Clinical Presentations of Treatable Lysosomal Storage Disorders – Gaucher, Fabry and Pompe disease and Mucopolysaccharidosis I

a report by

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There are currently more than 45 known lysosomal storage disorders (LSDs). As a group, LSDs occur in approximately one in 5,000 live births. All LSDs share a common pathogenesis, i.e. a genetic defect in one or more specific lysosomal enzymes, activator protein or membrane protein, resulting in deficient enzymatic activity.[2] If a specific enzyme is deficient, the substrate it targets progressively accumulates, supposedly interfering with basic intracellular processes causing cellular death.[3] The resultant extracellular inflammatory response eventually leads to tissue damage and organ dysfunction through largely still unknown pathways.

It is not possible to generalise LSD symptoms. The different types of substrate stored, the different cell types affected by storage, and differences in organ involvement and rates of progression may lead to tremendous clinical variability, even within a single disease. Certain symptoms, especially when occurring in clusters suggesting a multi-systemic nature, should alert physicians to the possibility of an LSD. However, symptoms initially may seem innocuous and appear with other more common diseases, leading to delays caused by incomplete or faulty diagnosis (see *Table 1*). If diagnosed late and/or left untreated, patients are at risk of developing significant, irreversible damage and loss of body functions, as well as life-threatening complications.[2]

The clinical presentations of Gaucher, Fabry and Pompe disease and mucopolysaccharidosis I (MPS I) are summarised below, focusing on musculoskeletal manifestations, the symptoms of which are often the cause of a patient with lysosomal storage disorders presenting to the physician. Together with MPS II and VI, these four diseases represent the subgroup of LSDs that are now treatable with enzyme replacement therapy.

Gaucher Disease

In Gaucher patients, the deficiency of glucocerebrosidase leads to an accumulation of glucocerebroside in the lysosomes of cells of the macrophage lineage.[4] These engorged cells ('Gaucher cells') displace healthy normal cells, particularly in bone marrow and visceral organs. Gaucher disease often presents at paediatric age and, if the disease is diagnosed early in life, the clinical course will, in general, be more severe.[5] Bleeding tendency, anaemia and neutropoenia are among the key manifestations of Gaucher disease. An enlarged spleen may be one of the first signs and a less marked liver enlargement generally occurs later. Slight elevations of liver function tests may develop.[6] It is only in recent years that the extent, progression and clinical consequences of skeletal involvement – usually the most debilitating aspect – have become adequately appreciated. In most newly diagnosed Gaucher patients, adequate skeletal assessment (i.e. using magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DEXA)) will result in evidence of skeletal involvement being present. Infiltration of the bone marrow with Gaucher cells, best visualised using MRI, is thought to cause osteonecrosis, which occurs mostly in the femoral heads and the proximal humeri. Osteonecrosis frequently occurs at a site of previous bone crisis (acute bone pain often accompanied by fever, chills and high white blood cell count).[7] Bone marrow infiltration with Gaucher cells is thought to contribute – through release of cytokines and chemokines – to both local and generalised osteopoenia and osteoporosis. Osteonecrosis and osteoporosis increase the risk of pathological fractures, for which both the vertebrae and heads of major long bones are predilection places. Chronic or intermittent bone pain is often present. Arthritis-like symptoms with joint effusion are commonly observed in Gaucher patients.[35] Erlenmeyer flask deformity at the end of the long bones indicating aberrant bone apposition and remodelling can be demonstrated in almost all patients diagnosed in childhood.[8] Skeletal growth retardation, delayed puberty and impaired weight gain are very common among children and believed to be causally related to a hypermetabolic state.[4]

Fabry Disease

Fabry disease is caused by a defect in the gene encoding for alpha-galactosidase A.[9] The inability to catabolise glycosphingolipids results in progressive accumulation in vascular endothelial cells, neural cells, cardiomyocytes and various types of renal cells. Virtually all males with the defective gene develop the disease, mainly in the form of classical Fabry disease. Despite the X-chromosome-linked inheritance, females may be affected as severely as men. However, they may also remain asymptomatic although histological evidence of organ system involvement may be present.

Classic Fabry disease usually presents in childhood. Cutaneous vascular lesions clustered in the bathing trunk area – known as angiokeratomas – are the most obvious initial clinical features.[10] Episodic acroparesthesias occur in many patients exposed to illness, exercise, fatigue, stress or weather changes.[11] Crises are usually accompanied by fever, and erroneous diagnoses of rheumatoid arthritis or rheumatic fever are common. An impaired ability to perspire leads to heat, cold and exercise intolerance.[12] Corneal opacities, beginning as diffuse haziness and progressing to grey/brownish spiral streaks in the corneal epithelium ('cornea verticillata'), are often seen by slit-lamp microscopy.[13] Cataract, narrowing of arterioles, dilation of veins and exaggerated tortuosity of retinal and conjunctival vessels are not uncommon. Gastrointestinal symptoms may include nausea, vomiting, episodic diarrhoea, post-prandial bloating and pain, early satiety and difficulty gaining weight.[14] Progressive hearing loss and tinnitus are frequently reported.[15] Although renal dysfunction generally becomes apparent in the third or fourth decade of life, microalbuminuria, impaired concentration ability and urinary excretion of globotriaosylceramide (GL-3) as signs of involvement of renal cells have been reported in adolescents.[16] Untreated, progression to end-stage renal disease is inevitable, and life expectancy is further reduced by life-threatening complications involving the heart and central nervous system.

Table 1: Selection of Potential Misdiagnoses

Gaucher disease
'Household labels' such as growing pains or accidental fracture
Recurrent nose bleeding due to non-specified bleeding disorders
Leukaemia
Lymphoma
Osteomyelitis
Legg-Calvé-Perthes disease
Fabry disease
Rheumatoid or juvenile arthritis
Rheumatic fever
Fibromyalgia/chronic fatigue syndrome
Neurosis/malingering
Raynaud's syndrome
Multiple sclerosis
Lupus angiokeratomas
Growing pains
Petechiae
Pompe disease (infantile-onset)
Acute Werdnig-Hoffman disease
Danon disease
Endocardial fibroelastosis
Glycogen storage diseases III, IV, VI
Idiopathic hypertrophic cardiomyopathy
Mitochondrial disorders
Myocarditis
Pompe disease (late-onset)
Duchenne muscular dystrophy
Glycogen storage diseases III, V, VI
Limb girdle muscular dystrophy
Polymyositis
Rigid spine syndrome
Scapuloperoneal syndromes
Mucopolysaccharidosis I
(Juvenile) Rheumatoid arthritis
Arthrogryposis
Degenerative rheumatic disorder
Cartilage disease
Connective tissue disease (e.g. scleroderma)
Autoimmune disease

Pompe Disease

Pompe disease is caused by insufficient activity of acid glucosidase, an enzyme involved in the degradation of intralysosomal glycogen.[17] Glycogen accumulates within multiple cell types and tissues, leading to damage, particularly in cardiac, respiratory and skeletal muscle tissue. Pompe disease is a single disease continuum of clinical phenotypes. At the most rapidly progressive end of the continuum (infantile-onset), patients present with signs and symptoms of Pompe disease within the first 12 months of life. Other patients may present at any age in childhood or adulthood (late-onset).

It is estimated that approximately one-third of Pompe patients have the rapidly fatal infantile-onset form,[18] while the majority of patients present with the relentlessly progressive late-onset form.

Although patients may be asymptomatic at birth, the course of infantile-onset Pompe disease typically progresses rapidly within the first few months of life with massive deposition of glycogen resulting in progressive cardiomyopathy and generalised muscle weakness and hypotonia ('floppy baby' appearance).[17] Spontaneous movements decline and weakening of respiratory muscles (including the diaphragm), compounded by pooling secretions, begins to impair respiratory function. Feeding difficulties and poor weight gain may manifest early. Motor development is often completely arrested. Moderate hepatomegaly is usually found and sometimes macroglossia is present. As in the late-onset form, mental development is generally not affected. Death from cardiorespiratory failure generally occurs by age one year.

Late-onset Pompe disease can present anytime during early childhood up until adulthood and is typically followed by a progressive course in five to 25 years of life. Severe cardiac involvement is absent. In children, the disease may present with delayed motor milestones or loss of muscle function.[17] The first observations may be difficulty walking or climbing stairs, reflecting the gradual progression of muscle weakness, which is typically more severe in the legs than in the arms. Signs of involvement of the muscles of the trunk (scoliosis and back pain) and the main respiratory muscle – the diaphragm (shortness of breath) – may appear. In other cases, respiratory symptoms may surface prior to recognition of muscle weakness. Generally, there is hypotonia and eventual respiratory distress with morning headaches, orthopnoea, exertional dyspnoea, rapid eye-movement (REM) sleep, hypopnoea or apnoea and exercise intolerance. Some patients display an unsteady gait or toe walking, as well as the Gower sign. Relentlessly progressive muscle weakness can progress to wheelchair and/or ventilator dependency and, ultimately, death between early childhood or late adulthood.[17,19] Longer symptom duration appears to be associated with earlier wheelchair or ventilator dependency. A quality of life survey indicated that Pompe disease has a profound effect on adult sufferers' ability to do their work and household tasks, and to move about independently outside the home.[20] Many patients require home help, home ventilation, rehabilitation, physiotherapy and other forms of support.

Mucopolysaccharidosis I

MPS I is caused by a deficient activity of alpha-L-iduronidase, an enzyme involved in the degradation of glycosaminoglycans (GAG).[21] Progressive accumulation of GAG occurs in virtually all bodily tissues and particularly impairs the function of connective tissue, cartilage and joint fluids.

Although MPS I actually represents a spectrum of disease, a subclassification into Hurler disease (most severe and rapidly progressive), Hurler-Scheie disease and Scheie disease has proved to be useful in clinical practice. If untreated, Hurler patients generally do not live beyond five to eight years, with death most often the result of progressive neurological disease and cardiorespiratory failure. In Hurler-Scheie patients, life expectancy is generally 20 years or less. Hurler-Scheie patients, and in particular Scheie patients, may be diagnosed late, although symptoms are often already present at a young age.

Musculoskeletal complications include hip dysplasia, spondylolisthesis and atlanto-occipital instability. In all forms of MPS I, progressive arthropathy – initially without pain or inflammation – presents as an inability to fully stretch or bend digits and may be notable as early as age two years. Fine motor skills of the hand are impaired by flexion contractures of the joints and/or carpal tunnel syndrome, and a 'claw hand' deformity may develop. Subsequently, stiffness, pain and flexion contractures may develop in virtually all joints. Subjects may give a history of inability to participate in school sports and reduced physical capacity. Characteristics of Scheie syndrome are joint contractures and thickening of tendons in the absence of any local or systemic signs of

inflammation. Walking capacity decreases, toe walking can be observed, and patients may become wheelchair-bound.

Diffuse corneal clouding (associated with photosensitivity) is a feature of all forms, and glaucoma may occur. Respiratory symptoms include frequent ear, nose and throat (ENT) infections, obstructive sleep apnoea-hypopnoea and noisy breathing. Hearing loss is also common. Life-threatening cardiac pathology (e.g. progressive valvular stenosis/insufficiency evolving into dilated cardiomyopathy with congestive heart failure) occurs across the entire disease spectrum.

Diagnosis

Due to the phenotypic diversity, it may be a challenge to clinically suspect the diagnosis and patients may go unrecognised until the stage at which organ system damage has occurred, and patients may have struggled for years with debilitating symptoms for which there seemed to be no explanation. As patients may encounter several types of practitioner and specialist, multidisciplinary consultation is imperative for early diagnosis and therapeutic intervention.

The gold standard of diagnosis of LSDs is the assay of the activity of the deficient enzyme in peripheral blood leukocytes or cultured fibroblasts. In the case of Pompe disease, the enzyme assay in cultured skin fibroblasts, a muscle biopsy or purified lymphocytes can confirm the diagnosis.[17] In some Gaucher patients, the correct diagnosis may first be suspected after a bone marrow aspiration (for evaluation of chronic anaemia, thrombocytopenia or splenomegaly) shows Gaucher cells. However, bone marrow biopsy is not a preferred diagnostic tool given the invasiveness of the procedure. If clinical suspicion of MPS I exists, quantitative (and qualitative) determination of GAG in the urine may be a useful initial diagnostic step.

Pre-natal diagnosis may be requested in case of subsequent pregnancies in families with an affected child, or when a parent presents with a late-onset form. Pre-natal diagnosis can be made with either amniocentesis or, more commonly, direct enzyme analysis of uncultured chorionic villi cells. DNA analysis may be used as a supportive diagnostic method.

Therapeutic Management

LSD patients often undergo a variety of therapies and care. Palliative care, e.g. surgery, physical therapy or dialysis, can be effective in managing symptoms. However, they do not affect the biochemical cause of the disease and usually do not prevent disease progression. Cause-specific enzyme replacement therapy that addresses the underlying storage problem is available for the LSDs described above.

Enzyme replacement therapy involves regular intravenous administration of the deficient enzyme. In patients with type I Gaucher disease, cerezyme (imiglucerase) is the standard of care.[22] Cerezyme therapy provides exogenous enzyme for uptake into lysosomes of cells of the monocytic lineage, and for subsequent facilitation of the breakdown of stored substrate in lysosomes. Replacement of the missing enzyme using cerezyme has been shown to be convenient, well-tolerated, highly safe and efficacious in ameliorating symptoms and signs in most disease domains and in preventing progression to irreversible complications, e.g. of the skeleton.

The rationale of cause-specific therapy (replacing the missing or malfunctioning enzyme) has also proved to be effective for Fabry disease. Fabrazyme® (agalsidase beta) has proved to be safe and well tolerated, and to clear GL-3 from the vascular endothelium of the kidneys, heart and skin.[23] With this treatment, progression of the disease slows or may stabilise. Furthermore, Fabrazyme therapy significantly reduces the risk of renal, cardiac and cerebrovascular events, as demonstrated in a placebo-controlled trial.[26] Guidelines on the therapeutic management of Fabry patients have recently been published.[25]

Clinical trials in infants and toddlers have demonstrated that Myozyme® (alglucosidase alfa) markedly prolongs survival compared with a historical (untreated) cohort.[26] The oldest children who have been receiving enzyme therapy since infancy are now eight years old, whereas left untreated, infantile-onset patients generally die before one year of age. Myozyme has been demonstrated to have a positive effect on hypertrophic cardiomyopathy (expressed in terms of reduced left ventricular mass index) and progression to cardiorespiratory failure can be prevented or reversed. Treated patients can also attain motor milestones, that untreated children would not achieve. In late-onset patients, Myozyme leads to variable improvements such as a reduction or stabilisation of ventilator use, an increase or stabilisation in mobility and functional improvements in activities of daily living.[27]

Aldurazyme® (laronidase) therapy for MPS 1[31] has been demonstrated to safely and effectively alleviate many systemic signs and symptoms of this progressive multisystemic disease. Sustained, significant, clinically meaningful improvements in pulmonary function and functional capacity have been observed.

Immunoglobulin G (IgG) antibody formation towards the therapeutic protein may occur and patients who are positive for IgG antibodies may have a higher risk of developing a hypersensitivity reaction.[27,29–31]

Human stem-cell therapy has been shown to have some positive results in MPS I Hurler patients, especially when performed early in the course of the disease. Gene therapy is still only in pre-clinical (animal) studies and much research is needed, especially in identifying appropriate vectors for gene delivery.[2]

International panels of experts have been collaborating to develop or update recommendations for disease management. Such recommendations first became available for Gaucher disease, both for paediatric[5,7,32] and adult patients.[33,34,22]

Registry programmes that create a structured format for the long-term collection of data are in place for these LSDs and will contribute to a better understanding of the natural course of disease and long-term therapeutic outcomes. ■

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