The Clinical Presentation of Lysosomal Storage Disorders

James E. Wraith

Abstract- Lysosomal storage disorders (LSDs) are present from conception and produce a clinical phenotype that evolves with time. The introduction of new therapies has made early diagnosis a priority. Clues to the clinical diagnosis of a LSD can be found in the tempo of the illness especially if the central nervous system is involved. Loss of a previously acquired skill (regression) is very characteristic of this group of disorders. Other clinical clues can include a dysmorphic appearance or the presence of characteristic skeletal involvement (dysostosis multiplex), but in some disorders such as Pompe disease or Krabbe disease, these do not occur. The approach to diagnosis has to involve “screening” as there can be considerable overlap in clinical presentation (e.g. Gaucher disease and Niemann-Pick B). Both urine and blood testing are necessary and the majority of diagnoses can now be confirmed at a molecular level. Prenatal diagnosis is possible for all.

Key Words: Lysosome, Dysostosis multiplex, Cherry red spot, White cell enzymes

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INTRODUCTION

The lysosomal storage disorders (LSDs) show a very variable clinical phenotype. In some patients, the presentation may be in the neonatal period with hydrops fetalis, whereas in others, with the same enzyme deficiency (but probably a different genetic mutation), onset may be delayed until adult life. For most patients, the onset of symptoms is in infancy following an apparently normal period of early development.

The first signs may be some slowing of development and other neurological signs; in other patients, enlargement of the liver and spleen or a dysmorphic facial appearance may be noted. Recognition of these physical signs can assist in the selection of appropriate diagnostic tests. Confirmation of diagnosis should always be followed by appropriate genetic counselling.

In this review, the general clinical presentation of LSDs will be outlined and more detail will be given about those disorders primarily affecting the central nervous system.

Classification is often based on the storage product (s) present and this often helps in selecting which biochemical tests are appropriate but it does not help with the clinical approach to diagnosis as there is often considerable overlap between different groups of LSDs. For a comprehensive summary of storage products, enzyme deficiency and screening tests the reader is guided to...
this recent review\(^1\). The neonatal presentation of LSDs (with hydrops fetalis) has also been reviewed recently and will not be considered further\(^2\).

**CLINICAL PRESENTATION**

**Dysmorphism**

Patients with a storage disorder often have a characteristic facial appearance due to storage affecting the facial skeleton and overlying soft tissue. This is often labelled “coarse”, but most patients find this term objectionable. This facial phenotype is seen in its most florid form in mucopolysaccharidoses especially those of early onset and associated with severe learning difficulties (e.g. mucopolysaccharidosis type I, Hurler syndrome). In these patients, the hair is thick, abundant and dull. The lips and tongue are enlarged and there is often a persistent nasal discharge. A dark synophrys is a characteristic finding and affected children are often hirsute.

In some disorders e.g. mucolipidosis II (I-cell disease), facial dysmorphism can be identified at birth. In other conditions, the abnormalities only become apparent with time and it is important to remember that in some conditions (e.g. Tay-Sach disease, metachromatic leucodystrophy, Gaucher and Krabbe disease), facial appearance remains normal.

**Dysostosis multiplex**

This is the general term used to describe the bone changes seen in storage disorders. In a similar way to the dysmorphism, the most prominent bony changes are seen in the mucopolysaccharidoses (MPS). In some storage disorders, the bone disease results from a different mechanism. For instance, in Gaucher disease, marrow cavity expansion and vascular compromise produce abnormalities of remodelling, bone infarction and pathological fracture\(^3\). Dysostosis multiplex appears to be due to a defect in bone formation and turnover with the ribs, vertebrae, skull and long bones showing diagnostic radiological abnormalities.

**Hepatosplenomegaly**

Hepatosplenomegaly is a common finding in those disorders where somatic storage is usual (as opposed to disorders where primary storage occurs within the CNS such as Tay-Sach’s disease). It is a common feature in Niemann-Pick diseases A, B and C and Gaucher disease where it is often the presenting sign. In some patients, the organs become massively enlarged and almost fill the abdomen. In mucopolysaccharidoses and glycoproteinoses, the function of the organs is not compromised despite significant enlargement, other disorders e.g. Gaucher disease, however, can be associated with significant impairment.

**Other non-neurological involvement**

The heart is classically the main site of disease in infantile Pompe disease (Glycogen storage disease type II) and severe neuromuscular problems occur in older patients with more attenuated variants.

Renal disease is a characteristic feature of Fabry disease and end stage renal failure is common in affected males before death.

A wide range of cutaneous abnormalities are seen on patients with LSDs. The most common (and non-specific) skin eruption are angiokeratomas, often in the bathing trunk area which occur in a number of different disorders but are seen most floridly in Fabry disease and fucosidosis.

**Central nervous system disease**

Table 1 lists those disorders that primarily affect the central nervous system with little or no somatic abnormality such as organomegaly or dysostosis. The cause of the CNS dysfunction in LSDs is multifactorial and has been recently reviewed\(^4\). The end result is a characteristic pattern of abnormalities producing signs and symptoms that can be helpful to the diagnostic process. A

<table>
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<th>Table 1. Lysosomal storage diseases associated with primary CNS dysfunction</th>
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<tr>
<td>* Metachromatic leucodystrophy</td>
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<td>* Krabbe disease</td>
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<td>* Tay-Sachs and Sandhoff disease</td>
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<td>* Sialidosis</td>
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<td>* Mucolipidosis IV</td>
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<td>* Schindler disease</td>
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<td>* Neuronal ceroid lipofuscinoses</td>
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<td>* Cobalamin F disease</td>
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common thread across many of the disorders is the tempo of the illness. The majority of infants are normal at birth and the neurological abnormalities evolve over a period of time following a variable period of normal progress. The developmental profile is characterised by regression, with the loss of previously acquired skills being the hallmark of this process.

Most affected patients are macrocephalic (classically seen in Tay-Sachs’s disease) as a result of storage within the CNS. It should be noted, however that patients with mucolipidosis II (I-cell disease) often have a small head circumference and premature sutural fusion. Indeed, sutural synostosis seems to occur more commonly in LSDs when compared to the normal population. In addition to excessive storage, a number of disorders affect the cerebral white matter leading to demyelination, often visible on magnetic resonance image (MRI) scanning as central white matter involvement and usually termed “leucodystrophy” such as metachromatic leucodystrophy. In disorders affecting myelination in this way, presentation is usually with motor problems such as clumsiness and ataxia progressing to increasing spasticity with time and associated ultimately with cognitive involvement as well.

The age of onset of symptoms and the speed of progression of the disease varies depending on the specific enzyme deficiency. Very acute onset neurological abnormalities are seen for instance in Krabbe leucodystrophy where many patients in retrospect have abnormalities from the newborn period. In addition to the motor problems the majority of patients will develop other evidence of CNS dysfunction. Episodes of hyperacusis (sensitivity to sound) are often followed by the development of frank seizures that may be generalised, tonic-clonic, myoclonic or mixed. The incidence of seizures in the different enzyme deficiencies is variable, but seizure can be the dominant symptom in some disorders including the ceroid lipofuscinoses. Sensory loss with blindness and deafness is common and severe learning disability is the usual end result in those disorders with a major CNS component.

The extreme variability of the disorders leads to a different mode of presentation in attenuated, adult forms of the disease. In these patients a psychiatric presentation is more likely with very late or no cognitive decline.

**Ophthalmological signs**
A variety of eye abnormalities are seen in LSDs. Blindness from progressive retinal or central involvement is a late feature of many disorders (e.g. ceroid lipofuscinoses), but some are associated with more specific physical signs.

Corneal clouding due to abnormalities in glycosaminoglycan metabolism is seen in patients with mucopolysaccharidoses types I, IV, VI and VII. In mucolipidosis type IV, corneal opacification is often the presenting feature. Many other disorders such as the oligosaccharidoses and glycoproteinoses will develop some corneal clouding, often at a later stage of the illness and sometimes only visible with a slit-lamp examination.

In Fabry disease, eye signs are common and can be helpful in delineating female carriers of this X-linked disorder. In the cornea, haziness followed by streak-like opacities occur as the disease progresses and many patients develop a posterior cataract. In addition in this disorder and in fucosidosis, the retinal vessels are often very tortuous.

The most quoted ocular abnormality associated with LSDs is the macular cherry red spot. This has been classically linked with Tay-Sachs disease, but is seen in a number of others (Table 2). It is also important to note, that as retinal ganglion cells are progressively lost later in the course of the disorders, the macular abnormality may become less apparent with time.

Other eye abnormalities include disorders of ocular mobility. In Gaucher disease type III and Niemann-Pick

### Table 2. Disorders associated with a macular cherry red spot

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<th>Disorder</th>
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<td>Sialidosis I</td>
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<td>Galactosialidosis</td>
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<tr>
<td>Tay-Sachs disease</td>
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<td>Sandhoff disease</td>
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<td>GM1-gangliosidosis</td>
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<td>Niemann-Pick A (common) C (rare)</td>
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<tr>
<td>Metachromatic leucodystrophy (rare)</td>
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<tr>
<td>Krabbe disease (rare)</td>
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<td>Farber disease (rare)</td>
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C, a supranuclear ophthalmoplegia are classic physical signs leading to a defect in the initiation of either vertical or horizontal saccades. In both disorders this may be the only neurological abnormality for many years.

**SPECIFIC NEUROLOGICAL DISORDERS**

This section is not meant to be exhaustive but gives examples of disorders that present with primary CNS dysfunction.

**Sphingolipidoses**

In this group of disorders, there is a progressive accumulation of complex lipids that are often important, integral components of cell membranes, and as such, neurodegeneration is a common feature here.

**GM1-gangliosidosis**

Infantile, juvenile and adult onset forms of this disorder are recognised and all are caused by a deficiency of β-galactosidase. The severe form of the condition can present with hydrops fetalis and is associated with neonatal dysmorphism, severe hepatosplenomegaly, cherry red spot and skeletal dysplasia. Seizures and progressive learning difficulties lead to early death.

In the adult, there is usually no visceral involvement and the condition usually presents with dystonia and dysarthria. Myoclonic seizures and a slow intellectual decline have been reported in some patients. As expected the juvenile form of the disease produces an intermediate phenotype with death occurring in the first or second decade of life.

**GM2-gangliosidosis**

Three different genetic disorders (clinically identical) contribute to this group including Tay-Sachs (more prevalent in Ashkenazi Jews), Sandhoff’s diseases, and GM2 activator protein deficiency.

Wide clinical variation is again a feature of these disorders, although most clinicians will only be familiar with the classical infantile forms of the disease. These present in the first months of life with a combination of hypotonia and hyperacusis. Developmental delay is obvious by the end of the first year of life. More dramatic neurological dysfunction becomes apparent within the second year with loss of visual attentiveness, increasing spasticity and seizures. Infants are macrocephalic and have a cherry red spot on fundal examination. Death usually occurs around the third year of life.

Late onset forms of the disease are usually, but not invariably associated with hexosaminidase A deficiency (adult Tay-Sachs disease). A variety of presentations have been described in this age group including psychosis, dystonia, and anterior horn cell disease. An adult variant of Sandhoff’s disease has been reported presenting with spinocerebellar degeneration.

**Globoid cell leucodystrophy (Krabbe disease)**

Krabbe disease is caused by a deficiency of the enzyme galactocerebrosidase that results in the accumulation of a toxic intermediate psychoscine. The end result is a severe demyelination of both the central and peripheral nervous system. In the infantile form or classic Krabbe disease, the disorder is aggressive and relentless. It usually starts in the early weeks of life, although some patients have symptoms in the neonatal period. Hyperpyrexia, irritability, crying, dystonic spasms and fixed opisthotonic posturing are typical. Death usually follows the onset of loss of bulbar function at around the age of 12-18 months. Nerve conduction velocities are delayed due to demyelination of the peripheral nervous system and the protein content of cerebrospinal fluid (CSF) is always elevated.

In late onset forms, the clinical presentation can be very variable. Intellectual deterioration is not inevitable and optic atrophy, slowly progressive spasticity and tremor are more common.

**Metachromatic leucodystrophy**

The vast majority of patients have a primary defect in arylsphatase A (ASA) activity. A small minority have a defect in the saposin B activator protein necessary for normal enzyme activity. Once again a very wide clinical spectrum has been reported, but by far the commonest mode of presentation is the late-infantile form of the disease. Affected patients present between the ages of 12-18 months with motor impairment secondary to a dis-
turbance of both the central and peripheral nervous systems. There is very little visceral involvement outside of the nervous system. The disease progresses rapidly with nystagmus, optic atrophy, dementia, seizures and spastic quadriplegia. Most patients die well before the end of the first decade. Juvenile patients often present (between the ages of 5-15 years) with school failure or behavioural disturbance, often on a background of “slow learning”. Seizures may occur and the rate of progression of the disease can be very variable, with some patients deteriorating rapidly\(^1\), whilst others survive 10-15 years after diagnosis.

Adult onset MLD usually presents with psychiatric manifestations. Patients develop personality change, depression and occasionally frank psychosis\(^1\). In a psychiatric setting, subtle neurological abnormality such as mild ataxia or diminished tendon reflexes can easily be missed. A more obviously organic symptom such as a seizure may precipitate further investigation and if this includes imaging the typical white matter changes are found, leading to the diagnostic investigations.

**Gaucher disease types II and III**

Types II and III (neuronopathic Gaucher disease) represent a spectrum of disease both ends of which include some form of neurological involvement. Type II disease is severe and acute in onset and can be associated with a colloidion skin abnormality or hydrops fetalis\(^1\). More commonly bulbar involvement with a characteristic triad of strabismus, trismus and opisthotonus is present from the early weeks or months of life. Myoclonic seizures may also occur in the context of a rapidly progressive disorder, often fatal in the first 2 or 3 years of life\(^1\). Type III disease is a chronic disorder and oculomotor apraxia may be the only neurological abnormality (at least initially). Systemic symptoms are often severe in this form of the disease and some patients will eventually show neurological progression\(^1\).

**Niemann-Pick disease type C (NPC)**

NPC is a complex disorder\(^1\) associated with abnormalities in cholesterol trafficking within the cell. At least two different genes (NPC 1 and NPC 2) are involved although most patients (95%) have mutations in NPC 1. Extreme heterogeneity is seen in this disorder that can present with hydrops fetalis or liver failure in the newborn period or remain asymptomatic throughout life\(^1\). The most classic clinical presentation is in mid-childhood with an insidious onset of supranuclear gaze palsy, ataxia and seizures. Dementia follows and the associated dystonia and dysphagia are major management problems. A very mixed pattern of epilepsy may occur, but episodes of cataplexy and gelastic seizure are absolutely characteristic, and if present in a child with a progressive disorder are virtually diagnostic of NPC. The NPC 2 gene has recently been shown to be the HE 1 gene a ubiquitously expressed lysosomal protein identified previously as a cholesterol-binding protein\(^1\).

**ESTABLISHING THE DIAGNOSIS**

In general terms there is no simple diagnostic screening test which will detect all these disorders. The tests chosen will be guided by the clinical picture and in many patients a battery of screening tests on both blood and urine will be necessary to establish the exact biochemical diagnosis. Many different algorithms have been produced to aid the diagnostic process, but in clinical practice these are of little value because of the considerable heterogeneity seen with this group of disorders. If a clinician strongly suspects the presence of LSD but initial biochemical studies are normal, a tissue biopsy should be studied by electron microscopy to confirm the presence of lysosomal distension. If present further investigation is necessary and disorders not readily detected by blood or urine testing e.g. activator protein or saposin deficiency should be considered. Skin fibroblast culture is mandatory in this situation for diagnosis.

Initial diagnosis of a MPS disorder should be based on urine glycosaminoglycan excretion analysed by an electrophoretic method. Spot urine tests are inaccurate and may miss cases of MPS III and IV. If glycosaminoglycans are normal but MPS-like features are present, a disorder of glycoprotein metabolism or a mucolipidosis needs to be excluded. For these disorders, thin layer chromatography of urine oligosaccharide excretion may suggest a possible diagnosis but specific enzyme analysis using plasma, leukocytes or skin fibroblasts will also
be necessary. For the other LSDs specific enzyme assays should be performed and these are often offered as a screen of several enzymes performed on the same blood sample. More specialised tests on fibroblasts will be needed for the transport and activator protein defects.

REFERENCES