J Inherit Metab Dis (2007) 30:855–864
DOI 10.1007/s10545-007-0745-1

REVIEW

Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: A diagnostic approach

F. Sedel · B. Fontaine · J. M. Saudubray · O. Lyon-Caen

Received: 26 July 2007 / Submitted in revised form: 18 August 2007 / Accepted: 17 September 2007 / Published online: 22 October 2007

Summary Spastic paraparesis is a general term describing progressive stiffness and weakness in the lower limbs caused by pyramidal tract lesions. This clinical situation is frequently encountered in adult neurology. The diagnostic survey is usually limited to searching for acquired causes (spinal cord compression, inflammatory, metabolic, infectious diseases) and the so-called 'hereditary spastic paraparesis'. Although poorly recognized by neurologists, spastic paraparesis is also one of the multiple presentations of inborn errors of metabolism (IEMs) in children and adults. Pyramidal signs are usually included in a diffuse neurological or systemic clinical picture; however, in some cases spastic paraparesis remains the only symptom for years. Since these metabolic causes are often treatable, it is essential to include them in the general diagnostic approach to spastic paraparesis. Here we review IEMs causing paraparesis in adults.

Communicating editor: John Walter

Competing interests: None declared

F. Sedel · B. Fontaine · O. Lyon-Caen
Federation of Nervous System Diseases,
The Salpêtrière Hospital,
Pierre et Marie Curie University,
Paris, France

F. Sedel
Reference Center for Lysosomal Diseases,
The Salpêtrière Hospital,
Pierre et Marie Curie University,
Paris, France

B. Fontaine
INSERM, UMR 546, The Salpêtrière Hospital,
Pierre et Marie Curie University,
Paris, France

J. M. Saudubray
Department of Pediatrics and Metabolic Diseases,
Reference Center for Metabolic Diseases,
Necker-enfants malades Hospital,
René-Descartes University,
Assistance Publique-Hôpitaux de Paris,
Paris, France

F. Sedel (✉)
Federation of Nervous System Diseases,
Salpêtrière Hospital,
47 Boulevard de l'Hôpital,
75651 Paris, Cedex 13, France
e-mail: frederic.sedel@psl.aphp.fr

Abbreviations

CblC	cobalamin C disease
HSP	hereditary spastic paraparesis
IEM	inborn error of metabolism
MTHFR	methylene tetrahydrofolate reductase
NKH	nonketotic hyperglycinaemia

Introduction

Spastic paraparesis is a general term describing progressive stiffness and weakness in the lower limbs. The main acquired causes of spastic paraparesis include spinal cord compression by various processes (mainly cervical arthrosis), 'inflammatory' causes (multiple sclerosis, sarcoidosis, Goujerot–Sjögren syndrome), infections (HIV, HTLV1), and acquired metabolic diseases (B_{12} and folate deficiencies).

Hereditary spastic paraparesis (HSP) constitutes a heterogeneous group of genetic diseases that cause a length-dependent axonal degeneration of the pyramidal tracts (Fink 2003). To date, around 30 different

genetic loci have been identified with various modes of inheritance. Types of HSP are clinically classified as uncomplicated (or pure) when symptoms are limited to spastic paraparesis (often accompanied by urinary urgency and subtle signs of dorsal column impairment) and as complicated (or syndromic) when other neurological or systemic signs exist. Examples of additional signs are thin corpus callosum, peripheral neuropathy, leukoencephalopathy, cerebellar atrophy, mental retardation, cataract or macular degeneration. In adults, pure HSP is often caused by mutations in the *SPG4* gene, which account for 15–40% of all autosomal dominant HSP and around 10% of apparently sporadic cases (Depienne et al 2006). Complicated autosomal recessive HSP with corpus callosum atrophy, peripheral neuropathy, mild mental retardation and leukoencephalopathy is another frequent phenotype caused by mutations in the *SPG11* gene (Stevanin et al 2007). Other types of HSP are far less common and the cause of a large proportion of spastic paraparesis remains unknown.

Motor neurons forming pyramidal tracts are extraordinarily long cells, and their energy and transport requirements render these cells particularly vulnerable to degenerative or metabolic disorders. It is therefore not surprising that many inborn errors of metabolism (IEMs) can provoke spastic paraparesis. Mechanisms responsible for pyramidal tract lesions include complex molecule metabolic disorders that interfere with myelin metabolism (metachromatic leukodystrophy, Krabbe disease, homocysteine remethylation defect, adrenomyeloneuropathy), endogenous intoxication by small toxic metabolites (arginase deficiency, triple H syndrome, phenylketonuria), or defects in energy production (biotinidase deficiency). These metabolic causes are poorly known by physicians and are not mentioned in reviews dedicated to HSP. However, their diagnosis is important because genetic counselling can be provided and, in some cases, specific treatments exist that may slow or even reverse clinical signs (Saudubray et al 2006; Sedel et al 2007). The pattern of inheritance is often autosomal recessive but apparently sporadic cases are common. The clinical picture is usually not restricted to pyramidal signs and is more closely related to the 'complicated' phenotype; however, in some cases spastic paraparesis remains isolated for years.

Here, we will review IEMs in which spastic paraparesis is a prominent component of the clinical picture. We will focus on late-onset forms which can be encountered in an adult neurology department. These include diseases that truly begin in adulthood as well as mild forms with childhood onset.

Disorders of intermediary metabolism

Homocysteine remethylation defects

Spastic paraparesis can be a presenting sign of homocysteine remethylation defects. Involvement of the pyramidal tracts is due to demyelination caused by a deficiency in *S*-adenosylmethionine (AdoMet). AdoMet is necessary to methylate the myelin basic protein and certain lipids of the myelin sheath (Powers et al 2001; Surtees 1998). The diagnosis of homocysteine remethylation defects is suggested by a combination of hyperhomocysteinaemia (usually above 100 μmol/L) with normal or low blood methionine. The two main causes in adulthood are methylene tetrahydrofolate reductase (MTHFR) deficiency and cobalamin C disease (CblC) (reviewed in Ogier de Baulny et al 1998; Rosenblatt and Fenton 2001). In patients with MTHFR deficiency, folates are usually low, whereas in CblC, there is methylmalonic aciduria and eventually red cell macrocytosis.

Late-onset forms often begin with psychiatric signs (depression or psychosis) that may remain isolated for years or decades (Freeman et al 1975; Roze et al 2003). These may be followed by acute or subacute paraplegia (subacute combined degeneration of the spinal cord), polyneuropathy, confusion and eventually coma. Thromboembolic complications caused by chronic hyperhomocysteinaemia including cerebral strokes may be observed (Visy et al 1991). In addition, several patients have been reported who initially presented with an isolated spastic paraparesis (Haworth et al 1993; Powers et al 2001; Roze et al 2003). In most cases, the paraplegia became nearly complete within several months and rapidly led to tetraplegia and signs of bladder, proprioceptive and cognitive dysfunction. However, in some instances, spastic paraparesis remained slowly progressive for years (Haworth et al 1993; Roze et al 2003). Various combinations of betaine, folinic acid and hydroxocobalamin (Ogier de Baulny et al 1998) are very effective in halting disease progression, resolving psychiatric signs and cognitive dysfunction. However, spastic paraparesis is less responsive and when paraplegia has occurred it is usually permanent.

Urea cycle disorders and related disorders

Although episodes of hyperammonaemic encephalopathy constitute the classical presentation of urea cycle disorders (and related disorders such as citrullinaemia type II or triple H syndrome), two disorders—arginase deficiency and triple H syndrome—also involve pyramidal tracts. The reasons for these specific lesions are still unknown.

Arginase deficiency. Arginase is the last enzyme of the urea cycle and is necessary for the transformation of arginine into urea and ornithine. First symptoms of arginase deficiency are often noted between 2 and 4 years of age and usually consist of a progressive spastic paraparesis (Crombez and Cederbaum 2005). In some cases, paraparesis may appear in adolescents or young adults (Cowley et al 1998; Crombez and Cederbaum 2005). Intellectual disability and seizures may be observed. Only a minority of patients exhibit signs of protein intolerance and ammonia is often normal or mildly increased. A low-arginine diet and the use of ammonia chelators such as sodium benzoate can stabilize, prevent or even improve the neurological signs (Crombez and Cederbaum 2005).

Hyperornithinaemia–hyperammonaemia–homocitrullinuria (triple H syndrome) is due to a defect of ornithine transport through the mitochondrial membrane caused by mutations in the *ORNT1* gene. It can present at any age from the neonatal period through adulthood with a progressive spastic paraparesis (Miyamoto et al 2002; Salvi et al 2001). Protein intolerance and acute episodes of vomiting, confusion or coma due to hyperammonaemia are usually present. Other neurological features include mental retardation (which may not be present), seizures and cerebellar ataxia.

Biotinidase deficiency

Biotinidase deficiency is responsible for a defect in the endogenous recycling of biotin, a cofactor of several carboxylases implicated in the catabolism of branched-chain organic acids, gluconeogenesis and fatty acid synthesis. There is great phenotypic variability, from a severe childhood-onset multisystemic disorder to asymptomatic adults (Baykal et al 2005). These asymptomatic carriers are at risk of developing symptoms at any age. For instance, a few adolescents were reported who presented with acute visual loss due to bilateral optic atrophy and progressive paraparesis due to upper and lower motor neuron disease (Ramaekers et al 1993; Tokatli et al 1997; Wolf et al 1998). Some patients also exhibited skin rashes or hearing loss. Importantly, neurological and visual signs improved with low doses of biotin (Ramaekers et al 1993).

Phenylketonuria

Phenylketonuria is diagnosed with newborn screening programmes in most developed countries. Treatment with early dietary restriction of phenylalanine has greatly improved the prognosis of children with PKU. Most guidelines propose maintenance of the diet until 16 years of age. However, after discontinuation of the diet, a small proportion of adult patients may present with pyramidal tract signs or spastic paraparesis (McCombe et al 1992). Other neurological signs include cognitive deficits, dorsal column sensory loss, tremor and leukoencephalopathy. In addition, a few adult patients who escaped neonatal screening presented with a progressive spastic paraparesis (Kasim et al 2001; Weglage et al 2000). Other signs included dementia and optic atrophy. Symptoms improved after introduction of a low-phenylalanine diet (Kasim et al 2001).

Nonketotic hyperglycinaemia (NKH)

NKH is due to a defect in the glycine cleavage system leading to an endogenous intoxication with glycine. NKH usually presents with a severe encephalopathy in infancy. A few patients exhibited mild mental retardation and hypotonia in early childhood followed by acute behavioural problems or episodes of confusion and movement disorders in adolescence or adulthood (Dinopoulos et al 2005). In addition, a few adults with hyperglycinaemia and hyperglycinuria presented with a spastic paraparesis beginning in childhood or adolescence (Bank et al 1972; Steiman et al 1979). Additional features included optic atrophy, cerebellar ataxia and lower motor neuron disease. Since the glycine cleavage system was not investigated, the cause of hyperglycinaemia is still unclear in these particular cases presenting with spastic paraparesis (reviewed in Dinopoulos et al 2005).

Mild forms of dopamine synthesis defects

Mild forms of dopamine synthesis defects are mainly responsible for the so-called dopa-responsive dystonia, i.e. focal or generalized dystonia which responds dramatically to low doses of levodopa.

The most frequent cause is the partial defect in GTP cyclohydrolase, the first enzyme in the synthesis pathway of tetrahydrobiopterin BH_4 (Segawa et al 2003). In addition to dystonia or parkinsonism, patients may exhibit pyramidal signs and in some cases, lower limb dystonia can mimic spastic paraparesis (Nygaard et al 1990; Kong et al 2001; Patel et al 1995). Exceptional cases of tyrosine hydroxylase deficiency (Furukawa et al 2001; Schiller et al 2004), sepiapterin reductase deficiency (Friedman et al 2006), pyruvoyl tetrahydrobiopterin synthase deficiency (Tanaka et al 1987) or dihydropteridine reductase

deficiency (Pogson 1997) have also been reported in adults. However, most patients described so far exhibited mental retardation, epilepsy and pyramidal signs, in addition to the classical 'dopa-responsive dystonia'.

Cerebral folate deficiency syndrome

Recently, a syndrome of cerebral folate deficiency has been identified in children with very low 5-methyltetrahydrofolate concentration in CSF. Clinical signs arise in early infancy with psychomotor delay, autism, cerebellar ataxia, spastic paraplegia, movement disorders, epilepsy and microcephaly, followed by optic atrophy and hearing loss (reviewed in Ramaekers and Blau 2004). Interestingly, patients with this syndrome improved with high doses of folinic acid, a stable and metabolically active form of folate. It is not clear whether this syndrome represents a distinct inborn error of metabolism. The fact that all cases described to date appeared sporadic and the recent finding of autoantibodies against folate receptors suggest an acquired autoimmune mechanism (Ramaekers et al 2005). In addition, secondary cerebral folate deficiency has been observed in association with other disorders including Aicardi–Goutiere syndrome, Kearns–Sayre syndrome or Rett syndrome (Ramaekers and Blau 2004). Hansen and Blau (2005) also found cerebral folate deficiency in a 14-year-old girl who from 3 years of age exhibited a progressive spastic paraparesis, mental retardation and dystonia and who improved after folinic acid supplementation.

Homocarnosinosis

Homocarnosine (γ-aminobutyrylhistidine) is a dipeptide derived from histidine metabolism, and which is exclusively localized in the CNS. A single family with high levels of homocarnosine in the cerebrospinal fluid has been reported so far (Sjaastad et al 1976). Affected siblings presented with progressive childhood-onset spastic paraparesis, mental retardation and retinopathy.

Disorders of complex molecule metabolism

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis is a recessive autosomal disorder due to a defect in the mitochondrial enzyme sterol 27-hydroxylase involved in the synthesis of bile acids from cholesterol. The disease sometimes presents in childhood with nonspecific learning difficulties, juvenile cataracts, epilepsy and eventually chronic diarrhoea. Other signs of the disease typically appear between the 2nd and 4th decades and include tendon xanthomata, progressive spastic paraparesis, cerebellar ataxia, psychiatric signs, cognitive deficit and a sensorimotor demyelinating or axonal polyneuropathy (Verrips et al 2000). Brain MRI typically shows high signal on T2-weighted sequences involving dentate nuclei of the cerebellum, globus pallidus, corticospinal tracts and the periventricular white matter (Barkhof et al 2000). In addition, a spinal form of the disease termed 'spinal xanthomatosis' has been described in seven patients aged between 20 and 35 years who exhibited progressive spastic paraparesis with signs of proprioceptive dysfunction (Verrips et al 1999). All these patients had a history of juvenile cataracts but only one displayed tendon xanthomata. Spinal cord MRI showed a high T2-weighted signal of posterior columns and pyramidal tracts.

Peroxisomal diseases

Adrenoleukodystrophy (ALD) is an X linked recessive disorder due to a defect in the adrenoleukodystrophy protein involved in the peroxisomal transport of very long-chain fatty acids (Moser et al 2007). In adult males, the most frequent phenotype is adrenomyeloneuropathy (AMN), which represents around 40% of all forms of adrenoleukodystrophy. The presentation is that of a progressive spastic paraparesis with mild additional features including proprioceptive signs, signs of bladder dysfunction, and a mild axonal peripheral neuropathy. MRI can show high T2-weighted signal in the pyramidal tracts or more diffuse signal abnormalities (Aubourg et al 1992). After a mean of 10 years, around 20% of patients with AMN will progress into a more severe and rapidly progressing form of the disease called cerebral ALD (Van Geel et al 2001). Furthermore, adrenal insufficiency is present in around 70% of cases. Heterozygous women may remain asymptomatic, but in more than 50% of cases they present signs of mild myelopathy including brisk tendon reflexes or decreased pallaesthesia. In 15% of cases they will develop a truly progressive spastic paraparesis with first symptoms around the fourth decade. Peripheral neuropathy is usually absent in heterozygotes and there is virtually no risk of cerebral involvement or of adrenal insufficiency (Moser et al 2007). Dietary therapy with Lorenzo's oil normalizes the concentration of very long-chain fatty acids. Recent open studies have suggested that it could

Table 1 Diagnosis and treatment of inherited neurometabolic diseases presenting with spastic paraparesis in adults

Diseases	Mode of inheritance	Age at onset (years)[a]	Specific clinical and radiological signs associated with spastic paraparesis	Major biological disturbances	Treatment
Disorders of intermediary metabolism					
MTHFR deficiency	AR	50	Psychiatric troubles, confusion, coma, thromboembolic events, polyneuropathy *MRI*: leukoencephalopathy	Hyperhomocysteinaemia > 100 μmol/L, hypomethioninaemia, low folates	Folinic acid, betaine, vitamin B_{12}, riboflavin
CblC	AR	45	Psychiatric troubles, confusion, combined degeneration of the spinal cord, peripheral neuropathy, optic atrophy, retinitis pigmentosa, glomerular nephritis, thromboembolic events *MRI*: leukoencephalopathy, high signal of spinal pyramidal tracts and posterior columns	Hyperhomocysteinaemia > 100 μmol/L, hypomethioninaemia, methylmalonic aciduria	Hydroxocobalamin, folic acid; betaine
Arginase deficiency	AR	18	Nausea, vomiting, cephalalgia, confusion, triggered by high protein intake or situations of protein catabolism	Hyperargininaemia (hyperammonaemia is inconstant)	Protein restriction
HHH syndrome	AR	18	Episodes of nausea, vomiting, triggered by high protein intake. Cerebellar ataxia, mild mental retardation	Hyperornithinaemia, hyperammoniaemia, homocitrullinuria, orotic aciduria	Protein restriction, consider ornithine, arginine or citrulline supplementation
Biotinidase deficiency	AR	15	Bilateral optic atrophy, motor neuropathy, deafness, alopecia, seborrhoeic dermatitis	High lactate, high urinary 3OH-isovalerate, 3OH-propionate, lactate, 3-methylcrotonyl glycine, low biotinidase activity (erythrocytes)	Biotin
Phenylketonuria	AR	45	Optic atrophy, dementia, leukoencephalopathy, parkinsonism	Hyperphenylalaninaemia, hypotyrosinaemia	Low-phenylalanine diet
Nonketotic hyperglycinaemia	AR	<20	*Acute signs*: paroxysmal movement disorders, confusion, supranuclear gaze palsy *Chronic signs*: mental retardation, behavioural problems, cerebellar ataxia, optic atrophy, motor neuropathy	Hyperglycinaemia, hyperglycinuria, CSF/blood glycine ratio above 0.04	Sodium benzoate, dextromethorphan, ketamine
GTP cyclohydrolase 1 deficiency	AD	<10	Dystonia (may mimic spastic paraparesis), parkinsonism, diurnal fluctuations	Mutations in the *GTPCH1* gene, low biopterins, neopterins, HVA and 5HIAA in CSF	Levodopa, anticholinergic drugs, dopamine agonists

Table 1 (continued)

Diseases	Mode of inheritance	Age at onset (years)[a]	Specific clinical and radiological signs associated with spastic paraparesis	Major biological disturbances	Treatment
Other dopamine synthesis defects	AR	<10	Dystonia, mental retardation, hypersomnolence, pyramidal signs, epilepsy, oculogyric crisis	Low HVA in CSF, other abnormalities depend on the metabolic block	Levodopa, 5 hydroxytryptophan, BH_4 (depending on the metabolic defect)
Cerebral folate deficiency	Sporadic	<10	Generalized dystonia, deafness, cerebellar ataxia, spinal amyotrophy	Low methyltetrahydrofolate in CSF, normal folates in blood	Folinic acid
Homocarnosinosis	?	10	Mental retardation, retinitis pigmentosa	High levels of homocarnosine in CSF	Unknown
Disorders of complex molecule metabolism					
Cerebrotendinous xanthomatosis	AR	>50	Juvenile cataract, xanthomas, cerebellar ataxia, dementia, psychiatric signs, parkinsonism, chronic diarrhoea *MRI*: leukodystrophy involving dentate nuclei	High cholestanol	Chenodeoxycholic acid
Adrenomyeloneuropathy	X linked	>50	Spastic paraparesis, sensory signs, vesical dysfunction, adrenal insufficiency *MRI*: normal or high T2-weighted signal of pyramidal tracts	High plasma very long-chain fatty acids	Lorenzo's oil?
α-Methyl-acyl-CoA racemase deficiency	Any	48	Mental retardation, spastic paraparesis, epilepsy, cataract, retinitis pigmentosa, hypogonadism, diarrhoea	High pristanic acid, high peroxysomal bile acids	Low phytanic acid diet?
Metachromatic leukodystrophy	Any	>50	Psychiatric troubles, pyramidal signs, ataxia *MRI*: supratentorial periventricular leukodystrophy	Low arylsulfatase A in leukocytes, high urinary excretion of sulfatides	None or bone marrow transplantation
Krabbe disease	Any	>50	Spastic paraparesis, ataxia, tongue haemiatrophy, dysarthria *MRI*: posterior leukoencephalopathy with pyramidal tract involvement (may be normal)	Low galactocerebrosidase in leukocytes	None or bone marrow transplantation
Sjögren–Larsson	AR	<20	Ichthyosis, mental retardation, macular dystrophy with retinal white dots, leukodystrophy	Low fatty aldehyde dehydrogenase activity (fibroblasts), mutations in the FALDH gene	Zyleuton
Polyglucosan body disease	Adult	>50	Dementia, upper and lower motor neuron disease, bladder dysfunction, leukodystrophy	Evidence of polyglucosan bodies on axillary skin biopsy	None

AAC, amino acid chromatography (plasma and urines); AR, autosomal recessive; AD, autosomal dominant; MSUD, maple syrup urine diseases; OAC, organic acid chromatography (urine only); OTC, ornithine transcarbamylase deficiency; X, X-linked.

[a] Maximum age at onset of walking problems without treatment, based on the review of literature or of authors' own experience at present time (should be modified in the future).

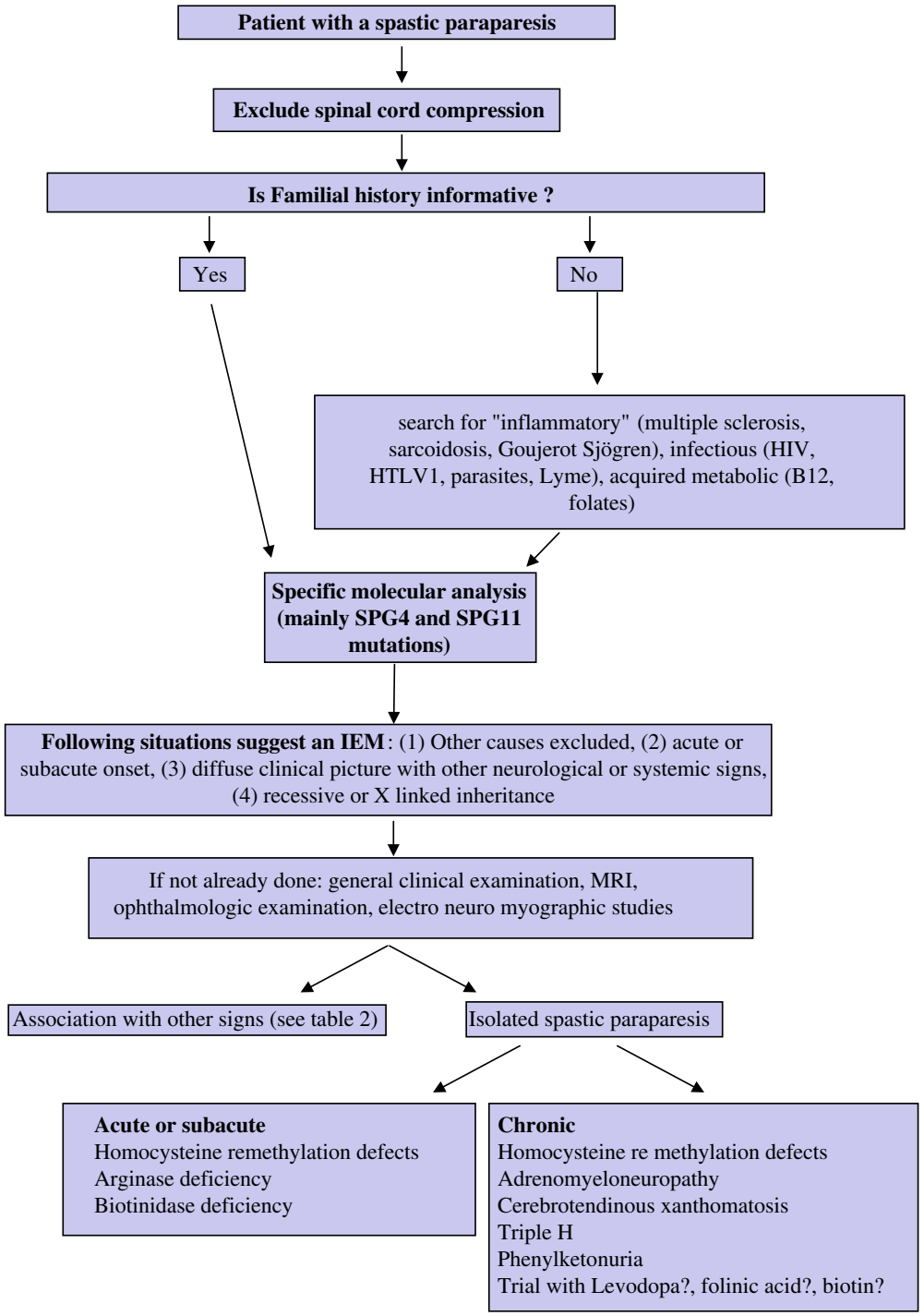

Fig. 1 Diagnostic approach in an adult patient with spastic paraparesis

prevent the occurrence of cerebral lesions in asymptomatic boys, and slow the disease progression in adults with adrenomyeloneuropathy (Moser et al 2007).

α-*Methylacyl-CoA racemase deficiency* results in a failure to metabolize peroxisomal bile acid intermediates and pristanic acid. In their first description of the disease, Ferdinandusse and colleagues (2000) reported the case of a 48-year-old woman with a progressive spastic paraparesis and a demyelinating polyneuropathy on electroneuromyographic studies.

Lysosomal diseases

Krabbe disease is caused by a deficiency in galactocerebrosidase. Accumulation of galactocerebroside and galactosylsphingosine upstream of the metabolic block

is toxic for oligodendrocytes and usually causes a severe leukodystrophy in children. Several patients with an adult-onset form of the disease have been reported (see, for example, Farina et al 2000; Fontaine et al 2003; Henderson et al 2003). In most cases, the clinical picture was a progressive spastic paraparesis, eventually associated with pes cavus, peripheral demyelinating motor neuropathy, decreased proprioceptive sensation, bulbar signs and increased cerebrospinal fluid protein levels. Brain MRI usually showed a characteristic leukoencephalopathy involving pyramidal corticospinal tracts, the splenium of the corpus callosum and the parietal and peritrigonal white matter. In addition, Bajaj and colleagues (2002) reported two siblings with progressive spastic paraparesis and mild sensory signs in the lower limbs but no abnormalities on brain MRI and electroneuromyographic studies.

Metachromatic leukodystrophy is caused by a deficiency in arylsulfatase A which catabolizes sulfatide. Progressive sulfatide storage causes myelin instability and oligodendrocyte toxicity. Adult-onset forms have been estimated to represent 20% of cases (Rauschka et al 2006). These late-onset forms often begin with psychiatric signs that may remain isolated for years. Other signs include spastic paraparesis, cognitive dysfunction, cerebellar ataxia, seizures, optic atrophy and a poorly symptomatic demyelinating peripheral neuropathy (Baumann et al 1991). Rauschka and colleagues (2006) have reported that patients with a P426L mutation in homozygous form displayed predominant spastic paraparesis or cerebellar ataxia at onset, followed by cognitive and psychiatric signs later on. In all cases, brain MRI showed a specific bilateral periventricular leukodystrophy sparing U fibres and predominating in frontal lobes.

Sjögren–Larsson syndrome

Sjögren–Larsson syndrome is caused by deficiency of fatty aldehyde dehydrogenase, involved in the catabolism of fatty aldehydes. This syndrome usually begins in infancy with severe ichthyosis, spastic paraparesis and mental retardation followed by a macular dystrophy with retinal dots and a leukoencephalopathy on brain MRI. However, cutaneous signs can remain isolated for years and spastic paraparesis may appear in adulthood (Willemsem et al 2001a). Zileuton, an inhibitor of leukotriene synthesis, is an effective treatment of the cutaneous symptoms (pruritis) and may be beneficial for the neurological disease (Willemsen et al 2001b).

Polyglucosan body disease

Polyglucosan body disease is defined neuropathologically by the presence of periodic acid–Schiff (PAS)-

Table 2 Subdivision of metabolic causes of spastic paraparesis according to associated signs

Sign	Cause
With episodes of confusion/nausea or vomiting	CblC, MTHFR, triple H, arginase deficiency
With leukoencephalopathy	CTX, CblC, MTHFR deficiency, metachromatic leukodystrophy, Krabbe disease, AMN, polyglucosan body disease, phenylketonuria
With polyneuropathy	CTX, MTHFR deficiency, CblC, Krabbe disease, α-methyl-CoA racemase deficiency, metachromatic leukodystrophy, biotinidase deficiency, AMN, biotinidase deficiency, polyglucosan body disease
With cerebellar ataxia	CTX, HHH syndrome
With visual findings	CblC (retinitis pigmentosa, optic nerve atrophy), CTX (cataract), biotinidase deficiency, phenylketonuria (optic neuropathy), homocarnosinosis, Sjögren–Larsson (retinopathy)
With cutaneous signs	CTX (xanthomas), biotinidase deficiency (alopecia, dermatitis), Sjögren–Larsson (ichthyosis), ALD/AMN (melanoderma)
With psychiatric signs	MTHFR deficiency, CblC, CTX, metachromatic leukodystrophy, ALD
With mental retardation	CblC, MTHFR, triple H, CTX, homocarnosinosis, Salla disease
With dystonia	Dopamine synthesis defects
With visceral signs	CTX (chronic diarrhoea), arginase deficiency, triple H (episodes of nausea, vomiting), adrenal insufficiency (AMN, ALD)

ALD, adrenoleukodystrophy; AMN, adrenomyeloneuropathy; CblC: cobalamin C disease; CDG, congenital defects of glycosylation; CTX, cerebrotendinous xanthomatosis; LCHAD, long-chain hydroxyacyl dehydrogenase deficiency; MTHFR, 5,10-methylenetetrahydrofolate deficiency; PBD, peroxysome biogenesis disorders; PDH, pyruvate dehydrogenase deficiency; RCD, respiratory chain disorders; TF, trifunctional protein deficiency.

positive inclusions containing glycogen in the central and peripheral nervous system. The mode of transmission is usually autosomal recessive and, in certain cases, mutations were found in the gene coding for the glycogen branching enzyme (Sindern et al 2003). The phenotype associates signs of pyramidal degeneration (progressive spastic paraparesis) with signs of lower motor neuron involvement, urinary disturbance, progressive dementia and leukodystrophy on brain MRI. Other signs include parkinsonism and polyneuropathy (Trivedi et al 2003). The diagnosis is based on the demonstration of polyglucosan accumulation on a peripheral nerve or an axillary skin biopsy.

Diagnostic approach to patients with spastic paraparesis

Spastic paraparesis is frequently encountered in adult neurology. After the elimination of common acquired causes and, eventually, genetic causes (see Fig. 1), clinical features suggesting an IEM must be recognized. This is the case when motor weakness appears acutely or subacutely and is associated with signs of a metabolic attack (alteration of consciousness, nausea, vomiting), when clinical signs are triggered by specific situations (surgery) or when there is involvement of multiple neurological functions or organs (for example, leukodystrophy, strokes, tendon xanthomata, ocular involvement, adrenal insufficiency, megaloblastic anaemia; see Table 2).

If spastic paraparesis remains apparently isolated, other clues should be looked for by performing brain MRI, nerve electrodiagnostic studies and ophthalmological examination. Metabolic investigations should then be informed by specific signs (see Table 2).

If spastic paraparesis is indeed pure, the question is still open whether some metabolic investigations should automatically be performed. The decision to make metabolic investigations should be balanced by several considerations: (1) Metabolic investigations are expensive and time consuming. (2) A systematic screening of IEMs in patients with isolated spastic paraparesis will certainly give a very low diagnostic yield. These negative points should be counterbalanced by the facts that (i) some IEMs may manifest as an isolated spastic paraparesis, before the occurrence of more specific symptoms; and (ii) some of the IEMs causing spastic paraparesis are treatable and these treatments are usually more effective if given at an early stage of the disease. Thus, being too restrictive in metabolic investigations would probably miss rare but treatable disorders.

Some disorders begin with an isolated spastic paraparesis and it is important to measure plasma very long-chain fatty acids, and total homocysteine, and make a trial of levodopa in all patients with an unexplained spastic paraparesis. Plasma ammonia, amino acid chromatography and cholestanol are other investigations that lead to the diagnosis of treatable disorders. However, the last are almost always associated with other specific signs (Tables 1 and 2).

References

Aubourg P, Adamsbaum C, Lavallard-Rousseau MC, et al (1992) Brain MRI and electrophysiologic abnormalities in preclinical and clinical adrenomyeloneuropathy. *Neurology* **42**: 85–91.

Bajaj NPS, Waldmann A, Orrell B, Wood NW, Bhatia KP (2002) Familial adult onset of Krabbe's disease resembling hereditary spastic paraplegia with normal neuroimaging. *J Neurol Neurosurg Psychiatry* **72**: 635–638.

Bank WJ, Morrow G 3rd (1972) A familial spinal cord disorder with hyperglycinemia. *Arch Neurol* **27**: 136–144.

Barkhof F, Verrips A, Wesseling P, et al (2000) Cerebrotendinous xanthomatosis: the spectrum of imaging findings and the correlation with neuropathologic findings. *Radiology* **217**: 869–876.

Baumann N, Masson M, Carreau V, Lefevre M, Herschkowitz N, Turpin JC (1991) Adult forms of metachromatic leukodystrophy: clinical and biochemical approach. *Dev Neurosci* **13**: 211–215.

Baykal T, Gokcay G, Gokdemir Y, et al (2005) Asymptomatic adults and older siblings with biotinidase deficiency ascertained by family studies of index cases. *J Inherit Metab Dis* **28**: 903–912.

Cowley DM, Bowling FG, McGill JJ, et al (1998) Adult-onset arginase deficiency. *J Inherit Metab Dis* **21**: 677–678.

Crombez EA, Cederbaum SD (2005) Hyperargininemia due to liver arginase deficiency. *Mol Genet Metab* **84**: 243–251

Depienne C, Tallaksen C, Lephay JY, et al (2006) Spastin mutations are frequent in sporadic spastic paraparesis and their spectrum is different from that observed in familial cases. *J Med Genet* **43**: 259–265.

Dinopoulos A, Matsubara Y, Kure S (2005) Atypical variants of non-ketotic hyperglycinemia. *Mol Genet Metab* **86**: 61–69.

Farina L, Bizzi A, Finocchiaro G, et al (2000) MR imaging and proton MR spectroscopy in adult Krabbe disease. *Am J Neuroradiol* **21**: 1478–1482.

Ferdinandusse S, Denis S, Clayton PT, et al (2000) Mutations in the gene encoding peroxisomal alpha-methylacyl-CoA racemase cause adult-onset sensory motor neuropathy. *Nat Genet* **24**: 188–191.

Fink JK (2003) The hereditary spastic paraplegias: nine genes and counting. *Arch Neurol* **60**: 1045–1049.

Fontaine B, Thenin JP, Viader F (2003) Gait disorders with insidious progression in a 60-year old woman. *Rev Neurol (Paris)* **159**: 695–699.

Freeman JM, Finkelstein JD, Mudd SH (1975) Folate-responsive homocystinuria and "schizophrenia". A defect in methylation due to deficient 5,10-methylenetetrahydrofolate reductase activity. *N Engl J Med* **292**: 491–496.

Friedman J, Hyland K, Blau N, MacCollin M (2006) Dopa-responsive hypersomnia and mixed movement disorder due to sepiapterin reductase deficiency. *Neurology* **67**: 2032–2035.

Furukawa Y, Graf WD, Wong H, et al (2001) Dopa-responsive dystonia simulating spastic paraplegia due to tyrosine hydroxylase (TH) gene mutations. *Neurology* **56**: 260–263.

Hansen FJ, Blau N (2005) Cerebral folate deficiency: life-changing supplementation with folinic acid. *Mol Genet Metab* **84**: 371–373.

Haworth JC, Dilling LA, Surtees RA, et al (1993) Symptomatic and asymptomatic methylenetetrahydrofolate reductase deficiency in two adult brothers. *Am J Med Genet* **45**: 572–576.

Henderson RD, MacMillan JC, Bradfield JM (2003) Adult onset Krabbe disease may mimic motor neurone disease. *J Clin Neurosci* **10**: 638–639.

Kasim S, Moo LR, Zschocke J, Jinnah HA (2001) Phenylketonuria presenting in adulthood as progressive spastic paraparesis with dementia. *J Neurol Neurosurg Psychiatry* **71**: 795–797.

Kong CK, Ko SF, Tong, Lam CV (2001) Atypical presentation of dopa-responsive dystonia: generalized hypotonia and proximal weakness. *Neurology* **57**: 1121–1124.

McCombe PA, McLaughlin DB, Chalk JB, Brown NN, McGill JJ, Pender MP (1992) Spasticity and white matter abnormalities in adult phenylketonuria. *J Neurol Neurosurg Psychiatry* **55**: 359–361.

Miyamoto T, Kanazawa N, Hayakawa C, Tsujino S (2002) A novel mutation, P126R, in a Japanese patient with HHH syndrome. *Pediatr Neurol* **26**: 65–67.

Moser HW, Mahmood A, Raymond GV (2007) X-linked adrenoleukodystrophy. *Nat Clin Pract Neurol* **3**: 140–151.

Nygaard TG, Trugman JM, de Yebenes JG, Fahn S (1990). Dopa-responsive dystonia: the spectrum of clinical manifestations in a large North American family. *Neurology* **40**: 66–69.

Ogier de Baulny H, Gerard M, Saudubray JM, Zittoun J (1998) Remethylation defects: guidelines for clinical diagnosis and treatment. *Eur J Pediatr* **157**(Supplement **2**): S77–83.

Patel K, Roskrow T, Davis JS, Heckmatt JZ (1995) Dopa responsive dystonia. *Arch Dis Child* **73**: 256–257.

Pogson D (1997) Issues for consideration in dihydropteridine reductase (DHPR) deficiency: a variant form of hyperphenylalaninaemia. *J Intellect Disabil Res* **41**: 208–214.

Powers JM, Rosenblatt DS, Schmidt RE, et al (2001) Neurological and neuropathologic heterogeneity in two brothers with cobalamin C deficiency. *Ann Neurol* **49**: 396–400.

Ramaekers VT, Blau N (2004) Cerebral folate deficiency. *Dev Med Child Neurol* **46**: 843–851.

Ramaekers VT, Brab M, Rau G, Heimann G (1993) Recovery from neurological deficits following biotin treatment in a biotinidase K_m variant. *Neuropediatrics* **24**: 98–102.

Ramaekers VT, Rothenberg SP, Sequeira JM, et al (2005) Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med* **352**: 1985–1991.

Rauschka H, Colsch B, Baumann N, et al (2006) Late-onset metachromatic leukodystrophy: genotype strongly influences phenotype. *Neurology* **67**: 859–863.

Roze E, Gervais D, Demeret S, et al (2003) Neuropsychiatric disturbances in presumed late-onset cobalamin C disease. *Arch Neurol* **60**: 1457–1462.

Rosenblatt D, Fenton WA (2001) Inherited disorders of folate and cobalamin transport and metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds; Childs B, Kinzler KW, Vogelstein B, assoc, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 3897–3933.

Salvi FM, Santorelli E, Bertini R, et al (2001) Clinical and molecular findings in hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. *Neurology* **57**: 911–914.

Saudubray JM, Sedel F, Walter JH (2006) Clinical approach to treatable inborn metabolic diseases: an introduction. *J Inherit Metab Dis* **29**: 261–274.

Schiller A, Wevers RA, Steenbergen GC, et al (2004) Long-term course of L-dopa-responsive dystonia caused by tyrosine hydroxylase deficiency. *Neurology* **63**: 1524–1526.

Sedel F, Lyon-Caen O, Saudubray JM (2007) Inborn errors of metabolism in adult neurology—a clinical approach focused on treatable diseases. *Nat Clin Pract Neurol* **3**: 279–290.

Segawa M, Nomura Y, Nishiyama N (2003) Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). *Ann Neurol* **54**(Supplement **6**): S32–45.

Sindern E, Ziemssen F, Ziemssen T, et al (2003) Adult polyglucosan body disease: a postmortem correlation study. *Neurology* **61**: 263–265.

Sjaastad O, Berstad J, Gjesdahl P, Gjessing L (1976) Homocarnosinosis. 2. A familial metabolic disorder associated with spastic paraplegia, progressive mental deficiency, and retinal pigmentation. *Acta Neurol Scand* **53**: 275–290.

Steiman GS, Yudkoff M, Berman PH, Blazer-Yost B, Segal S (1979) Late-onset nonketotic hyperglycinemia and spinocerebellar degeneration. *J Pediatr*. **94**: 907–911.

Stevanin G, Santorelli FM, Azzedine H, et al (2007) Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. *Nat Genet* **39**: 366–372.

Surtees R (1998) Demyelination and inborn errors of the single carbon transfer pathway. *Eur J Pediatr* **157**: S118–S121.

Tanaka K, Yoneda M, Nakajima T, Miyatake T, Owada M (1987) Dihydrobiopterin synthesis defect: an adult with diurnal fluctuation of symptoms. *Neurology* **37**: 519–522.

Tokatli A, Coskun T, Ozalp I (1997) Biotinidase deficiency with neurological features resembling multiple sclerosis. *J Inherit Metab Dis* **20**: 707–708.

Trivedi JR, Wolfe GI, Nations SP, et al (2003) Adult polyglucosan body disease associated with lewy bodies and tremor. *Arch Neurol* **60**: 764–766.

Van Geel BM, Bezman L, Loes DJ, Moser HW, Raymond GV (2001) Evolution of phenotypes in adult male patients with X-linked adrenoleukodystrophy. *Ann Neurol* **49**: 186–194.

Verrips A, Nijeholt GJ, Barkhof F, et al (1999) Spinal xanthomatosis: a variant of cerebrotendinous xanthomatosis. *Brain* **122**(Pt 8): 1589–1595.

Verrips A, Hoefsloot LH, Steenbergen GC, et al (2000) Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. *Brain* **123**: 908–919.

Visy JM, Le Coz P, Chadefaux B (1991) Homocystinuria due to 5,10-methylenetetrahydrofolate reductase deficiency revealed by stroke in adult siblings. *Neurology* **41**: 1313–1315.

Weglage J, Oberwittler C, Marquardt T (2000) Neurological deterioration in adult phenylketonuria. *J Inherit Metab Dis* **23**: 83–84.

Willemsen MA, IJlst L, Steijlen PM, et al (2001a) Clinical, biochemical and molecular genetic characteristics of 19 patients with the Sjogren–Larsson syndrome. *Brain* **124**: 1426–1437.

Willemsen MA, Lutt MA, Steijlen PM, et al (2001b) Clinical and biochemical effects of zileuton in patients with the Sjogren–Larsson syndrome. *Eur J Pediatr* **160**: 711–717.

Wolf B, Pomponio RJ, Norrgard KJ (1998) Delayed-onset profound biotinidase deficiency. *J Pediatr* **132**: 362–365.