapy is well established for individuals with Fabry disease and significantly improves survival and quality of life (Pisani *et al.*, 2012), reasserting the need for accurate and expedient diagnosis. In a randomized clinical trial of Niemann-Pick type C patients treated with oral miglustat, a reversible inhibitor of glycosphingolipid synthesis, miglustat successfully stabilized key neurological manifestations of the disease in paediatric and adult patients (Patterson *et al.*, 2007). Other chemical chaperone approaches, substrate reduction therapies, and stop-codon read-through strategies have been used in several other lysosomal storage diseases or are in development (Boustany, 2013), and are beyond the scope of this review.

Mitochondrial disorders

Dysfunctional mitochondria play a central role in the pathogenesis of various neurological disorders including multiple sclerosis, Alzheimer’s disease, Parkinson’s disease and stroke. Mitochondrial dysfunction increases production of reactive oxygen species which may contribute to oxidative stress, potentially leading to neuronal injury, neurodegeneration and, ultimately, clinical disability (Witte *et al.*, 2010; Friese *et al.*, 2014). Biochemical defects in respiratory chain complex I activity have been proposed as contributory to the pathogenesis of multiple sclerosis, and the lack of complex IV activity in demyelinated axons supports axonal dysfunction as a contributor to disease progression in multiple sclerosis (Mahad *et al.*, 2009). The capacity for remyelination and axonal repair, critical factors in delaying or preventing progressive disease, also seem to be dependent on healthy mitochondria.

Given these indicators that mitochondrial dysfunction is integral to multiple sclerosis pathology, it is not surprising that several mitochondrial respiratory chain defects, caused by defined mutations in nuclear or mitochondrial DNA (mtDNA) may present with neurologic syndromes sharing characteristics with multiple sclerosis (Iñiguez *et al.*, 1998). Clinical features, MRI appearances and diagnostic testing strategies for these disorders are outlined in Table 2. Prominent myopathy, cardiomyopathy or cardiac conduction abnormalities, external ophthalmoplegia, early severe optic neuropathy that does not recover, seizures,

Table 2 Mitochondrial disorders with potential to mimic multiple sclerosis

Disorder	Gene(s); molecular genetic pathogenesis	Inheritance mechanism	Clinical presentation in adult-onset disease	'Typical' MRI appearances	Recommended diagnostic testing
Leber hereditary optic neuropathy (LHON)	mtDNA: MT-ND4, MT-ND6, MT-ND1; other mtDNA genes ^a mtDNA mediated degeneration of retinal ganglion cell layer; variable, gender-specific penetrance; effect of environmental modifiers	mitochondrial	Bilateral, painless, subacute visual failure with central field loss in young adult life, typically with more complete penitance in males; tremor, peripheral neuropathy, myopathy, and movement disorders more common in individuals with LHON than in controls ('LHON-plus'); females with LHON may develop MS-like illness ('Harding disease')	Often normal in patients with 'pure' LHON; multifocal WM disease mimicking demyelinating lesions of MS seen in LHON patients with apparently pure optic neuropathy as well as in 'LHON-plus' and Harding disease phenotypes	mtDNA sequencing (leucocytes, muscle or cultured fibroblasts) Fundal examination/retinal photography (oedema of peripapillary nerve fiber layer, retinal telangiectasia, increased vascular tortuosity) Visual evoked potentials (absent or delayed) <i>Also consider:</i> Muscle biopsy with respiratory chain activity (partial defects of complex I in some cases)
MELAS/MERRF	mtDNA: typically MT-TL1 and MT-ND2 in MELAS; MT-TK in MERRF; other mtDNA genes ^b Decreased activity of respiratory chain complexes or constituent subunits	mitochondrial	Seizures (prominent myoclonus in MERRF), gait instability/ataxia (often initial manifestation in MERRF), myopathy, stroke-like episodes, sensorineural deafness, dementia, PEO, hemianopsia, pigmentary retinopathy, peripheral neuropathy; growth delay, cardiomyopathy, dysrhythmia	MELAS: acute and chronic stroke-like episodes with GM/WM T ₂ /FLAIR hyperintensity, typically involving the posterior cerebrum, thalamus, and not conforming to major vascular territories; in acute phase lesions typically do not restrict diffusion as is seen in ischaemic stroke; elevated lactate on MR spectroscopy; MERRF: multicystic or cavitating leukoencephalopathy, cerebral, cerebellar or brain stem atrophy; basal ganglia calcification/necrosis	Optical coherence tomography (temporal thickening of RNFL) Electroretinography (exclude retinal dysfunction as cause of visual loss) Lactate/pyruvate, plasma/CSF (often increased) mtDNA sequencing (muscle or cultured fibroblasts) ^{b,c} Muscle biopsy with respiratory chain activity (RRF in MELAS and MERRF; CCO-positive staining in MELAS; partial defects of complexes I and/or IV seen in MELAS; defects of all mtDNA-dependent complexes may be seen in MERRF) Amino acids, plasma (increased alanine) Organic acids, urine (increased lactate metabolites) Lactate/pyruvate, plasma/CSF (increased)
Leigh disease	SURF1 and other nuclear genes; MT-ATP6 and other mtDNA genes^d Most mtDNA or nuclear mutations cause decreased activity of respiratory chain complexes or constituent subunits; some mutations disrupt tRNAs	AR/X-linked; mitochondrial	Spasticity, dystonia, weakness, hypo- or hyperreflexia, seizures (myoclonic or generalized tonic-clonic; infantile spasms), cerebellar ataxia, peripheral neuropathy; dysphagia, persistent vomiting, thermoregulatory dysfunction; optic atrophy, retinitis pigmentosa; liver and renal disease; cardiomyopathy	Bilateral, symmetrical T ₂ /FLAIR hyperintense lesions in brain stem and/or basal ganglia (especially putamina) are characteristic; lesions affecting the mammillothalamic tracts, substantia nigra, medial lemniscus, medial longitudinal fasciculus, spinothalamic tracts, and cerebellum	mtDNA (muscle or cultured fibroblasts ^c) or nuclear gene sequencing Amino acids, plasma (increased alanine) ^e <i>Also consider:</i> Muscle biopsy and respiratory chain activity (may see intracytoplasmic neutral lipid droplets, RRF rare; CCO-negative fibers seen in individuals with Leigh-related mtDNA mutations; normal respiratory chain activity of isolated defects in complexes I or IV)

(continued)

cerebrovascular disease, peripheral neuropathy, pigmentary retinopathy, and diabetes mellitus may all serve as clinical clues differentiating this group of disorders from multiple sclerosis. Myoclonic epilepsy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibres (MERRF), and Leber's hereditary optic neuropathy (LHON) are caused by specific mutations or structural rearrangements in mtDNA, and can present with spasticity, ataxia and optic neuropathy. Leigh disease encompasses a heterogeneous group of conditions, some of which are caused by autosomal recessively-inherited mutations in nuclear genes that are disruptive to mitochondrial function or maintenance, and some by mutations in mtDNA itself. Non-Mendelian/maternal transmission, if observed, is strong evidence for a mitochondrially-inherited condition; however, given the epidemiology of multiple sclerosis (females affected more frequently than males; increased risk of multiple sclerosis in first-degree relatives) it is not unusual to see multiple sclerosis in a patient with a similarly affected mother. Further, the absence of family history does not exclude the diagnosis of a mtDNA-encoded disorder, owing to the phenomena of incomplete penetrance and heteroplasmy in mtDNA disorders. *POLG* is a nuclear gene encoding polymerase gamma, a DNA polymerase in humans that effects mtDNA replication and repair.

LHON, caused by specific point mutations in mtDNA (typically at positions 3460, 11778, or 14484) encoding complex I of the respiratory chain, merits special consideration because of its particularly strong associations with multiple sclerosis, occurring with ~50 times higher frequency in patients with multiple sclerosis than would be expected by chance (Palace, 2009), an association referred to as 'LHON-plus' or 'Harding disease'. Subpopulations of multiple sclerosis patients (those with early/severe optic neuritis) appear to harbour characteristic LHON mutations at high frequencies (Leuzzi *et al.*, 1997). Curiously, although LHON is of lower penetrance among females harbouring mtDNA mutations, the coexistence of the disorder with multiple sclerosis-like illness occurs with a similar female preponderance as is observed in isolated multiple sclerosis. Harding reported three females with LHON harbouring m.11778G>A mutations who did not have extraocular symptoms but had white matter lesions on MRI mimicking multiple sclerosis (Harding *et al.*, 1992), and MRI appearances in LHON commonly closely mimic those observed in multiple sclerosis (Inglese *et al.*, 2001; Lerman-Sagie *et al.*, 2005; Küker *et al.*, 2007; Fig. 2A–C). Unmatched oligoclonal bands have been detected in multiple patients (Palace, 2009). Some authors have proposed that specific mtDNA mutations traditionally associated with LHON are associated with and predispose to multiple sclerosis; an inflammatory process and clinical course similar to that observed in 'LHON-plus' has also been described in patients with MELAS (Maruyama *et al.*, 1998), although MELAS is predominantly a grey matter disorder.

Late-onset autosomal recessive Leigh disease is clinically and genetically heterogeneous and has been associated with missense mutations in *SURF1* as well as several other nuclear genes and mtDNA mutations, and is characterized by motor regression, dementia and dystonia. Although Leigh disease, like MELAS, is primarily a disorder of grey matter, its clinical course may be acute, gradually progressive, or relapsing, and there are historical reports of misdiagnosis with multiple sclerosis (Malojčić *et al.*, 2004). Clues to Leigh disease or other mitochondrial disorders on MRI in suspected multiple sclerosis include symmetric bilateral T₂ hyperintense lesions in the basal ganglia, or multifocal grey matter involvement. Common variants in two prominent mitochondrial Leigh disease genes, *MT-ATP6* and *MT-ND2*, have been associated with multiple sclerosis (Vyshkina *et al.*, 2008).

Mutations in *POLG* have also been associated with multiple sclerosis-like presentations in several patients. The clinical spectrum of *POLG*-related disorders comprise a continuum of overlapping phenotypes including a subset of ataxia-neuropathy disorders, which overlap with MELAS/MERRF phenotypes and presenting with optic neuritis, white matter hyperintensities, unmatched oligoclonal bands in CSF, and variable axonal polyneuropathy (Degos *et al.*, 2014). Other *POLG* mutations result in infantile-onset hepatocerebral disease (Alpers-Huttenlocher syndrome) with no clinical resemblance to multiple sclerosis. Although heterozygous *POLG* mutations can cause ophthalmoplegia phenotypes, most other *POLG*-related phenotypes, including ataxia-neuropathy, are recessively inherited. Heterozygous mutations in *OPA1*, another nuclear gene, also cause dysfunction and misdirection of mitochondria in neural tissue; the most common phenotype is insidiously progressive childhood-onset optic nerve atrophy, although a proportion of patients have extraocular neurologic involvement including ataxia and/or spastic paraplegia. Some patients have diffuse white matter hyperintensities on MRI with prominent involvement of periventricular white matter (Yu-Wai-Man *et al.* 2010; Pretegianni *et al.*, 2011). Several patients with pyruvate dehydrogenase complex deficiency, classically described as a severe infantile-onset disease, have been described with later-onset presentations including recurrent, episodic ataxia. These patients are usually males with specific missense mutations of *PHDA1*, a nuclear gene, and may have Leigh-like grey matter appearances and other basal ganglia changes on MRI (Barnerias *et al.*, 2010) that are unlikely to mimic 'typical' MRI findings observed in multiple sclerosis.

Other metabolic leukodystrophies, leukoencephalopathies and myelopathies

'Leukodystrophy' refers to a group genetic disorders primarily involving myelin pathology and with prominent white matter involvement, while 'leukoencephalopathy' is a

generic, largely radiological term encompassing many genetic (and acquired) disorders with diffuse white matter abnormalities on MRI and including some disorders where neuropathology is primarily axonal. Although many lysosomal disorders (discussed above) are classifiable as leukodystrophies, several other leukodystrophies and leukoencephalopathies potentially presenting in adulthood are not classifiable as disorders of lysosomal or peroxisomal function, or as mitochondrial disorders. Several of these disorders can present with spastic paraparesis, or with other neurological features that can mimic multiple sclerosis (Table 3). Other neurometabolic disorders that mimic multiple sclerosis and that are treatable or potentially treatable with pharmacotherapy include urea cycle disorders, acute intermittent porphyria, biotinidase deficiency, cerebrotendinous xanthomatosis, and some disorders of vitamin B₁₂ or folate metabolism. Some patients with urea cycle disorders, acute intermittent porphyria, and some methylmalonic acidemias may be candidates for liver transplantation.

Two primary urea cycle disorders (arginase deficiency and the hyperornithinaemia-hyperammonaemia-homocitrullinaemia syndrome) are known to onset with spasticity and diplegia of late-onset in rare patients. Both disorders can present with liver disease and life-threatening hyperammonaemia and are managed with dietary protein restriction and pharmacologic ammonia scavengers, and patients with diplegia may improve clinically with treatment (Prasad *et al.*, 1997). Several historical reports attest to the potential of adult polyglucosan body disease, caused by defective glycogen branching and allelic to glycogen storage disease type IV, to be confused with multiple sclerosis. Although adult polyglucosan body disease is recessively inherited, progressive gait disturbance and cognitive decline have also been reported in heterozygotes (Paradas *et al.*, 2014). Management for adult polyglucosan body disease is currently supportive only.

Neurologic phenotypes common to nutritional or autoimmune B₁₂ deficiency and inherited disorders of B₁₂ metabolism include paraesthesias, ataxia, impaired proprioception, and spasticity. Many patients also have megaloblastic anaemia. Several late-onset forms of many inherited disorders of B₁₂ metabolism have been described, including methylmalonic acidemia (MMA), mutase type, and some cobalamin defects, and may share characteristics with nutritional/autoimmune B₁₂ deficiency and with multiple sclerosis. The cobalamin C defect has been reported in association with adult-onset myelopathy, neuropsychiatric disturbance and patchy white matter T₂ hyperintensities on MRI, which may involve the cord (Thauvin-Robinet *et al.*, 2008; Huemer *et al.*, 2014). Optic atrophy presenting with acute visual loss has been reported in mutase deficiency methylmalonic acidemia (Pinar-Sueiro *et al.*, 2010). MTHFR deficiency, most often characterized by early-childhood clinical onset, also has late-onset forms with white matter disease on MRI and progressive myelopathic gait disturbance. Reported patients lacked a history of relapses and were negative for unmatched CSF oligoclonal

bands (Haworth *et al.*, 1993). Screening plasma B₁₂ levels, as well as quantification of methylmalonic acid (MMA) in plasma and/or urine, are already recommended for all individuals for whom the diagnosis of progressive multiple sclerosis is considered; we also recommend additional screening of plasma homocysteine if there is any reasonable suspicion for these disorders, since B₁₂ and methylmalonic acid will be normal in patients with MTHFR deficiency or cobalamin E or G defects.

Adolescents and adults with partial biotinidase deficiency with diffuse white matter disease and spastic paraparesis have also been described; this condition is subject to newborn screening in many countries, can be diagnosed with straightforward biochemical testing, and is treatable with oral biotin (vitamin B₇) supplementation.

Cerebrotendinous xanthomatosis is an autosomal recessive lipid storage disease that is also classified as a leukodystrophy, and characterized by infantile-onset diarrhoea, cataracts, and adolescent or adult-onset tendon xanthomas and progressive neurological disease causing cerebellar signs, spasticity, dystonia, parkinsonism, and peripheral neuropathy. MRI may show diffuse cerebral and cerebellar atrophy with variable T₂ abnormalities involving deep and subcortical white matter which may overlap with abnormalities seen in multiple sclerosis. When present, characteristic symmetric T₂ hyperintensity in the dentate nuclei is suggestive of this disorder (De Stefano *et al.*, 2001). Cerebrotendinous xanthomatosis is a potentially treatable condition with clinical symptoms stabilizing with administration of chenodeoxycholic acid (Yahalom *et al.*, 2013).

Many patients with acute intermittent porphyria, an autosomal dominant defect of haem metabolism with limited penetrance, experience recurrent attacks of poorly localized abdominal pain; some patients experience acute neurologic deficits or psychiatric symptoms for which pathomechanisms are poorly characterized. Such patients may have evidence of both peripheral nerve and CNS disease. Many patients harbouring pathogenic *HMBS* mutations (and who have symptomatic family members) have 'latent' porphyria and remain asymptomatic throughout their lives. A proportion of patients have hyperintense white matter lesions on MRI that can occur in a multiple sclerosis-like distribution (Bylesjö *et al.*, 2004). In relation to haem and iron metabolism, iron is known to accumulate in the CNS in multiple sclerosis, although the pathomechanisms for this phenomenon and its contribution to multiple sclerosis pathogenesis are incompletely understood. Iron may modify disease activity in multiple sclerosis by promoting production of pro-inflammatory mediators, mitochondrial dysfunction, and reactive oxygen species production (Williams *et al.*, 2012). In one large multiple sclerosis cohort, there was no enrichment for mutations in *HFE*, the gene for haemochromatosis (Ramagopalan *et al.*, 2008). Although other inherited disorders of metabolism of iron and other metals [including neurodegeneration with brain iron accumulation (NBIA), and Wilson disease] may rarely involve white matter, they do not

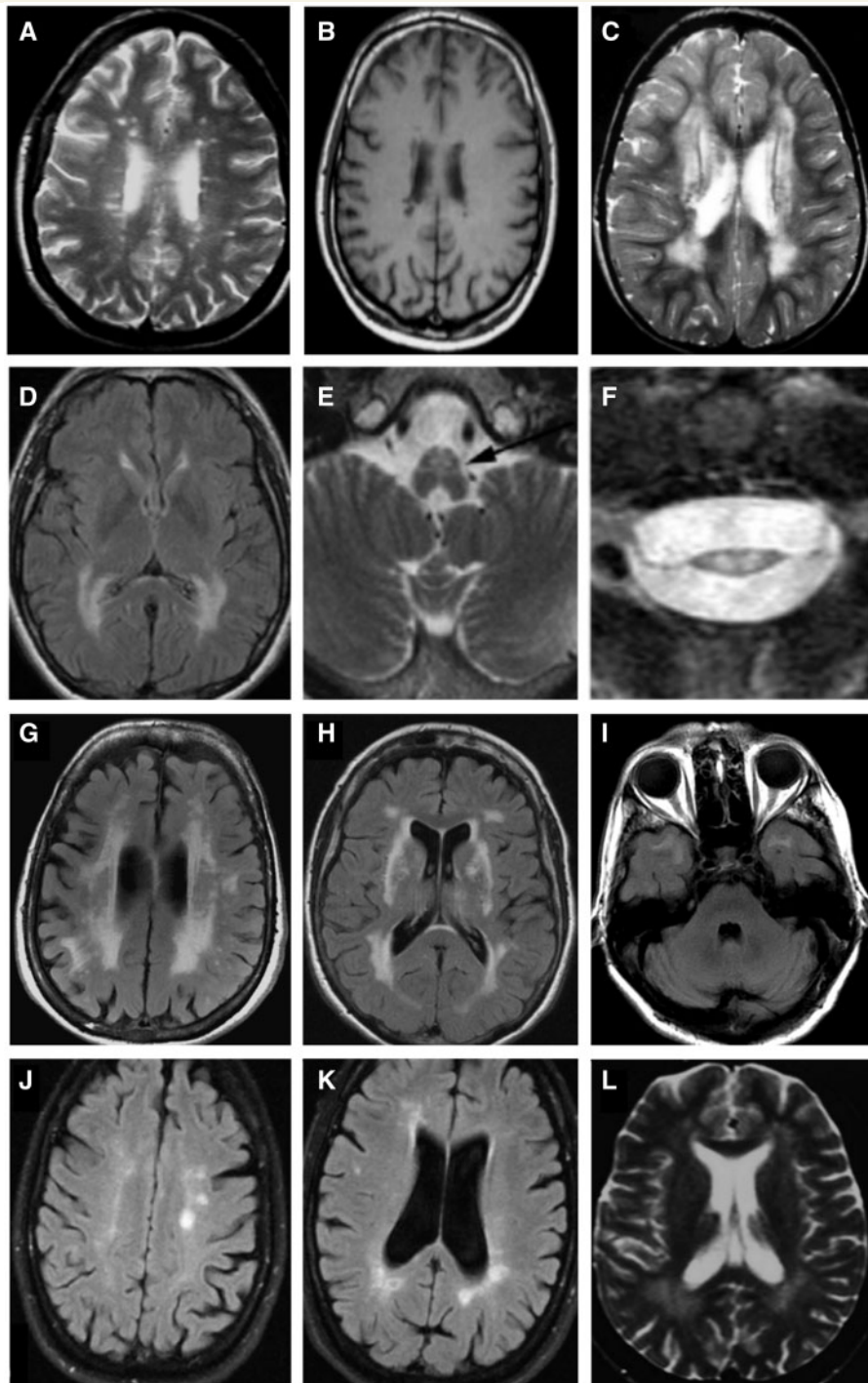


Figure 2 Selected magnetic resonance images from miscellaneous hereditary conditions mimicking multiple sclerosis. (A) Axial FLAIR image of a 36-year-old female with spastic paraparesis and painless visual loss, known to harbour the m.11778G>A mtDNA mutation, diagnostic of LHON-plus, also known as Harding's disease. Numerous foci of hyperintensity of the periventricular and deep white matter strongly resemble appearances seen in multiple sclerosis (reproduced with permission, Küker *et al.*, 2007). Four years after presentation, this patient developed bilateral optic atrophy, ataxia, and internuclear ophthalmoplegia. (B) Axial T₁-weighted image of another patient with LHON showing white matter lesions with hypointense signal, indistinguishable from multiple sclerosis (reproduced with permission, Inglese *et al.*, 2001). (C) Axial T₂-weighted image demonstrating more confluent T₂ hyperintense white matter disease in a third LHON patient (reproduced with permission, Lerman-Sagie *et al.*, 2005). (D–F) Axial FLAIR and T₂-weighted imaging through the brain (D), brainstem (E) and cervical cord (F) in three individual patients with adult-onset Alexander disease. The female patient in (D) presented at 43 years of age with bulbar weakness; patients (E) and (F) presented with lower extremity weakness. The images demonstrate confluent posterior predominant T₂ hyperintensity in the periventricular and deep white matter (D) together with atrophy of medullary pyramids (arrow in E) and marked thinning and T₂ hyperintensity in the cervical cord (F) (reproduced with permission, Pareyson *et al.*, 2008). (G–I) Axial FLAIR imaging in a patient with CADASIL. Patchy and

(continued)

typically mimic multiple sclerosis clinically and generally have distinct radiological features (van Wassenae-van Hall *et al.*, 1995; Hayflick *et al.*, 2006).

Non-metabolic leukodystrophies/leukoencephalopathies and small artery disorders

Several other heritable disorders of white matter can mimic multiple sclerosis, form a heterogeneous group, and are not strictly classifiable as metabolic diseases (Table 4). Adult-onset Alexander disease is caused by heterozygous, usually missense, mutations in *GFAP*; both sporadic cases (with *de novo* mutations) and familial cases with autosomal dominant transmission and incomplete penetrance have been described (Li *et al.*, 2006; Balbi *et al.*, 2010). Alexander disease is characterized by fibrinoid bodies in astrocytes and classically described as an infantile-onset disorder presenting with macrocephaly, growth failure, seizures, and progressive neurological impairment. In recent years, knowledge of the clinical spectrum has expanded, with late-onset disease now thought to account for at least a quarter of all cases of Alexander disease. The clinical course of late-onset disease entails progressive gait ataxia, spasticity and pyramidal signs, bulbar signs, and autonomic features, and can mimic multiple sclerosis (Tschampa *et al.*, 2011); unlike infantile-onset Alexander disease, a very low incidence of macrocephaly and mental retardation is observed in adult-onset disease (Pareyson *et al.*, 2008). Thirty-five per cent of adult patients in one series had palatal myoclonus, which is only rarely seen in other disorders and may be a useful diagnostic clue (Balbi *et al.*, 2010). Adult patients may have T₂ hyperintensities in periventricular and deep white matter (Fig. 2D), and atrophy and T₂ signal abnormalities of the medulla oblongata and cervical cord on MRI (Fig. 2E and F), which may also be seen in multiple sclerosis. Sixty-five to 75% of patients with adult-onset Alexander disease in two series had white matter hyperintensities on MRI in varying distributions which have potential to be mistaken for multiple sclerosis (Farina *et al.*, 2008; Yoshida *et al.*, 2011). MRI can be normal in some adult patients.

Autosomal dominant leukodystrophy is associated with duplications of the lamin B1 (*LMNB1*) gene, causing lamin B1 overexpression, resultant defects in oligodendroglial differentiation, and subtotal demyelination. The disorder has been misdiagnosed as multiple sclerosis, and was originally identified as a distinct disorder in two large Irish-American kindreds sharing a common founder duplication allele (Padiath *et al.*, 2006). Leukoencephalopathy with brainstem and cord involvement and lactate elevation (LBSL) is an autosomal recessive disorder of white matter caused by mutations in *DARS2*. It is characterized by slowly progressive pyramidal, cerebellar, and dorsal column dysfunction, manifesting as cerebellar ataxia and spasticity, with a predominance of lower extremity involvement, and dysarthria (Isohanni *et al.*, 2010). Onset is typically in adolescence or early adulthood, but the disorder exhibits phenotypic heterogeneity and may be incompletely penetrant in some families (Labauge *et al.*, 2011). MRI shows a pattern of homogeneous, often enhancing white matter disease, and involvement of brain stem and spinal tracts. Increased lactate is often present spectroscopically in abnormal white matter. One Finnish study screened for two common *DARS2* mutations in 321 patients with multiple sclerosis; no enrichment for these mutations was observed (Isohanni *et al.*, 2010). Hereditary diffuse leukoencephalopathy with spheroid cysts (HDLS) is an autosomal dominant disorder that may resemble primary progressive multiple sclerosis (Keegan *et al.*, 2008), and is caused by mutations in *CSF1R*. Most cases are inherited from an affected parent, although *de novo* cases are also reported (Rademakers *et al.*, 2011). This disorder typically becomes symptomatic in early adulthood and has a prominent psychiatric or cognitive impairment phenotype. White matter disease on MRI may be asymmetric and patchy and mimic multiple sclerosis, developing confluence later. Significant grey matter pathology, brainstem atrophy and cerebellar abnormalities are minimal or absent.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a progressive, debilitating cerebrovascular disorder that typically follows a stepwise course, with symptomatic onset in the fourth or fifth decade. More than 90% of individuals with CADASIL have autosomal dominantly-inherited heterozygous mutations in *NOTCH3*; *de novo* mutations are

Figure 2 Continued

confluent hyperintensity in the periventricular white matter (G) with involvement of the external capsules (H) and subcortical white matter of the temporal poles (I) are characteristic. (J and K) Axial FLAIR imaging of a 49-year-old female patient with *PLP1* disease (hereditary spastic paraplegia, SPG2 type) presenting with a phenotype mimicking primary progressive multiple sclerosis. She had a 10-year history of progressive spastic paraplegia, dysarthria, and ataxia. Her son had died in childhood of a previously undiagnosed severe neurodevelopmental disorder. Multifocal T₂ hyperintensities are seen in the periventricular and deep white matter near the atria and occipital horns of the ventricles, together with and other scattered foci of T₂ signal in the white matter, mimicking multiple sclerosis (reproduced with permission, Warshawsky *et al.*, 2005). She had abnormal visual-evoked potentials bilaterally and CSF was positive for unmatched oligoclonal bands. (L) Axial T₂-weighted image in a 22-year-old female with hereditary spastic paraplegia, SPG11 type, presenting with subacute gait disturbance, urge incontinence, and mild, subjective cognitive disturbance. Confluent T₂ hyperintensity is seen in the posterior white matter together with small, scattered foci elsewhere in the brain (reproduced with permission, Romagnolo *et al.*, 2014).

Table 3 Other leukodystrophies and leukoencephalopathies and neurometabolic diseases with potential to mimic multiple sclerosis

Disorder	Gene; biochemical/cellular defect	Inheritance mechanism	Clinical presentation in adult-onset disease	'Typical' MRI appearances	Recommended diagnostic testing
Urea cycle disorders	ARG1, SLC25A15 Defects in the metabolism of waste nitrogen from protein catabolism	AR	Progressive SP, bladder dysfunction, neurocognitive deficits, seizures; also liver disease, episodic hyperammonaemia	Multicystic WM lesions with subcortical predominance; cortical and cerebellar atrophy, demyelination, stroke-like lesions, basal ganglia calcifications	Amino acids, plasma (elevated arginine in arginase deficiency; increased ornithine in HHH) Homocitrulline, urine (increased in HHH) Ammonia, plasma (may be increased) Molecular testing of ARG1 and/or SLC25A15
Adult polyglucosan body disease	GBE1 Failed glycogen branching with accumulation of polyglucosan bodies in neural tissue	AR ^d	Gait disturbance, bladder spasticity, mixed UMN/LMN involvement, sensory loss predominantly in the distal lower extremities, and mild cognitive difficulties	Predominantly periventricular and to a lesser extent subcortical T ₂ /FLAIR hyperintense WM abnormalities, esp. posterior internal capsule, pyramidal tracts, medial lemniscus of pons/medulla, cerebellar peduncles, dentate, anterior medulla; atrophy of medulla and cord	GBE activity, fibroblasts/muscle (decreased) Molecular testing of GBE1 Sural nerve biopsy (polyglucosan inclusions)
Acute intermittent porphyria	HMBS Neurotoxicity from 5-aminolevulinic acid	AD	Acute neurovisceral attacks of abdominal pain, in some cases with mental changes, seizures; focal neurological symptoms, and peripheral neuropathy	Diffuse, patchy T ₂ hyperintensities in periventricular WM in some patients	Porphobilinogen, urine (PBG, increased during acute attacks) Molecular testing of HMBS
Disorders of vitamin B₁₂ (cobalamin), homocysteine, and folate metabolism	MUT, MMACHC, MTHFR; others Variable and overlapping mechanisms depending on specific disorder	AR	Tubulointerstitial renal disease, basal ganglia stroke, growth failure, optic nerve atrophy, episodic metabolic acidosis, lethargy/coma, vomiting, dehydration in mutase deficiency; myelopathy, SP, neuropsychiatric features, nystagmus, maculopathy, or optic atrophy in cblC defect; myelopathy and spasticity in MTHFR deficiency	Swelling and hyperintensity of supratentorial WM, thinning of CC in severe cases, bilateral T ₂ hyperintensity in dorsal columns of the spinal cord; signal abnormalities variable between individual disorders; abnormalities potentially reversible with treatment	Homocysteine, plasma (increased in cblC, D, E, F, G, J and X defects and MTHFR deficiency) Methylmalonic acid, plasma/urine (increased in mutase deficiency and cblA, B, C, D, F, J and X defects) Organic acids, urine (increased 3-hydroxypropionic, 2-methylcitric in mutase deficiency) Free carnitine, plasma (normal or decreased) Vitamin B₁₂, plasma Molecular testing of specific gene or gene(s)
Biotinidase deficiency	BTD Failure to recycle biotin causing reduced activity of all biotin-dependent enzyme complexes	AR	Affected older children and adolescents may exhibit motor weakness, SP and decreased visual acuity; other clinical features include seizures, developmental delay, hearing loss, alopecia, immunodeficiency and eczema; manifestations partially/completely reversible with biotin	Periventricular and subcortical WM T ₂ hyperintensity followed by atrophy	Biotinidase activity, plasma (decreased) Molecular testing of BTD <i>Also consider:</i> Organic acids, urine (increased 3-hydroxyisovaleric and 3-methylcitric acids and increased methylcrotonylglycine) Acylcarnitine profile, plasma (increased C3 and/or C5OH acylcarnitines) Lactate, plasma (may be mildly increased)

(continued)

Table 3 Continued

Disorder	Gene; biochemical/cellular defect	Inheritance mechanism	Clinical presentation in adult-onset disease	'Typical' MRI appearances	Recommended diagnostic testing
Cerebrotendinous xanthomatosis	<i>CYP27A1</i> Inactive sterol 27-hydroxylase protein leads to increased production of cholestanol	AR	Pyramidal and/or cerebellar signs, SP, dys-tonia, parkinsonism, peripheral neuropathy, neuropsychiatric symptoms, seizures; premature atherosclerosis; cataracts, xanthomas, chronic diarrhoea	Diffuse cerebral and cerebellar atrophy with variable nonspecific T ₂ /FLAIR signal abnormalities in deep and sub-cortical white matter, sometimes with parieto-occipital predominance; symmetric T ₂ hyperintensity in the dentate nuclei and basal ganglia; brain stem and cerebellar white matter can become involved as disease progresses; decreased NAA and increased lactate on MRS	Cholestanol and bile alcohols, plasma (increased) Cholesterol and chenodeoxycholic acid, plasma (decreased) Molecular testing of <i>CYP27A1</i> Slit lamp ophthalmologic exam (cataracts) <i>Also consider:</i> Cholestanol and apolipoprotein B, CSF (increased) Nerve conduction studies

AD = autosomal dominant; AR = autosomal recessive; cblC = cobalamin C defect; CC = corpus callosum; GBE = glycogen branching enzyme; HHH = hyperornithinaemia-hyperammonaemia-homocitrullinaemia syndrome; LMN = lower motor neuron; MRS = magnetic resonance spectroscopy; MTHFR = methyltetrahydrofolate reductase; NAA = N-acetylaspartate; SP = spastic paraparesis; UMN = upper motor neuron; WM = white matter.

^a Heterozygous *GBE1* mutations reported in some clinically affected individuals.

uncommon, most individuals having an affected parent. Missense mutations located distally in the *NOTCH3* transcript may confer a less specific phenotype with predisposition to age-related progression of small vessel vasculopathy-associated white matter lesions and a high incidence of progressive disability compared to controls. CARASIL, a similar autosomal recessive disorder, shares phenotypic characteristics with CADASIL and is caused by homozygous or compound heterozygous mutations in *HTRA1* (Fukutake *et al.*, 1995). The pathologic hallmark of CADASIL is electron-dense granules in the media of arterioles that can often be identified by electron microscopic evaluation of skin biopsies; these appearances are not observed in CARASIL. On MRI, CADASIL/CARASIL have a predilection for involving subcortical white matter of the anterior temporal lobes, frontoparietal regions near the vertex, and the bilateral external capsules, but may also exhibit diffuse leukoencephalopathy that may mimic multiple sclerosis (Fig. 2G–I; O’Riordan *et al.*, 2002).

Exome sequencing recently identified several adult patients with autosomal recessive *CIC-2* chloride channel deficiency with clinical and imaging features resembling multiple sclerosis. These patients had leukoencephalopathy with MRI signal abnormality in the posterior limb of the internal capsule and middle cerebellar peduncles, and presented with variable clinical features including optic neuropathy, spasticity, and cerebellar ataxia; some patients had chorioretinopathy. Among individuals with adult-onset disease, age of onset ranged from 30–57 years. All identified patients were homozygous or compound heterozygous for *CLCN2* mutations (Depienne *et al.*, 2013). Finally, several families with X-linked Charcot–Marie–Tooth disease (CMTX) have been described in which individuals have presented with, in addition to the mixed axonal demyelinating polyneuropathy that characterizes the disease, ‘relapsing-remitting’ neurological deficits (including transient limb weakness, hemiparesis, or dysarthria) and transient CNS white matter changes often with confluence and posterior or parietal predominance (Hanemann *et al.*, 2003; Sato *et al.*, 2012). In some individuals these episodes seemed to be triggered by physical exertion or high altitude (Paulson *et al.*, 2002).

Hereditary spastic paraplegias

Hereditary spastic paraplegias are a heterogenous and expanding group of disorders characterized by slowly progressive paraparesis and spasticity. Historically, these disorders have been broadly classified as ‘uncomplicated’ if neurological impairment is limited to progressive spastic paraparesis, hypertonic urinary bladder disturbance, and diminution of lower-extremity vibration sensation and proprioception. The primary pathology is axonal degeneration, which is maximal in distal corticospinal tracts and dorsal column fibres (Harding, 1993). There may be a family history of similarly affected individuals, especially in dominantly-inherited subtypes; however, absence of a family history should not exclude hereditary spastic paraplegias,

as many subtypes exhibit incomplete or variable penetrance in some families, result from *de novo* mutations, or follow an autosomal recessive inheritance mechanism. MRI is often normal, helping to differentiate hereditary spastic paraplegia from multiple sclerosis and other conditions, but may reveal mild global atrophy, atrophy of the corpus callosum, non-specific white matter lesions, T₂ hyperintensity in the internal capsule, and cord atrophy (Casali *et al.*, 2004; Hourani *et al.*, 2009), making exclusion of a multiple sclerosis diagnosis challenging in some cases. A recent study revealed alterations in multiple diffusion-tensor indices in many patients, suggesting widespread disruption of myelin integrity (Aghakhanyan *et al.*, 2014). Uncomplicated autosomal dominant forms include types 3A, 4, 6, 8, 10, 13, 17, 31 and 33; types 5A, 7 and 11 are autosomal recessive, and X-linked forms have been described. While many cases of hereditary spastic paraplegia have prominent clinical features that are unlike those seen in multiple sclerosis (e.g. amyotrophy, mental retardation), others may present with dysarthria, optic disc pallor or other features that overlap with multiple sclerosis.

PLP1 disease is classified as X-linked hereditary spastic paraplegia under many schemes, with segmental duplication of Xq22 the most common molecular mechanism described. The classic phenotype of *PLP1* disease is early childhood-onset Pelizaeus-Merzbacher disease in young males, although numerous reports of attenuated disease exist, particularly in female heterozygotes with adult-onset spastic paraplegia phenotypes (Hurst *et al.*, 2006), designated as the SPG2 subtype of hereditary spastic paraplegia. SPG2 has been documented in association with mutations involving specific domains of the *PLP1* protein transcript or less-conserved gene regions, and some gene truncations. Adult patients with SPG2, as well as clinically asymptomatic obligate carrier mothers of males with classical Pelizaeus-Merzbacher disease, have been described with non-specific periventricular and subependymal white matter changes on MRI, and cystic changes in the basal ganglia (Fig. 2J and K; Battini *et al.*, 2003; Warshawsky *et al.*, 2005; Hurst *et al.*, 2006). A young female presenting with subacute gait disturbance and periventricular white matter lesions was recently described with biallelic pathogenic mutations in *SPG11* (Fig. 2L; Romagnolo *et al.*, 2014). Using a whole exome sequencing approach in combination with bioinformatics and functional validation, several additional putative hereditary spastic paraplegia genes were recently identified (Novarino *et al.*, 2014), although as yet, the potential for these hereditary spastic paraplegia subtypes to mimic multiple sclerosis has not been evaluated.

Other miscellaneous Mendelian disorders of relevance to multiple sclerosis

Other Mendelian genes can harbour highly penetrant, rare variants implicated in specific disorders that overlap with

multiple sclerosis. Familial haemophagocytic lymphohistiocytosis is a genetically heterogeneous autosomal recessive disorder characterized by proliferation/infiltration of macrophages and T-lymphocytes; adult disease has been reported. Several reports exist of cases with severe CNS manifestations, and multiple sclerosis has been reported with higher frequency among patients harbouring *PRF1* mutations and polymorphisms (Camiña-Tato *et al.*, 2010). Neurological features may include spasticity, cranial nerve palsies, ataxia, quadriplegia and blindness. Other findings, including fever, cytopenias, rash, lymphadenopathy, liver dysfunction, and haemophagocytosis are not universally present, and the overall picture can mimic acute disseminated encephalomyelitis as well as multiple sclerosis.

Friedreich ataxia usually results from biallelic trinucleotide expansions in *FRDA*, a nuclear gene, and causes degeneration of dorsal columns, spinocerebellar and pyramidal tracts, dorsal root ganglia, and peripheral nerves. On MRI, atrophy of the medulla and upper cervical cord is common, and in late onset forms, cerebellar atrophy and cerebellar white matter abnormalities become evident (Bhidayasiri *et al.*, 2005). It and other hereditary ataxias can mimic multiple sclerosis, although this group of disorders typically have clinical characteristics that are clearly distinguishable from multiple sclerosis.

Familial Mediterranean fever (FMF), which typically presents with recurrent febrile episodes with or without abdominal pain, is caused by recessively-inherited mutations in *MEFV*, encoding pyrin and implicated in the regulation of the pro-inflammatory cytokine interleukin 1 β . *MEFV* mutations and polymorphisms have been identified at higher frequencies in patients with multiple sclerosis compared to healthy control groups; it has been suggested that endothelial dysfunction in familial Mediterranean fever may disrupt blood–brain barrier integrity, an important element in the evolution of inflammatory lesions and plaques (Alpayci *et al.*, 2012).

Other miscellaneous rare disorders merit consideration in a discussion of hereditary mimics of multiple sclerosis. Gerstmann-Straussler-Scheinker syndrome is a rare, usually autosomal dominant prion disease with a protracted course encompassing a progressive ataxia syndrome, with MRI and CSF findings suggestive of a demyelinating-inflammatory process. It has been noted that certain vascular malformation disorders (cerebral angiomas; von Hippel-Lindau disease) may cause progressive neurological features punctuated by acute clinical deteriorations, and radiological appearances that could potentially be confused with multiple sclerosis (Natowicz and Bejjani, 1994).

Discussion

Despite significant recent advances in the understanding of multiple sclerosis pathogenesis and revisions to diagnostic criteria, there remains no pathognomonic clinical or

Table 4 Non-metabolic leukodystrophies and leukoencephalopathies with potential to mimic multiple sclerosis

Disorder	Gene; biochemical/cellular defect	Inheritance mechanism	Clinical presentation in adult-onset disease	'Typical' MRI appearances	Recommended diagnostic testing
Adult-onset Alexander disease	GFAP Mutant glial fibrillary acidic protein causes disordered modulation of the morphology and motility of astrocytes	AD	Bulbar/pseudobulbar signs: palatal myoclonus, dysphagia, dysarthria, spasticity, hyperreflexia, ataxia, nystagmus, dysmetria, incontinence, constipation, orthostatic hypotension, seizures, diplopia	Atrophy and T ₂ hyperintensity of medulla and cervical cord in almost all patients; cerebral T ₂ WM hyperintensities in most, often with frontal predominance; hyperintensity and swelling involving basal ganglia and thalamus; MRI can be normal	Molecular testing of GFAP Also consider CSF studies (increased $\alpha\beta$ -crystallin, heat shock protein 27, and glial fibrillary acidic protein)
Autosomal Dominant Leukodystrophy (ADLD)	LMNB1 Lamin B1 overexpression causing defective oligodendroglial differentiation	AD	Early autonomic dysfunction, cognitive impairment, pyramidal lesions, cerebellar dysfunction, typical onset age 30–50 years	Subtle to extensive symmetrical WM T ₂ hyperintensities with frontoparietal predominance; may also involve middle cerebellar peduncles, brainstem; typically periventricular WM is spared or less affected than other regions; atrophy of corpus callosum and brain stem	Molecular testing of LMNB1 (for common duplication first; use quantitative PCR or FISH initially)
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	DARS2 Dysfunctional mitochondrial aspartyl-tRNA synthetase	AR	Slowly progressive cerebellar ataxia, spasticity, abnormal proprioception/vibration sense, dysarthria; epilepsy and/or learning disability in some patients	Confluent or patchy T ₂ hyperintensities in cerebral WM, dorsal columns and lateral corticospinal tracts of cord, and medulla; relative sparing of the U-fibres; abnormalities may also be seen in corpus callosum, internal capsule, cerebellar peduncles, spinocerebellar tracts and cerebellar WM	Molecular testing of DARS2 Also consider Magnetic resonance spectroscopy (increased lactate in abnormal cerebral white matter)
Hereditary diffuse leukoencephalopathy with spheroid cysts (HDLS)	CSF1R Disordered cell-surface cytokine receptor; dysregulation of survival, proliferation, differentiation, and function of CNS microglia	AD	Executive dysfunction with frontal lobe signs, memory decline, personality changes, motor impairment, seizures; usual age of onset 25–45 years	Bifrontal or bifrontoparietal T ₂ /FLAIR hyperintensities in deep, subcortical, and periventricular WM; often asymmetric and patchy, becoming confluent with time; involvement of corpus callosum and corticospinal tract lesions common; brain stem atrophy and contrast enhancement in brain parenchyma usually absent	Molecular testing of CSF1R Also consider CSF studies (increased neurofilament light protein)
Cerebral Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL/CARASIL)	NOTCH3; HTRA1 Aggregation and accumulation of mutant Notch3 protein in cerebral vasculature causing multifactorial toxicity	AD (CADASIL) AR (CARASIL)	Progressive cerebrovascular disease from mid-adulthood, progressing to spastic paraplegia and dementia; migraine and mood disturbance	Classically T ₂ -hyperintense WM lesions involving the temporal pole and external capsule; numerous subcortical infarcts; optic nerves and cord typically spared	Molecular testing of NOTCH3 and/or HTRA1 (as determined by mode of inheritance and presence/absence of electron-dense granules in media of arterioles) Also consider Skin biopsy (electron dense granules in arteriolar media seen in CADASIL only)
CLC-2 chloride channel deficiency leukoencephalopathy	CLCN2 Abnormal chloride ion and water homeostasis causing white matter oedema	AR	Cerebellar ataxia, SP, optic neuropathy; cognitive defects, headache, retinopathy	Restricted diffusion with T ₂ hyperintensity in midbrain cerebral peduncles, middle cerebellar peduncles, and posterior limb of internal capsule; possible WM hyperintensity more diffusely	Molecular testing of CLCN2
X-linked Charcot-Marie-Tooth disease (CMTX)	GJB1 Predicted reduction in number/efficiency of gap junctions between oligodendrocytes and astrocytes in CNS	X-linked	Usually accompanied by demyelinating polyneuropathy with amyotrophy, distal weakness, and pes cavus; episodic or persistent ataxia and dysarthria; sensorineural hearing loss in some families; males generally more severely affected; "relapsing" events triggered by e.g. high altitude	Non-enhancing periventricular, symmetrical, confluent white matter abnormalities with posterior predominance; T ₁ hypointensity in splenium of CC and middle cerebellar peduncles; new CNS abnormalities may appear acutely, especially at altitude	Molecular testing of GJB1 (connexin 32) Nerve conduction study (demyelinating/axonal polyneuropathy with moderately slowed NCV)

AD = autosomal dominant; AR = autosomal recessive; CC = corpus callosum; FISH = fluorescent in situ hybridization; MRS = magnetic resonance spectroscopy; NCV = nerve conduction velocity; SP = spastic paraparesis; WM = white matter.

investigative finding for the diagnosis of multiple sclerosis. Misdiagnosis occurs (Rudick and Miller, 2012; Solomon *et al.*, 2012; Solomon and Weinschenker, 2013) and remains a challenging problem with significant repercussions. Diagnostic criteria have been designed to increase sensitivity, resulting in lowered specificity to the extent that patients with other disorders, both inherited and acquired, have the potential to meet McDonald Criteria when ‘no better explanation’ for symptoms, signs, or investigational findings is elicited by the treating physician. This highlights the importance of expanding the diagnostic evaluation to exclude other, rarer conditions when one or more ‘red flags’ are present. Although a relapsing–remitting course can be mimicked by, for example, various mitochondrial disorders (pyruvate dehydrogenase complex deficiency, Leigh disease, MELAS) Fabry disease, and X-linked Charcot–Marie–Tooth disease, awareness of these red flags is especially important for clinicians evaluating patients meeting criteria for (or carrying tentative diagnoses of) primary progressive multiple sclerosis, as most other heritable mimics of multiple sclerosis are more likely to exhibit a progressive disease course. Patients meeting diagnostic criteria or suspected of having primary progressive multiple sclerosis are a particularly heterogeneous group of patients whose presentation is typically characterized by spasticity or myelopathic signs with insidious onset, but who generally have fewer perivascular inflammatory white matter lesions on MRI than relapsing patients (Revesz *et al.*, 1994). Overall clinical presentation and even MRI characteristics in primary progressive disease may overlap with, or be indistinguishable from, that seen in adult-onset forms of several rare Mendelian genetic conditions. Primary progressive patients are generally older than relapsing patients at onset, are more likely to be male, have a greater prevalence of motor impairment and cognitive impairment at diagnosis (Wachowius *et al.*, 2005) and show poor response to immunomodulatory therapies (Miller and Leary, 2007). Although some genetic or inherited metabolic disorders may exhibit a relapsing course, most such conditions have slow, insidiously progressive or stepwise neurologic decline, without clear remissions. Paediatric multiple sclerosis is almost always relapsing at presentation with a prominent inflammatory component at symptomatic onset (Banwell *et al.*, 2007; Krupp *et al.*, 2007).

The most recent McDonald Criteria for diagnosis of multiple sclerosis (Polman *et al.*, 2011), especially those for multiple sclerosis ‘with progression from onset’, are more sensitive and less specific than previous iterations (Polman *et al.*, 2005) and no longer stipulate presence of oligoclonal bands as an absolute requirement. In practice, many neurologists do not routinely evaluate CSF, although it is generally recognized that CSF evaluation remains an important aid in the confirmation of multiple sclerosis, especially in atypical patients. Oligoclonal bands are themselves non-specific and incompletely sensitive; their absence does not exclude multiple sclerosis (Solomon *et al.*, 2012) and

patients with other disorders may have them, reflecting non-specific CSF inflammatory disease. The presence or absence of oligoclonal bands is therefore an imperfect discriminator, but patients whose multiple sclerosis diagnosis is already in doubt and who are negative for unmatched oligoclonal bands in CSF should be subjected to particularly rigorous scrutiny. In all types of multiple sclerosis, oligoclonal bands are of lower prevalence in non-Caucasian individuals (Link and Huang, 2006); this may be of particular relevance to primary progressive disease, where a higher percentage of patients are non-Caucasian (Naismith *et al.*, 2006). CSF protein may be elevated in multiple sclerosis, but is also of poor specificity and sensitivity.

Several ‘red flag’ clinical, paraclinical and MRI characteristics of a patient’s presentation and disease course should prompt careful consideration of specific Mendelian genetic or mitochondrial disorders in the differential diagnosis of an individual presenting with a multiple sclerosis-like illness and are outlined in Table 5. These ‘flags’, together with family history, patient age, sex and ethnicity (specific inherited disorders occur with high prevalence in specific populations) should be routinely considered in the evaluation of such patients. In addition to disorder-specific features outlined in earlier sections, clinical red flags include absent ocular involvement, absent callosal lesions (Dawson’s fingers) on MRI, absent cord lesions on MRI, positive family history of (unexplained) neurologic symptoms, early or very late (>70 years) age of onset, presence of unexplained non-CNS pathology, and absence of clinical remissions (Rudick *et al.*, 1986; Miller *et al.*, 2008). Although collectively these red flags have some utility, the discriminating power of each ‘flag’ individually is low, as illustrated by presence of one or more flags in many ‘true’ multiple sclerosis patients. Primary progressive patients in particular always fulfill ‘absence of clinical remission’, which in part explains additional uncertainty that often accompanies a primary progressive multiple sclerosis diagnosis. With specific reference to alternative inherited disorders, ‘family history of multiple sclerosis’, ‘early age of onset’ and ‘presence of non-CNS disease’ have been suggested as flags, but again, each ‘flag’ individually has poor discriminatory power; many patients with ‘true’ multiple sclerosis have affected family members, and a clear genomic basis for multiple sclerosis is now well established. In a collaborative genome-wide association study (GWAS) involving almost 30 000 patients with multiple sclerosis and ~50 000 controls (Beecham *et al.*, 2013), 110 low penetrance susceptibility variants were established at 103 loci. Patients with autosomal recessive disorders (or incompletely penetrant autosomal dominant disorders) frequently lack any discernible family history. ‘Early age of onset’ is also a poor discriminator; the phenomenon of paediatric multiple sclerosis is well established, as is, increasingly, the recognition of attenuated or adult-onset inherited conditions exhibiting overlap with multiple sclerosis. For females with X-linked disorders (*PLP1* disease/SPG2, Fabry

Table 5 Fifty-six ‘red flag’ clinical, laboratory, and radiologic characteristics raising suspicion for Mendelian diseases in patients evaluated for multiple sclerosis or with ‘multiple sclerosis-like’ phenotypes

Disease characteristic	Red Flag ^a	Examples of alternative inherited disorders
Clinical neurologic or neuro-ophthalmologic features		
Peripheral neuropathy/delayed NCV	Major	CMTX, KD, MLD, X-ALD/AMN, cblC defect, <i>PLP1</i> disease, CTX, mito disease, POLG, APBD
Myopathy	Major	Mito disease, POLG
Amyotrophy	Major	Specific HSP subtypes
Retinopathy	Major	Mito disease, cblC defect
Prominent cerebrovascular disease	Major	CADASIL, FD
Prominent neuropsychiatric disease/dementia	Intermediate	MLD, WD, HDLS, CTX, cblC defect
Isolated, progressive or intermittent ataxia	Intermediate	FA, spinocerebellar ataxia, CTX, PDH deficiency
Apparently isolated myelopathy	Minor	X-ALD/AMN, cblC defect
Early, severe optic nerve involvement	NA	LHON, X-ALD, <i>OPA1</i> disease, <i>CLCN2</i> disease
Prominent dystonia/parkinsonism	NA	NPC, CHD, <i>MLC1</i> disease, CTX, NBIA, WD, APBD, Leigh disease and other mito disease
Prominent bulbar symptoms	NA	AOAD, KD
Prominent epilepsy	NA	MLD, cblC defect, POLG, MELAS/MERFF, other mito disease
Palatal myoclonus	NA	AOAD
Hearing loss	NA	FD, NPC, Leigh disease, other mito disease
Vertical supranuclear gaze palsy (VSGP)	NA	NPC
Gelastic cataplexy	NA	NPC
Tongue hemiatrophy	NA	KD
Relapsing-remitting neurological symptoms or stroke-like episodes	NA	PDH deficiency, MELAS/MERFF, CMTX; cblC defect, MTHFR deficiency, CADASIL, FD
Gender discrepancy in clinical neurological phenotype or more severely affected brothers/male maternal relatives (implying X-linked disease)	NA	FD, X-ALD/AMN, <i>PLP1</i> disease/SPG2; CMTX, PDH deficiency
Extra-neurologic features		
Renal disease	Major	FD, MMA
Cutaneous angiokeratomas	Major	FD
Liver disease	NA	UCD, mito disease, POLG, NPC, WD
Cardiomyopathy	NA	FD, mito disease
Tendon xanthomas	NA	CTX
Early cataract/lenticular opacity	NA	FD, WD, CTX
Symptomatic anaemia	NA	WD, MMA/cobalaminopathies
Adrenocortical insufficiency	NA	X-ALD/AMN
Recurrent abdominal pain	NA	AIP, FME, FD
Chronic diarrhoea	NA	CTX, mito disease
Laboratory findings		
Elevated lactate, plasma	Major	mtDNA disorders, POLG, PDH deficiency; MMA
Elevated CK, plasma	NA	Mito disease, POLG
Elevated mean corpuscular volume	NA	MMA/cobalaminopathies
Haemolytic anaemia	NA	WD
Persistently elevated methylmalonic acid, plasma/urine (with normal B ₁₂)	NA	MMA/cobalaminopathies
Hyperhomocysteinaemia and/or homocystinuria	NA	cblC defect; MTHFR deficiency
Neuroimaging appearances		
Pattern/distribution of white matter involvement		
Frontal (anterior) predominance	NA	MLD, HDLS, ADLD
Parieto-occipital (posterior) predominance	NA	X-ALD, KD, CTX
Periventricular predominance	NA	APBD
Symmetric, confluent white matter abnormalities	Intermediate	MLD, SPG11, CMTX, other leukodystrophies and leukoencephalopathies
Anterior temporal lobe, external capsule	NA	CADASIL/CARASIL
Sparing of the U-fibres	NA	MLD, CXT, APBD, Krabbe
Early involvement of U-fibres	NA	MTHFR deficiency, mito disease, APBD
Sparing of the corpus callosum	NA	APBD, <i>MLC1</i> disease
Corticospinal/pyramidal tract involvement	NA	KD, HDLS, X-ALD/AMN, mito disease
Other findings		
Cerebellar/brainstem signal abnormality	NA	AMN, CTX, AOAD, ADLD, POLG, APBD
Gadolinium contrast enhancement	NA	X-ALD/AMN, POLG, AOAD
T ₂ hyperintensities of dentate nucleus	Major	CTX, WD, mito disease
T ₁ hyperintensities of pulvinar	Major	FD
Symmetric T ₂ hyperintensity of basal ganglia	Major	Leigh disease, other mito disease; CTX
Calcification on CT	Intermediate	Mito disease
Elevated white matter lactate on MRS	Intermediate	Mito disease, LBSL, X-ALD

(continued)

Table 5 Continued

Disease characteristic	Red Flag ^a	Examples of alternative inherited disorders
Cystic change or degeneration of white matter	NA	PLP1 disease/SPG2, CLC2, mito disease
'Eye of the tiger' appearance to GP	NA	NBIA
Prominent brainstem/upper cord atrophy	NA	AOAD
Prominent cerebellar atrophy	NA	CHD, NPC, spinocerebellar ataxia
Cord hyperintensity	NA	cb1C defect, MTHFR deficiency, CTX, mito disease, B ₁₂ /folate deficiencies, AOAD, LHON

^aMajor, intermediate, and minor red flags as determined by Miller et al., 2008 (NA, not addressed).

ADLD = autosomal dominant leukodystrophy; AIP = acute intermittent porphyria; AMN = adrenomyeloneuropathy; AOAD = adult-onset Alexander disease; APBD = adult polyglucosan body disease; cb1C = cobalamin C defect; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CHD = Chédiak-Higashi disease; CK = creatine kinase; CLC2 = CLC2 disease; CMTX = X-linked Charcot-Marie-Tooth disease; CTX = cerebrotendinous xanthomatosis; FD = Fabry disease; FMF = familial Mediterranean fever; GP = globus pallidus; HDLS = hereditary diffuse leukoencephalopathy with spheroids; KD = Krabbe disease; LBSL = leukoencephalopathy with brain stem involvement and lactate elevation; MLD = metachromatic leukodystrophy; MMA = methylmalonic acidemia; MRS = magnetic resonance spectroscopy; MTHFR = methylenetetrahydrofolate reductase; NBIA = neurodegeneration with brain iron accumulation; NCV = nerve conduction velocity; NPC = Niemann-Pick disease type C; PDH = pyruvate dehydrogenase deficiency; POLG = polymerase gamma-related disease; UCD = urea cycle disorders; X-ALD = X-linked adrenoleukodystrophy.

disease, X-linked adrenoleukodystrophy, X-linked Charcot-Marie-Tooth disease), disease severity and age of onset may be determined by the pattern of X-inactivation.

For the patient who is 'redialigned' with an inherited disorder, there are several key practical implications: (i) availability of therapeutic interventions for some conditions; (ii) anticipation of natural history of the newly diagnosed disorder, including involvement of other tissues and organs, and expected prognosis; (iii) genetic counselling and/or testing opportunities for relatives of the proband; and (iv) avoidance of risks associated with the erroneous multiple sclerosis diagnosis including side effects of immunomodulatory therapies. For clinicians and researchers, more accurate and timely diagnosis of multiple sclerosis, and improved characterization of patient cohorts, reduces the risk of spurious conclusions from clinical or basic research. In the years ahead, clinically-applicable sequencing technologies are expected to become even more comprehensive, and less expensive, and many rare Mendelian and mitochondrial disorders appear destined to become more accessible to novel therapeutics, some of which are already in development or in clinical trials. For these reasons it is now more important—and more realistic—than ever to accurately recognize rare genetic disorders that masquerade with multiple sclerosis-like phenotypes.

Funding

Dr Honce receives research funding from Biogen Idec. Dr Weisfeld-Adams, Dr Katz Sand and Dr Lublin have no relevant funding or financial conflicts of interest to disclose.

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