NEUROLOGICAL INVESTIGATIONS

Diagnosis of inherited metabolic disorders affecting the nervous system

Phillip D Swanson

The number of metabolic disorders that can produce neurological symptoms is daunting. The clinician cannot simply send off to the laboratory a blood sample and ask for a metabolic "screen" that will detect a hypothetical metabolic abnormality. The range of possible conditions must be narrowed to the most likely before deciding which investigative approach should be taken. Most biochemical disorders encountered by neurologists are genetically determined. Thus one of the most important elements of the history is the family history. It is not sufficient to ask "has anyone in your family had a neurological problem?". The clinician must be aware of the different forms of inheritance patterns (autosomal dominant, autosomal recessive, X linked, mitochondrial) and must obtain enough information to construct a meaningful family tree. Directed questions must be asked about siblings as well as parents, grandparents, uncles, aunts, cousins, and children. Table 1 lists features that characterise single gene inheritance patterns.1,3

Most of the clear cut genetic diseases are due to single gene abnormalities. There are several different mechanisms, however, that produce abnormal genes. A point mutation of a single DNA nucleotide can result in a different amino acid being coded for in the resulting polypeptide or protein. There can be deletion of a segment of a gene or insertion of one or more nucleotides. Duplication of a gene has been reported in Charcot-Marie-Tooth disease type 1A. Unstable expansions of portions of a gene (trinucleotide repeats) are being increasingly found in autosomal dominant neurodegenerative diseases. The pace of new discoveries in medical genetics is incredibly rapid. Many of the new discoveries have led to diagnostic methods that were unanticipated only a few years ago.

Certain terms used by medical geneticists should be familiar to neurological practitioners. Anticipation refers to a disease beginning earlier and often being more severe in succeeding generations. In some autosomal dominant disorders, such as myotonic dystrophy and spinocerebellar ataxia 1, this phenomenon seems to be related to the length of an expanded trinucleotide repeat in the abnormal gene.4 Penetration refers to the proportion of subjects with the abnormal gene who will develop symptoms if they live long enough. The degree of expression of a genetic disease refers to the variation of severity of the phenotype that is seen in a patient population. Mosaicism refers to variation among different cells and tissues in the chromosome complement. This occurs normally in women due to lyonisation, in which one of each cell's two X chromosomes is randomly inactivated. Mitochondrial disorders (see later) are associated with heteroplasmasy, a term that refers to variation in the proportion of normal or genetically abnormal mitochondria in different tissues.

In autosomal dominant disorders, multiple generations are usually affected, although this might not have occurred if the affected patient represents a new mutation. Male to male transmission only occurs with autosomal dominant transmission. Each child of an affected parent will have a 50% chance of having or not having the abnormal gene. Autosomal recessive disorders occur when expression of the disease requires the abnormal gene to be inherited from both parents, so that the affected person's cells have two abnormal alleles. Many autosomal recessive disorders are associated with defective enzymes. The low level of enzyme activity often leads to accumulation of the enzyme substrate with resultant toxicity to susceptible cells. The carrier parents seldom manifest symptoms because the normal gene codes for normal enzyme that is active enough to prevent substrate accumulation. Consanguineous marriages between cousins are more common in families with autosomal recessive diseases.

<table>
<thead>
<tr>
<th>Table 1 Some characteristics of single gene inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of inheritance</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Autosomal dominant</td>
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<tr>
<td>Autosomal recessive</td>
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<tr>
<td></td>
</tr>
<tr>
<td>X Linked</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Mitochondrial</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Adapted from table 9-1.1

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P D Swanson
Diagnosis of inherited metabolic disorders affecting the nervous system

*X Linked* disorders are due to abnormal genes located on the X chromosome. Clinical disease characteristically occurs in males who have inherited the abnormal gene from a carrier mother. Occasionally the mother or daughter with one normal and one abnormal gene will manifest symptoms, which almost always are milder than in the affected son or father, who has only one X chromosome. Male to male transmission cannot occur because a son receives the X chromosome from his mother.

Mitochondrial disorders are due to abnormalities in genes (deletions, point mutations) located in mitochondrial DNA. Both male and female mitochondria are derived from the ovum rather than the sperm. Both males and females can be affected by mitochondrial disorders, but father to child transmission does not occur. Because tissues and cells vary in the proportion of normal and abnormal mitochondria they carry (heteroplasmy), the expression of the disorder in different tissues and in different subjects can be extremely variable.

This contribution will not include much discussion of diseases that primarily affect muscle or nerve, as these have been the subjects of previous articles in this series. Some metabolic conditions, however, including metachromatic leukodystrophy and certain mitochondrial disorders that affect both central and peripheral structures, will be included. Non-genetic metabolic conditions such as hypoglycaemia, hepatic encephalopathy, deficiency diseases, and electrolyte disorders will not be discussed. Emphasis will be on conditions that are seen in adults by neurologists but many of these disorders will be variants of diseases that usually have their first manifestations in infancy or childhood. The first section contains brief discussions of categories of metabolic disease likely to be encountered by neurologists. The second section contains a discussion of differential diagnoses of metabolic conditions that might produce particular complexes of neurological symptoms, including mental retardation, dementia, ataxias, motor neuron disease, movement disorders, and stroke.

### Categories of metabolic disorders

**Aminoacidurias and organic acidemia**s

These are the classic disorders of infancy and childhood associated with mental retardation and seizures. The *aminoacidurias* include phenylketonuria, maple syrup urine disease, homocystinuria, and other disorders listed in table 2. Screening the urine for amino acids is routinely done in clinical chemistry laboratories. Although it would be very unusual for first symptoms to occur in adult life, patients with treated phenylketonuria eventually will be seen as adults by neurologists.

**Organic acidemias,** including methylmalonic acidemia and propionic acidemia, usually have their onset in infancy. Symptoms of dehydration are associated with ketoacidosis, hypoglycaemia, and hyperammonaemia. Diagnosis is made by urinalysis for organic acids, and can be confirmed by measuring activity of the abnormal enzyme in cultured fibroblasts.

These disorders are becoming better understood since the advent of modern molecular investigative techniques. For example, it is now known that there are three genes located on three different chromosomes (1, 6, 19) that code for the structural proteins unique to the deficient enzyme (branched chain ketoacid dehydrogenase complex [BCKAD]) in maple syrup urine disease. Mutations in different components of the complex can lead to variable clinical manifestations.  

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical features</th>
<th>Increased substances</th>
<th>Enzyme defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>Mental retardation</td>
<td>Phenylalanine, Phenylpyruvic acid</td>
<td>Phenylalanine hydroxylase</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>Ketonuria, infantile seizures</td>
<td>Branched chain aminoacids (leucine, isoleucine, valine)</td>
<td>Branched chain ketoacid dehydrogenase complex</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Ectopia lentis, stroke</td>
<td>Homocystine</td>
<td>Cystathionine β-Synthase</td>
</tr>
<tr>
<td>Non-ketotic hyperglycinemia</td>
<td>Coma, progressive encephalopathy</td>
<td>Glycine</td>
<td>Glycine clearance system (4 proteins)</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>Ketonuria</td>
<td>Methylmalonic acid</td>
<td>Methyl-malonyl CoA murase</td>
</tr>
<tr>
<td>Propionic acidemia</td>
<td>Ketonuria</td>
<td>3-hydroxypropionic acid</td>
<td>Propionyl CoA carboxylase</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>Ketonuria</td>
<td>Isovaleric acid</td>
<td>Isovaleryl CoA dehydrogenase</td>
</tr>
<tr>
<td>Glutaric acidemia Type 1</td>
<td>Progressive encephalopathy</td>
<td>Glutaric, 3-hydroxyglutaric acids</td>
<td>Glutaric CoA dehydrogenase</td>
</tr>
<tr>
<td>Glutaric acidemia Type 2</td>
<td>Spasticity, choreoathetosis</td>
<td>Glutaric acid</td>
<td>Electron transfer flavoprotein (ETF) and ETF ubiquinone oxidoreductase</td>
</tr>
<tr>
<td>γ-Hydroxybutyric aciduria</td>
<td>Mental retardation, seizures</td>
<td>γ-Hydroxybutyric acid</td>
<td>Succinic semialdehyde dehydrogenase</td>
</tr>
</tbody>
</table>
LYSOSOMAL DISORDERS

The term lysosome was proposed by DeDuve et al in 1955 for intracellular granules that were rich in hydrolytic enzymes. A lysosomal disease is associated with an abnormally enzyme that results in defective breakdown of the storage substrate. The product accumulates and eventually alters cell function. Because hydrolytic enzymes are present in many tissues, the diagnosis of the accumulated product or of the enzyme deficiency usually can be made with readily accessible tissues such as peripheral white blood cells or skin fibroblasts. Although most of these disorders produce symptoms at a young age, some mutations, as in adult onset GM1 gangliosidosis, lead to onset of symptoms later in life.

Lysosomal disorders can be subcategorised according to the type of accumulated storage product. The two principal groups are lipid storage diseases and mucopolysaccharidoses. As these conditions have been more fully characterised, it has become clear that a great deal of heterogeneity exists among them, in many cases due to different point mutations in the gene. Thus these disorders should be considered in the differential diagnosis of atypical degenerative disorders.

Lipid storage diseases

Table 3 lists the lipid storage diseases that cause neurological dysfunction. These disorders are diagnosed either by finding high concentrations of substrate in tissues or by showing pronounced reduction in concentrations of the lysosomal enzyme responsible for degrading the accumulated storage substance.

In each disorder, subtypes have been delineated. In Gaucher’s disease, associated with accumulation of glucocerebrosides, and in Niemann-Pick disease, with sphingomyelin accumulation, hepatosplenomegaly is prominent in all types; however, only types 2 and 3 Gaucher’s disease and types A and C Niemann-Pick disease are associated with neurological deterioration. Globoid leukodystrophy (Krabbe’s disease), metachromatic leukodystrophy (MLD) and Tay-Sachs disease are inherited as autosomal recessive disorders and can be diagnosed by measurement of enzyme concentrations in peripheral white blood cells or cultured skin fibroblasts. Clinical variants are found in each disorder. In MLD some mutations in the arylsulphatase A gene on chromosome 22 have been correlated with different phenotypes. Similarly, in Tay-Sachs disease over 20 mutations including nucleotide insertions, deletions, and substitutions on the α subunit (chromosome 15) and the β subunit (chromosome 5) of the hexosaminidase enzyme have been described. Late onset cases may develop weakness, fasciculations, ataxia, and psychiatric symptoms.

GM1 gangliosidosis, due to deficiency of the lysosomal enzyme β-galactosidase, can produce symptoms in infancy, childhood, or adult life. At least 16 mutations have been identified in the β-galactosidase gene. Severity of the diseases can be correlated with the amount of residual enzyme activity, the infantile form having no demonstrable activity and the adult forms having 4–8% of normal activity. Leinekugel et al found that 10–15% of β-hexosaminidase A and arylsulphatase A activities were sufficient to degrade substrate.

The adult form of the disorder is slowly progressive and may produce gait disorders, involuntary choreoathetoid movements, bradykinesia, or dementia. Storage of GM1 ganglioside can be much more pronounced in the striatum than in other parts of the brain by comparison with younger onset patients, in whom storage is more widespread.

Diagnosis is confirmed by finding much reduced lysosomal acid β-galactosidase activity in leucocytes. Single base mutations can be found on the β-galactosidase gene. The 5' isoleucine (ATC) → threonine (ACC) mutation in the gene is common in Japanese adult onset GM1 gangliosidosis.

Mucopolysaccharidoses

These lysosomal disorders are associated with accumulation of complex glycosaminoglycans (mucopolysaccharides), due to genetic defects resulting in deficiencies of degradative enzymes. The stored substances include dermatan sulphate, hepan sulphate, keratan sulphate, and chondroitin 4/6 sulphates, which are detectable in the urine. Of the 12 described disorders all are autosomal recessive

<table>
<thead>
<tr>
<th>Disease</th>
<th>Neurological symptom</th>
<th>Major lipid accumulated</th>
<th>Enzyme defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher’s</td>
<td>Hepatosplenomegaly, neurological deterioration</td>
<td>Glucocerebrosides</td>
<td>Glucocerebroside-β-glucosidase</td>
</tr>
<tr>
<td></td>
<td>in type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niemann-Pick</td>
<td>Hepatosplenomegaly, psychomotor deterioration</td>
<td>Sphingomyelin</td>
<td>Sphingomyelin enzyme A</td>
</tr>
<tr>
<td></td>
<td>in types A and C</td>
<td></td>
<td>(type C)</td>
</tr>
<tr>
<td>Globoid</td>
<td>Progressive encephalopathy, seizures, spasticity</td>
<td>Galactocerebrosides</td>
<td>Galactocerebroside β-Galactosidase</td>
</tr>
<tr>
<td>leukodystrophy(Krabbe’s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Progressive encephalopathy, neuropathy, ataxia, spasticity</td>
<td>Sulphatide</td>
<td>Arylsulphatase A</td>
</tr>
<tr>
<td>Fabry</td>
<td>Pain, rare strokes, X linked, renal insufficiency, skin lesions</td>
<td>Ceramide trihexoside</td>
<td>Ceramide trihexoside α-Galactosidase</td>
</tr>
<tr>
<td>Tay-Sachs</td>
<td>Progressive encephalopathy</td>
<td>GM1, ganglioside</td>
<td>Hexosaminidase A</td>
</tr>
<tr>
<td>Tay-Sachs variant</td>
<td>More rapid progression</td>
<td>Glucosylase and GM3</td>
<td>Hexosaminidase A and B</td>
</tr>
<tr>
<td>GM1, gangliosidosis</td>
<td>Dementia, progressive ataxia, choreoathetosis</td>
<td>GM3, ganglioside</td>
<td>β-Galactosidase 16 point mutations</td>
</tr>
</tbody>
</table>

Table 3 Common lipid storage diseases
except for Hunter syndrome which is X linked recessive. Among these conditions are Hurler's, Scheie's, Sanfilippo, Morquio's, and Maroteaux-Lamy diseases, and $\beta$-glucuronidase deficiency. Clinical signs such as coarse facial features, corneal clouding, hearing difficulties, hepatosplenomegaly, or joint abnormalities are usually detected during the first year of life. Later, developmental delay or mental regression may become apparent.

PEROXISOMAL DISORDERS

The peroxisome is an organelle that is found in most tissues. It contains over 40 enzymes including oxidases and catalase. Moser et al list 11 disorders attributable to defects in peroxisomal enzymes.22-25 These include disorders of peroxisome biogenesis (Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum's syndrome, and hyperpipelicolic acidemia). The first two of these disorders can be associated with neonatal seizures, hypotonia, and developmental delay.

Of the disorders associated with peroxisomal enzyme abnormalities, X linked adrenoleukodystrophy is the most likely to be seen by neurologists.

Adrenoleukodystrophy and adrenomyeloneuropathy are X linked disorders and are associated with raised blood concentrations of very long chain fatty acids (VLCFAs) due to impaired peroxisomal $\beta$-oxidation. The genetic defect seems to result from deletions in the peroxisomal membrane protein gene.26 Some different phenotypes occur.22-26 Neurologists are most likely to encounter an adult patient with adrenomyeloneuropathy, with slowly progressive paraparesis as the main neurological manifestation and adrenocortical failure as a common occurrence. Adult onset cerebral adrenoleukodystrophy is manifested by dementia, confusional states, and sometimes progressive ataxia or psychiatric disturbances.27 Symptom progression is usually slower in patients with adult onset.

Assays for VLCFAs (C24:0, C26:0) are carried out in specialised lipid laboratories using gas liquid chromatography or mass spectrometry. Although the vast majority of patients have raised plasma concentrations of these fatty acids, an occasional family will have VLCFA concentrations within the usual "normal" range.28 Molecular genetic analysis now makes it possible to detect point mutations within the adrenoleukodystrophy gene.29

MITOCHONDRIAL ENCEPHALOPATHIES

A high index of suspicion is aroused for the presence of a disorder involving an abnormal mitochondrial gene if there are clinical features of Leigh's disease (subacute necrotising encephalomyelopathy), Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinal pigmentary degeneration, and other symptoms), MELAS (mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes), MERRF (myoclonic epilepsy with ragged red fibres), Leber's hereditary optic neuropathies, or NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa).30-36 Various other features have been seen including short stature, deafness, diabetes mellitus, peptic ulceration, severe constipation, and migraine.

Mutations in mitochondrial DNA have been discovered in patients with several clinical presentations. Deletions of mitochondrial DNA are common in Kearns-Sayre syndrome.2 In MELAS, point mutations include an A $\rightarrow$ G mutation at nt3243 in 80% of cases, as well as T $\rightarrow$ C mutations at nt3271 and at nt9957, and an A $\rightarrow$ G mutation at nt11084. An A $\rightarrow$ G nt5344 mutation has been found in MERRF, and a T $\rightarrow$ G or T $\rightarrow$ C mutation at nt8993 in Leigh's syndrome.37 38

Diagnostic laboratory tests include: (a) serum pyruvate and lactate concentrations; (b) muscle biopsy to assess for the presence of ragged red fibres, and as a source of mitochondrial DNA analysis; and (c) molecular genetic studies on blood or muscle in a specialised laboratory to assess for known mutations.

DISORDERs ASSOCIATED WITH EXPANDED TRINUCLEOTIDE REPEATS

One of the most exciting developments in neurology has been the discovery of neurogenetic diseases in which the abnormal gene mutation results in expansion of a repeated sequence of trinucleotides. Table 4 lists many

Table 4  Disorders associated with unstable expanded trinucleotide repeats

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Chromosome</th>
<th>Extended trinucleotide</th>
<th>Normal</th>
<th>Disease</th>
<th>Translation of repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X syndrome (FRX1)</td>
<td>X</td>
<td>CGG</td>
<td>6-25</td>
<td>Premutation: 52-200</td>
<td>No</td>
</tr>
<tr>
<td>Fragile X E (FRXE)</td>
<td>X</td>
<td>GCC</td>
<td>6-25</td>
<td>Disease: 200 $\rightarrow$ 1000</td>
<td>No</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>19q</td>
<td>CTG</td>
<td>30</td>
<td>Premutation: 42-180</td>
<td>No</td>
</tr>
<tr>
<td>Bulbar spinocerebellar atrophy (Kennedy's syndrome)</td>
<td>Xq11-12</td>
<td>CAG</td>
<td>17-26</td>
<td>Disease: 40-52</td>
<td>Yes</td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>4p16.3</td>
<td>CAG</td>
<td>11-34</td>
<td>37-121</td>
<td>Yes</td>
</tr>
<tr>
<td>Autosomal dominant spinocerebellar ataxias</td>
<td>6p22-23</td>
<td>CAG</td>
<td>19-36</td>
<td>42-81</td>
<td>Yes</td>
</tr>
<tr>
<td>Spinoocerebellar ataxia 1</td>
<td>14q32.1</td>
<td>CAG</td>
<td>13-36</td>
<td>68-79</td>
<td>Yes</td>
</tr>
<tr>
<td>Machado-Joseph disease</td>
<td>12p12-ter</td>
<td>CAG</td>
<td>7-23</td>
<td>49-75</td>
<td>Yes</td>
</tr>
</tbody>
</table>
of the presently known disorders of this type.\textsuperscript{36-54} They are either X linked or autosomal dominant disorders and include the dominant spinocerebellar ataxias SCA1 and Machado-Joseph disease; \textit{C} Huntington's disease, \textit{C} fragile X syndrome, myotonic dystrophy, and spinal bulbar muscular atrophy (Kennedy's syndrome). In many of these disorders, the length of the expanded trinucleotide repeat is unstable. Succeeding generations have expansions of greater length which may be associated with earlier onset and more severe disease manifestations. It is likely that additional neurodegenerative disorders will be added to this list.\textsuperscript{55}

Genetics laboratories have the capability of definitively diagnosing the presence or absence of some of these disorders on a single sample of blood, using molecular genetic techniques. Commercial availability is limited at this time.

\section*{Disorders of copper metabolism}

Two diagnosable genetic disorders are associated with defects in copper metabolism: Menkes' disease and Wilson's disease.

Menkes' "kinky hair" (steely hair) disease is an X linked disorder with manifestations in early infancy.\textsuperscript{55} Infants feed poorly, become hypothermic, gain weight slowly, develop seizures, and show progressive neurological deterioration. They have colourless, friable hair which has a characteristic microscopic appearance. Danks \textit{et al} suggested that the disease was due to a disorder of copper metabolism.\textsuperscript{55} The gene has been isolated and is a copper transporting ATPase. Until recently, diagnosis if suspected clinically was established by demonstrating low ceruloplasmin and serum copper concentrations and abnormalities in fibroblast copper uptake.\textsuperscript{54,55} In the newborn, however, copper and ceruloplasmin are normally low, so reliable detection of abnormally low concentrations cannot be made until the third or fourth week of life. The diagnosis can be made by DNA analysis.\textsuperscript{56}

Wilson's disease is an autosomal recessive disorder due to an abnormal gene at q14.3 on chromosome 13. This gene codes for a copper transporting P-type ATPase that is presumably important for hepatic incorporation of copper into ceruloplasmin and for excretion of copper into bile.\textsuperscript{57-59} The enzyme is also expressed in the kidney. Twenty-five mutations have been identified in the Wilson's disease gene, accounting for the great variability in clinical symptomatology.\textsuperscript{60} The pathogenetic role of reduced synthesis or impaired function of the copper transporting protein ceruloplasmin is not clear.\textsuperscript{59} In the course of Wilson's disease, increased storage of copper occurs in liver, brain, cornea (Kayser-Fleischer ring in Descemet's membrane), and kidneys. Neurological and psychiatric symptoms can occur secondary to deposition of copper in the brain or as a result of hepatic encephalopathy due to copper induced liver damage. The diagnosis can and should be made before the onset of symptoms in close relatives of affected patients.\textsuperscript{62-64} The diagnosis can be made with the assistance of the following laboratory findings.\textsuperscript{63} (a) increased excretion of copper into the urine (normal <30 \(\mu g/24\) h); (b) decreased serum concentration of total copper (normal 85–145 \(\mu g/dl\)); (c) decreased serum concentration of ceruloplasmin (normal range 25–45 mg/dl); about 5% of cases will have normal ceruloplasmin concentrations.\textsuperscript{65}

\section*{Symptomatic approach to the diagnosis of inherited metabolic disorders}

\subsection*{Mental retardation or deterioration}

\textbf{Fragile X syndrome}

Over 100 \(X\) linked mental retardation syndromes are known at the present time.\textsuperscript{66} Of these, fragile \(X\) syndrome is the leading genetic cause of mental retardation.\textsuperscript{67} The syndrome is so named because of the instability of the \(X\) chromosome when incubated in folic acid deficient media.\textsuperscript{68,69} This was the first neurological disorder to be associated with an unstable trinucleotide repeat sequence.\textsuperscript{70,71} Clinically, patients may have prominent ears, large testicles, high arched palates, and behavioural deficits. Definitive diagnosis can be made by the demonstration of an expanded trinucleotide CGG repeat sequence. Abnormality in the FMR1 gene results in lack of production of the FMR1 protein.

Diagnosis of mental deterioration or progressive encephalopathy in infants may require various metabolic tests if the suspected diagnosis is not already obvious.\textsuperscript{72} A metabolic screen of the urine carried out by a hospital laboratory usually includes a nitroprusside-cyanide test, a ferric chloride test, tests for ketoacids and mucopolysaccharides, and two dimensional amino acid chromatography. Serum analyses for amino acids and organic acids will usually be diagnostic for aminoacidurias and organic acidemias. Studies to search for other disorders mentioned (Menkes' disease, lipid storage diseases) will require special testing by genetics laboratories.

\subsection*{Juvenile or adult patients presenting with dementia}

Laboratory investigations are of limited usefulness in dementia diagnosis. The most common dementing illnesses such as Alzheimer's disease are not yet diagnosable biochemically on a routine basis. In a few families with familial Alzheimer's disease, point mutations have been found in the gene on chromosome 21 that codes for the amyloid precursor protein (APP) gene.\textsuperscript{73,74} Most families, however, do not have these mutations. In young onset families, linkage analysis has located the gene defect to a locus on chromosome 14.\textsuperscript{75} Ultimately it may be possible to diagnose the disorder by molecular genetic techniques. At present, diagnosis of the rare APP mutation can be carried out only by specialised research laboratories studying this disorder.
In some patients with progressive cognitive impairment, a high degree of suspicion based on clinical or radiological clues may justify carrying out further metabolic studies to confirm a suspected diagnosis (table 5). Vitamin B-12 deficiency rarely produces dementia alone but should be excluded.

**Huntington’s disease**
The diagnosis of Huntington’s disease can now be confirmed by commercially available DNA testing. The presence of an extended CAG repeat in the Huntington’s disease gene on chromosome 4 establishes the diagnosis. A normal allele has less than 35 CAG repeats. The Huntington’s disease gene has more than 38 repeats in 98–99% of cases.78

**Leukodystrophies**
In addition to multiple sclerosis and progressive multifocal leukoencephalopathy, cerebral white matter can be affected by several metabolic disorders, with dementia as a major symptom. These include adult onset metachromatic leukodystrophy (MLD), adrenoleukodystrophy, Pelizaeus-Merzbacher disease, Krabbe’s disease, and cerebrotendinous xanthomatosis (CTX). In each disorder, symptoms are progressive, usually over months to years. Inherited in an autosomal recessive manner, MLD would likely be associated with clinical or EMG/nerve conduction velocity evidence of a peripheral neuropathy. Adrenoleukodystrophy might be associated with adrenal insufficiency and, as it is an X linked disorder, would occur predominantly in males. Patients with cerebrotendinous xanthomatosis usually develop prominent xanthomas in large tendons such as the Achilles tendon.

**Adrenoleukodystrophy**—This disorder is characterised by varying modes of onset at different ages. Most affected people are male, as the disorder is X linked. Some heterozygous women may, however, develop spastic paraparesis.79 The phenotypes delineated by Moser et al are: childhood cerebral (48%), adolescent cerebral (5%), adult cerebral (3%), adrenomyeloneuropathy (25%), adrenoleukodystrophy (10%), asymptomatic (8%).80 The disorder is suspected in children with learning disorders and dementia. Adrenomyeloneuropathy usually begins with progressive paraparesis.

**Pelizaeus-Merzbacher disease**—This disorder is X linked. Symptoms usually begin in infancy or childhood, but onset in early adulthood has been reported.77 Symptoms include psychomotor delay and later, dementia, dystagmus, ataxia, spasticity, and involuntary movements. Mutations in the gene coding for proteolipid protein result in defective myelin. Mutations in the proteolipid protein gene can now be determined in genetics laboratories.78,79 Prenatal diagnosis is also possible.80

**Canavan’s disease**—Another rare leukodystrophy is Canavan’s disease, characterised by infantile and juvenile forms with severe progressive neurological deterioration. Raised urinary N-acetylaspartic acid and deficiency of the enzyme aspartoacylase in skin fibroblasts confirm the diagnosis.81

**Lipid storage diseases**
Metachromatic leukodystrophy (MLD) and Krabbe’s disease (globoid leukodystrophy), as well as other lipid storage diseases such as GM, gangliosidosis and type 3 Gaucher’s disease can produce dementia as part of more generalised neurological deterioration. Urinary sulphatides will be abnormally increased in MLD. In the other conditions, confirmation of clinical suspicion will require white blood cell or fibroblast enzyme determinations carried out by a specialised laboratory.

**Neuronal ceroid lipofuscinosis (Batten’s disease and variants)**—This is a disorder associated with storage of a complex lipopigment. The disease has not yet been characterised enzymatically, although linkage analysis has located the gene for the infantile form (CLN1) to chromosome 1p32, and that for the juvenile form (CLN3) to chromosome 16p12.82,83 Patients usually develop retinal degeneration, myoclonus, seizures, and dementia. Diagnosis is made by demonstrating accumulated storage product inuffy coat or in skin biopsies, which show curvilinear bodies or a “fingerprint” pattern on electron microscopy. The early onset forms are autosomal recessive. Both autosomal dominant and autosomal recessive inheritance has been reported in the adult form (Kufs’ disease) which is not associated with pigmented retinal degeneration.84,85

**ATAXIAS**
Progressive ataxia can result from several conditions that have metabolic causes. The MRI will have assisted in diagnosing multiple sclerosis, cerebellar neoplasms, and the diagnoses of alcoholic cerebellar degeneration and

---

**Table 5 Disorders associated with dementia**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>In known families; genetics laboratory for DNA point mutation in the APP gene</td>
</tr>
<tr>
<td>B-12 deficiency</td>
<td>Serum B-12 level; Schilling test</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Genetics laboratory for DNA screen (CAG &gt; 37 repeats)</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>Lipid laboratory for plasma VLCFA</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease</td>
<td>Genetics laboratory for PLP gene</td>
</tr>
<tr>
<td>Canavan’s disease</td>
<td>Urine for N-acetylaspartic acid; Fibroblasts for aspartoacylase</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Arylsulphatase A</td>
</tr>
<tr>
<td>GM, gangliosidosis</td>
<td>β-galactosidase</td>
</tr>
<tr>
<td>Globoid leukodystrophy</td>
<td>Galactocerebrosidase</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis</td>
<td>Lipid laboratory for cholesterol</td>
</tr>
<tr>
<td>Cereoid-lipofuscinosis</td>
<td>EM ofuffy coat for curvilinear bodies</td>
</tr>
</tbody>
</table>

VLCFA = very long chain fatty acids; PLP = proteolipid protein; APP = amyloid precursor protein; EM = electron microscopy.
paraneoplastic syndromes will have been considered.

Genetic causes are of special importance in this group of disorders. As yet the diagnosis of Friedreich's ataxia is based on clinical, not biochemical findings. The genetics laboratory can, however, assist in diagnosing several of these disorders, including spinocerebellar ataxia type I (SCA-1) and Machado-Joseph's disease.44 46

Ataxia-telangiectasia, an autosomal recessive disorder, is the most common cause of ataxia in children under the age of 10.72 Usually the diagnosis is evident clinically, with ataxia, nystagmus, choreoathetosis, and characteristic auricular and conjunctival telangiectases being evident. The abnormal gene on chromosome 11q22-23, which is important for DNA repair, has recently been identified.67 The gene product is likely to be a phosphatidylinositol-3'-kinase. Presumably more definitive DNA diagnostic testing will become available. Symptoms of ataxia-telangiectasia can begin in early adult life.48 Some serum abnormalities are found in patients with this disorder, including raised α-fetoprotein in 95% of cases, alterations in serum immunoglobulins, and raised carcinoembryonic antigen concentrations.69

Autosomal dominant cerebellar ataxias are being reclassified as their genetic defects are discovered. Abnormal genes have been found on chromosomes 6, 11, 12, 14, and 16.42-46 66 90-92 Dubourg et al sampled DNA from 88 families with inherited ataxias and from 16 patients with sporadic ataxia to determine the frequency of the SCA1 mutation on chromosome 6.12 Twelve of the families and none of the sporadic cases carried the SCA1 mutation (unstable expanded CAG repeat).

Clinical characteristics do not readily distinguish the subtypes of cerebellar ataxias.49 Many patients will have additional signs such as extensor plantar responses, decreased vibration sense, ophthalmoplegias, and increased or decreased tendon reflexes. In SCA1, instability of the mutation is more common with male transmission and the age of onset of symptoms is lower in patients with a higher number of CAG repeats (anticipation).

Dentatorubral-pallidolysiasis atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder, usually classified under the ataxias. The disorder can be associated with myoclonus, chorea, dementia, and seizures. Juvenile and adult onsets are reported.44 The disorder may be misdiagnosed as Huntington's disease.48 The molecular defect is an expanded CAG repeat on the gene located on chromosome 12p and can be diagnosed by molecular analysis.49 50

Another disorder that may present with ataxia is Cerebroretinodinous xanthomatosis. This condition is suspected in a patient who has tendon pathological findings. The genetics laboratory can, however, assist in diagnosing several of these disorders, including spinocerebellar ataxia type I (SCA-1) and Machado-Joseph's disease.44 46

Ataxia with isolated vitamin E deficiency (AVED)—Patients have been described with progressive ataxia and other features of Friedreich's disease, in which vitamin E concentrations were reduced in the absence of malabsorption.105 In the patient described by Stumpf et al, serum vitamin E concentrations were below 1.0 (normal 5-20) μg/ml and could be restored to normal with an oral dose of 800 mg/day of DL-α-tocopherol.105 This disorder is autosomal recessive. The gene maps to chromosome 8q13.104 105 Affected patients have mutations in the α-tocopherol transfer protein resulting in impaired ability to incorporate α-tocopherol into lipoproteins.106

A-β-lipoproteinaemia—Patients with this disorder usually develop steatorrhea in infancy followed in the second decade by progressive ataxia and peripheral neuropathy.72 The patients have absence of serum β-lipoproteins and very low concentrations of α-tocopherol. Dietary supplementation with high doses of vitamin E (100 mg/kg/day) may arrest the neurological manifestations.107 This condition is associated with defective genes coding for the larger subunit of the microsomal triglyceride transfer protein (MTP), resulting in abnormal VLDL secretion and impairing delivery of vitamin E and other fat soluble substrates.108

The autosomal recessive disorder Friedreich's ataxia is associated with an α-fetoprotein deficiency on chromosome 9. Because of clinical similarities to AVED, it has been suggested that the Friedreich's ataxia gene may also be involved in α-tocopherol metabolism.109

Ataxia associated with mitochondrial disorders—Ataxia can be a feature of several of the mitochondrial disorders, especially the MERRF and MELAS syndromes, and the rare syndrome termed NARP.44 The presence of retinitis pigmentosa should raise the index of suspicion for NARP, which is sometimes due to a point mutation at bp8993 resulting in substitution of arginine for leucine in subsequence 6 of the mitochondrial H₃ATPase. Patients with this disorder may have seizures, muscle weakness, mental retardation and long tract signs with symptoms beginning from infancy to late adulthood.

MOTOR NEURON DISEASE

Most patients with suspected amyotrophic lateral sclerosis (ALS) have no known biochemical defect. Kennedy's syndrome (spinul bulbar muscular atrophy) may clinically resemble the bulbar form of ALS, though progression is usually slow. A genetics
Ataxia-telangiectasia, choreoathetosis, and dopamine responsiveness in pallidoluysian atrophy are associated with inherited metabolic disorders such as Wilson’s disease, dopa responsive dystonia, and ataxia-telangiectasia. These disorders are characterized by movement disturbances, including chorea, dystonia, and dystonia plus additional symptoms such as ataxia, gait disturbance, and ophthalmological findings like Kayser-Fleischer rings.

**Table 6** Metabolic disorders associated with involuntary movements

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of movement</th>
<th>Associated features</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington’s disease</td>
<td>Chorea</td>
<td>Dementia</td>
<td>Molecular analysis for CAG repeat expansion</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Tremor, dystonia</td>
<td>Hepatic insufficiency</td>
<td>Ceruloplasmin, serum and urine copper</td>
</tr>
<tr>
<td></td>
<td>Chorea</td>
<td>Kayser-Fleischer ring</td>
<td>Molecular analysis for CAG repeat expansion</td>
</tr>
<tr>
<td>Dentatorubral pallidoluysian atrophy (DRPLA)</td>
<td>Chorea</td>
<td>Ataxia, myoclonus, dementia</td>
<td>Ceruloplasmin, serum and urine copper</td>
</tr>
<tr>
<td>GM, gangliosidosis</td>
<td>Dystonia, Choreoathetosis</td>
<td>Gait disturbance</td>
<td>Leucocyte lysosomal acid β-galactosidase activity</td>
</tr>
<tr>
<td>Dopa responsive dystonia</td>
<td>Dystonia</td>
<td>Levodopa responsiveness</td>
<td>Research laboratory for GTP cyclohydrolase mutation</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Choreoathetosis</td>
<td>Ataxia, arachnoid, and cutaneous telangiectases</td>
<td>Decreased α-fetoprotein, immunoglobulin abnormalities</td>
</tr>
</tbody>
</table>

**Other metabolic causes of dystonia**

Adult onset of dystonia can occur in GM, gangliosidosis. The disorder is autosomal recessive and is diagnosed by showing pronounced reduction of activity of the enzyme β-galactosidase which can be measured in leucocytes. Progressive dopa responsive dystonia has been recently reported to be associated with mutations in a gene on chromosome 14q22.1-22.2 which codes for the enzyme GTP cyclohydrolase 1.

**Other movement disorders**

Choreic movements are characteristic of Huntington’s disease, which is discussed in the section on dementia. Another disorder in which chorea can occur is ataxia-telangiectasia discussed in the section on ataxias.

**Stroke**

Metabolic causes of stroke are rare, but must be considered in children and young adults presenting with an acute ischaemic event. Disorders to consider include MELAS syndrome, homocystinuria, sulphite oxidase deficiency, and Fabry’s disease. MELAS syndrome can be associated with stroke-like episodes in young adults. Diagnosis may be difficult (see section on mitochondrial disorders) and requires strong suspicion and communication with a genetics laboratory specialising in mitochondrial disorders.

**Homocystinuria** is much more common than sulphite oxidase deficiency. Both disorders may be suspected by the presence of ectopia lentis. Chronic homocysteine infusions in baboons produce sustained endothelial cell loss and result in accelerated atherosclerosis. It has been suggested that moderate homocysteinaemia in otherwise normal subjects may be a risk factor for atherosclerotic stroke. The disorder is due to an inborn error of cystathionine synthase. Urinary amino acid screen will detect raised concentrations of homocysteine. Sulphite oxidase deficiency can be associated with stroke-like episodes in infancy and childhood. Amino acid screening of the urine must be done carefully and on fresh urine, and should show the presence of S-sulphocysteine. S-sulphocysteine and sulphite are also detectable in plasma. Basal ganglia infarction in children, and adult onset chorea and dementia have been reported in propionic acidemia.

**Fabry’s disease**

This X linked lysosomal storage disease is associated with accumulation of trihexose ceramide due to deficiency in the enzyme ceramide trihexose a-galactosidase (table 3). At an early age, patients develop pinpoint skin lesions, especially on the abdomen. Trihexose ceramide accumulates in blood vessel walls, in kidney, and in myocardium. Death is usually due to renal or heart failure. Patients have been reported to develop episodic stroke-like symptoms and headaches. Small infarcts have been found in cerebral hemispheres, associated with proliferative
changes in vessel intima and media, presumably due to glycolipid deposition.\textsuperscript{123}

\textbf{Summary}

Knowledge of the molecular causes for genetic diseases that affect the nervous system is rapidly expanding. Especially striking has been the finding in several autosomal dominant neurodegenerative disorders that unstable expansions of trinucleotide repeats are responsible for the genetic disorder and that the length of the repeat can be correlated with the age of onset and the severity of symptoms. Phenotypic heterogeneity in many disorders associated with enzyme deficiencies can often be linked to the amount of residual enzyme activity occurring with different gene mutations.

Making a specific diagnosis of a neurological disorder associated with genetically determined metabolic defects requires access to a laboratory that can assist in arranging for appropriate testing to be carried out. In some disorders such as the aminoacidurias diagnostic metabolic studies can be performed in hospital clinical chemistry laboratories. In others, such as the lysosomal storage diseases, a laboratory that carries out special lipid and protein assays and white blood cell enzyme assays will be necessary. DNA mutational analyses are becoming commercially available for diagnosing many disorders such as mitochondrial diseases and those conditions associated with expanded trinucleotide repeats. It may be necessary to contact individual research laboratories when confronted with a disorder that has been newly discovered or that is very rare. A computerised directory of specialised laboratories that perform disease specific testing for genetic disorders should be useful in choosing the appropriate diagnostic or research laboratory.

Diagnosis of inherited metabolic disorders affecting the nervous system


51 Fujii Y, Kuhl DPA, Pizzuti A. Variation of the CUG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 1992;67:


NEUROLOGICAL STAMP

**Rosa canina** (dog rose)

The Roman naturalist Pliny attributed the name dog rose to a belief that the plant’s root could cure the bite of a mad dog. It is not clear if the dogs were rabid. The use of the dog rose in prescriptions dates back to Hippocrates but precisely what for is unclear. As a medicinal plant it came into full bloom in the second world war. When Britain was unable to import fresh citrus fruits the government organised the gathering of dog rose fruits, or hips, which were known to be a rich source of vitamin C. Processed into syrup the rose hips helped to prevent scurvy and, today, the plant is valued as a rich source of vitamin C.

The dog rose is illustrated as part of a commemorative set issued for the International Congress of Pharmacology held in Prague in 1971 (Stanley Gibbons 1980, Scott 1773).

L F HAAS
Diagnosis of inherited metabolic disorders affecting the nervous system.

P D Swanson

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