

Rheumatologic features of lysosomal storage diseases

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Abstract: Lysosomal storage diseases are rare metabolic disorders, some of which can now be treated using enzyme replacement therapies. Because the time point of treatment initiation significantly influences the outcome in Gaucher disease, Fabry disease, and mucopolysaccharidosis type I, early diagnosis is of utmost importance. All three disorders can present with musculoskeletal symptoms in early stages, therefore, the rheumatologist may be the first to be contacted by these patients. Here, we present three characteristic lysosomal storage disease cases to increase awareness in the rheumatological community of the typical symptom constellations associated with these rare but treatable disorders.

Introduction: lysosomal storage diseases are rare inherited metabolic diseases in which an enzyme is deficient, leading to lysosomal storage of the undegraded substrate. This group of diseases includes a number of mucopolysaccharidoses and oligosaccharidoses, and the sphingolipidoses Gaucher disease and Fabry disease first described by Philippe Charles Ernest Gaucher in 1882 and Jonathan Fabry in 1898, respectively. The stored substances involved in Gaucher disease and Fabry disease, the lipids glucocerebroside, and globotriaosylceramide (GL-3) were characterized only decades later, and identification of the lysosomal enzymes behind the two sphingolipidoses in the 1960s eventually led to the development of enzyme replacement therapy.

Most of the mucopolysaccharidoses are also named after the person who first described the associated syndrome, although the disease first described in 1919 by Gertrud Hurler (Hurler disease) and the mild or adult form of the disease first described by Harold Scheie in 1962 (Scheie disease) have since proven to be variants of mucopolysaccharidosis type I (MPS I). Once the defective enzyme was identified, enzyme replacement therapy was also developed for MPS I.

Some lysosomal storage diseases are now treatable and clinical experience shows that the development of irreversible complications can be successfully hindered with early treatment. However, early diagnosis and recognition of the key symptoms of these rare diseases is a challenge. Often, patients with lysosomal storage diseases first seek medical assistance on the basis of musculoskeletal symptoms. It is therefore important that the rheumatologist be able to recognize and identify the symptoms of these diseases. With this goal in mind, the key symptoms of these lysosomal storage diseases are summarized and discussed here.

Gaucher disease

Case report

A 28-year-old woman was referred to us for chronic shoulder pain and splenomegaly. She had one healthy sister and healthy parents.

Blood chemistry showed mild thrombocytopenia ($128 \times 10^9/l$) and an accelerated sedimentation rate (50 mm/h, Westergren method). The diagnostic assessment of other inflammatory markers revealed elevated interleukin-2 receptor levels (1,820 ng/ml). Other humoral blood chemistry parameters were normal. Several blood cultures were germ-free. X-rays of the shoulder showed no osteodestruction. A T1-weighted MRI of the shoulder and humerus detected the hypointense signal and diffuse bone marrow pattern typical of Gaucher disease. Reduced β -glucocerebrosidase activity in leukocytes confirmed the diagnosis.

Pathophysiology

Gaucher disease, the most common sphingolipidosis, is an autosomal recessive metabolic disorder caused by deficient activity of the lysosomal enzyme β -glucocerebrosidase. Based on epidemiological studies in The Netherlands and in Australia, it is assumed that one in every 50,000-60,000 live births is affected. The gene encoding this enzyme is located on chromosome 1 (q21-31) and the phenotypic heterogeneity of Gaucher disease can be attributed to more than 200 known mutations.

The enzyme defect leads to glucocerebroside accumulation in the lysosomes of macrophages. Lipid-laden macrophages, "Gaucher cells", are found in the reticuloendothelial system, leading to a multisystemic disease with visceral enlargement and bone marrow displacement. Further aspects of the disease such as coagulation abnormalities and chronic stimulation of the immune system can be explained by chronic activation of storage cells and delivery of proteins such as cytokines. Further proteins derived from Gaucher cells are chitotriosidase and CCL 18, a chemokine of

the CC family; both can be markedly elevated in Gaucher disease and the level of chitotriosidase reflects the body burden of storage cells and the severity of visceral disease.

Signs and symptoms

Gaucher disease can lead to a broad spectrum of clinical manifestations. Depending on the type of neurological involvement, Gaucher disease can be subclassified as acute (type II), chronic neuronopathic (type III), or nonneuronopathic (type I). The nonneuronopathic form, which represents more than 85% of cases, is characterized by hepatosplenomegaly, anemia, thrombocytopenia, and bone involvement with pain and functional impairment of the locomotor apparatus. Bone marrow infiltration and defective bone remodeling result in osteopenia and avascular necrosis with predilection sites in femoral heads, lumbar vertebrae, and proximal humeri. Osteonecrosis of the femoral head and spine instability may lead to immobility. Arthritis-like symptoms with joint effusions and pain are also observed in Gaucher patients and subchondral infiltration of Gaucher cells and further inflammatory tissue changes may explain this pattern.

Therapy

Enzyme replacement therapy with imiglucerase is the therapy of choice in nonneuronopathic and chronic neuronopathic Gaucher disease. This regimen is very effective in reversing hematological and visceral changes at doses between 15 and 60 U/kg bodyweight (b.w.), administered once every 2 weeks by intravenous infusion.

Fabry disease

Case report

A 25-year-old male patient was referred to us for the evaluation of proteinuria, polyarthralgia, and increasing lassitude. Beginning at age 7, he had suffered from recurring episodes of pain involving the hands, ankles, and feet. These episodes sometimes lasted for days and were accompanied by fever and chills without any swelling or redness of joints.

His mother suffered from atrial fibrillation and chronic heart failure before she died at age 63. The grandmother experienced chronic renal failure, underwent hemodialysis for 3 years, and died at age 66. The brother seems to be unaffected.

Numerous diagnostic evaluations led to the diagnoses of juvenile rheumatoid arthritis and rheumatic fever. Subsequently, the patient received NSAIDs and multiple prolonged courses of penicillin. At the age of 21, mild proteinuria (300 mg/day) and a rash on the flanks and buttocks were recognized. Two years later, difficulty in hearing and increasing lassitude without constitutional symptoms appeared. Twenty-four hours of protein excretion was about 3g.

On admission, the patient displayed significant edema in both ankle regions. There was a prominent rash of nonblanching angiokeratomas in the waist, buttocks, and upper thigh regions. A slit-lamp investigation revealed whorled corneal opacities (cornea verticillata). Serum creatinine was 159 $\mu\text{mol/l}$ and urinary protein excretion was 4,800mg/day. Maltose crosses, indicating lipiduria, were detected in the urine when viewed under the microscope with polarized light. A renal biopsy revealed classic glomerular foam cells. Electron microscopy of renal biopsy material showed the presence of characteristic myeloid bodies. The patient was diagnosed with Fabry disease when plasma alpha-galactosidase A (alpha-Gal A) activity was found to be markedly decreased.

Pathophysiology

Fabry disease, an X-linked lysosomal storage disorder, is caused by an alpha-Gal A deficiency that result in the accumulation of GL-3. The progressive glycosphingolipid accumulation, particularly in endothelial cells, leads to renal, cardiac, and cerebrovascular complications. Fabry disease is panethnic with an estimated incidence of 1:400,000 in men. The disease predominantly affects males; heterozygous females may be affected to a mild or more severe extent depending on random X-chromosomal inactivation.

Signs and symptoms

The classic phenotype

Males with classic Fabry disease usually develop severe renal, cardiac, and cerebrovascular complications. Before renal replacement therapy was available, the average life span of affected males was approximately 40 years. Clinical manifestations begin in childhood or adolescence with episodes of pain in the extremities (acroparesthesia). Because pain is most intense in the hands, feet, wrists, and ankles and is frequently associated with fever, the erroneous diagnoses of either juvenile rheumatoid arthritis or rheumatic fever are common. Characteristic nonblanching angiokeratomas may develop between the umbilicus and thigh. A whorled corneal opacity may be seen on slit-lamp investigation. Hypohidrosis with heat- and exercise-intolerance is also common in male Fabry patients. By adulthood, renal involvement usually becomes obvious with proteinuria and a reduction in renal function progressing to end-stage renal disease. Typical cardiac manifestations include left ventricular hypertrophy, valvular abnormalities (especially mitral

insufficiency), cardiomyopathy, and arrhythmias (in particular, atrial fibrillation). Cerebrovascular manifestations are early stroke, transient ischemic attacks, white matter lesions, hemiparesis, dizziness, tinnitus, and hearing loss. Gastrointestinal symptoms may include diarrhea.

Manifestation in female patients heterozygous for the aberrant gene

Clinical manifestations in women range from asymptomatic to full-blown disease comparable to affected males. Asymptomatic carries may have a normal life span. Affected women may suffer from acroparesthesias in adolescence or may develop cardiac or, more rarely, renal disease in adulthood. Beyond 40 years of age, some women may suffer from substantial left ventricular hypertrophy and cardiomyopathy. End-stage renal disease is very rare in female Fabry patients.

Organ variants

Male patients with residual alpha-Gal A activity (for example, due to point mutations) have a milder, later onset course of disease. Men with cardiac variants usually become symptomatic with cardiomegaly and mild proteinuria during the fourth decade of life when classic patients would already be severely affected.

Enzymatic and molecular diagnosis

In males with the classic phenotype, the disease is readily diagnosed by measuring alpha-Gal A activity in plasma or leukocytes. In contrast, females may display normal to low enzyme activities. Therefore, direct demonstration of a mutation in at least one allele of the alpha-Gal A gene may be necessary for the diagnosis of Fabry disease in many women.

Therapy

Infusion of alpha-Gal A supplies the deficient enzyme and reverses GL-3 accumulation in affected tissues throughout the organism. For these reasons, enzyme replacement therapy is initiated in all affected men once the diagnosis was established. Affected children and adolescents are treated when severe acroparesthesia, exercise-intolerance, or fatigue are present. Females with substantial disease manifestations should also be treated with enzyme replacement therapy.

Regulatory approval for two forms of alpha-Gal A (gene-activated human alpha-Gal A, INN: agalsidase alpha) and recombinant human alpha-Gal A (INN: agalsidase beta) was granted in the European Union and for agalsidase beta in the US. Both products are similar with comparable specific activities and glycosylation. Formation of IgG antibodies against the protein moiety of the molecules can result in infusion reactions. Despite slight differences in glycosylation patterns, the immunogenicity of both products appears to be identical. The only notable difference relates to the approved dose for intravenous administration: agalsidase alpha at 0.2 mg/kg and agalsidase beta at 1 mg/kg b.w.

The two products were evaluated in separate clinical trials with different doses and end-points. Agalsidase alpha infusions (0.2 mg/kg at biweekly intervals) were shown to be safe and effective in reducing pain in a phase III trial. Treatment with agalsidase beta (1 mg/kg b.w. at biweekly intervals) achieved complete clearance of GL-3 in the vascular endothelia of kidney, heart, and skin within 6 months. Renal mesangial and interstitial cells cleared after 6-12 months, while renal podocytes and cardiomyocytes took longer to clear life-long accumulation of GL-3.

Mucopolysaccharidosis type I

Case report

A 28-year-old 185-cm-male working for an insurance company was diagnosed by his GP with a heart murmur and echocardiography revealed mitral valve thickening. Corneal clouding was also detected. As a child, the patient was unable to participate in school sports and physical performance was reduced. Hip dysplasia was diagnosed at the age of 10 and the patient complained of impaired mobility and stiffness of the fingers. Several examinations in rheumatology and orthopedic specialist units failed to confirm crucial findings, in particular, no humoral signs of rheumatic systemic disease. He did no siblings; his parents were healthy.

The patient was referred to a unit that specialized in inherited metabolic disorders for further evaluation with a preliminary diagnosis of mucopolysaccharidosis. The patient showed no coarsening of facial features or other highly visible signs of mucopolysaccharidosis. Nevertheless, an increased urinary excretion of heparan and dermatan sulfates suggested a diagnosis of MPS. A deficiency of α -iduronidase in leukocytes eventually confirmed the diagnosis of MPS I-Scheie.

Pathophysiology

The lysosomal enzyme α -L-iduronidase is deficient in MPS I patients. This enzyme plays an important role in the degradation of heparan sulfate and dermatan sulfate by cleaving iduronic acid and a deficiency in α -L-iduronidase activity leads to primary accumulation of glycosaminoglycans (GAGs) in the lysosomes. Lysosomal storage results in progressive damage to cells, tissues, and organs and an increased urinary excretion of heparan sulfate and dermatan

sulfate; urinary GAG excretion can be measured for diagnostic purposes. The incidence of MPS I is estimated to be 1:120,000. MPS I is autosomal recessively inherited. The α -L-iduronidase gene is located on chromosome 4p16.3.

Clinical symptoms and prognosis

The Scheie and Hurler phenotypes of MPS I represent the two opposing poles of a broad clinical spectrum of MPS I disease; intermediate manifestations are often described as Hurler/Scheie. The Hurler type MPS I has the most severe manifestations: Severe mental retardation is combined with hepatosplenomegaly, dysostosis multiplex, corneal clouding, dwarfism, cardiac manifestations, coarse facial features, and death in the first decade of life. The diagnosis of Hurler disease is often made during the first year of life due to the characteristic and readily visible signs of the disease.

In contrast, the attenuated forms of the disease, Scheie or Hurler/Scheie, have more variable, milder, and delayed clinical manifestations. Patients may undergo normal growth and may have normal facial features. When adults are diagnosed with MPS I, diagnosis is more difficult and patients may be misdiagnosed due to the lack of mental retardation, coarse facial features, dwarfism, or macrocephaly seen in the classic Hurler phenotype. Hepatosplenomegaly or skeletal changes are often less distinct and less progressive and life expectancy may be normal. Impairment of the locomotor apparatus is often the primary symptom in attenuated phenotypes. Patients may report painful tip of the foot due to a shortening of the Achilles tendon or limited digital motoric function due to joint contractures. In children, carpal tunnel syndrome or hip dysplasia, often identified during routine ultrasound examinations in newborns, can result in a diagnosis of MPS I. At the time of diagnosis, the majority of the patients have already developed corneal clouding and thickening of heart valves.

Therapy

Causal therapies available for MPS I are stem cell transplantation and enzyme replacement therapy with recombinant human α -L-iduronidase (INN: laronidase) 100Units/kg b.w. given once weekly by infusion. Stem cell transplantation is an option for the early treatment of visceral and central nervous system pathology in Hurler disease, i.e., before the age of 2 years. Placebo-controlled studies using enzyme replacement therapy with laronidase showed a decrease in GAG excretion and liver size and improvements in forced vital pulmonary capacity and 6-min walking test distance in patients with Scheie and Hurler/Scheie phenotype. Improvement of the motility of the shoulder joint could be demonstrated in the subgroup of the most severely affected patients.

While enzyme replacement therapy does not have an effect on some skeletal damage, joint motility can nevertheless be improved. Further investigations will have to demonstrate whether treatment initiation at an even earlier stage can prevent joint contractures.

Discussion

With the availability of enzyme replacement therapy, early diagnosis has become the most important factor in determining the course of lysosomal storage diseases. Because all three disorders frequently present with musculoskeletal symptoms in early stages, the rheumatologist may play a crucial role in determining the overall outcome for the individual patient. Which symptom constellations should prompt rheumatologists, pediatricians, and orthopedic surgeons to consider the diagnosis of one of these rare genetic diseases?

Bone pain due to progressive bone marrow infiltration with typical tissue macrophages is the leading musculoskeletal symptom in Gaucher disease. Radiology may demonstrate osteopenia, focal osteolysis or osteosclerotic lesions, aseptic osteonecrosis, or pathological fractures. Particularly, if these symptoms are observed in the context of persisting hepatosplenomegaly and/or hypersplenism, a diagnostic workup for Gaucher disease is mandatory. Because Gaucher cells are able to activate proinflammatory cytokines, acute episodes of bone symptoms can be accompanied by a sudden onset of fever and general malaise. If the pathologic bone process is localized in proximity to the joint, the clinical manifestation can mimic mono- or oligoarthritis. Other differential diagnoses of Gaucher disease include sickle cell disease, familial autoinflammatory diseases, various causes of avascular bone necrosis, and, in adult patients, multiple myeloma.

Similarly, pain may be the first reported symptom in Fabry disease; however, the character of the pain is completely different. Younger patients may report acral pain, burning sensations, numbness, and paresthesias, which can occur as a Fabry crisis along with fever, malaise, and elevated serological parameters of inflammation. Neurological examination typically does not reveal any pathological findings. Fabry disease should be suspected if any of the following additional conditions are present: intolerance of heat or cold exposure, hypohidrosis, angiokeratoma, abdominal cramps or diarrhea, or cornea verticillata. The family history with respect to renal, cardiovascular, and cerebrovascular events can also be very helpful in establishing the diagnosis. The acral symptoms in combination with temperature intolerance may lead to a misdiagnosis as Raynaud's syndrome. Later in the course of the disease, visceral symptoms such as proteinuria and renal insufficiency, cardiomyopathy, cardio- and cerebrovascular events, and dermal symptoms can present a challenge for the rheumatologist in the differentiation from collagen vascular diseases and vasculitides.

MPS I in the form of the classical Hurler syndrome is characterized by the typical dysostosis multiplex and dwarfism and should not present a diagnostic challenge in a rheumatological setting. However, diagnosis of the Scheie syndrome variant of MPS I may be challenging because the appearance of the patient can be completely normal and musculoskeletal complaints may be the initial symptoms: joint contractures and thickening of tendons and aponeurotic membranes in the absence of any local or systemic signs of inflammation are characteristic of Scheie syndrome. Mucopolysaccharidoses are a leading cause of carpal tunnel syndrome in childhood. An investigation of possible MPS I should be initiated if these particular changes occur in combination with corneal cloudiness, valvular heart disease, or thickening of the skin. The tendon alterations associated with the Scheie syndrome can be differentiated from inflammatory rheumatic diseases, such as spondyloarthritides, by the absence of any tenderness or serological markers of inflammation.

A systematic overview of epidemiology and genetics of lysosomal storage diseases and characteristic clinical and laboratory findings is given in Table 1.

Storage disease	Subtypes	Incidence and inheritance	Key physical features	Key discriminating features	Key diagnostic tests
Gaucher disease	Nonneuronopathic, acute neuronopathic, and chronic neuronopathic subtypes	Incidence: 1:50,000; Autosomal recessive	Nonneuronopathic Gaucher: splenomegaly, bone pain, bleeding tendency, and growth retardation. Acute and chronic neuronopathic forms develop additional neurologic manifestations	Persistent splenomegaly (>4 weeks) in connection with musculoskeletal symptoms (arthritis-like symptoms, bone pain, and avascular necrosis)	β -glucocerebrosidase activity in leukocytes; plasma chitotriosidase
Fabry disease	Classic phenotype, female carriers, isolated cardiac and/or renal variants	Incidence: 1:40,000; X-chromosomal	Acroparesthesia, angiokeratoma, hypohidrosis, proteinuria, chronic renal failure, left-ventricular hypertrophy, chronic heart failure, stroke, and cornea verticillata	Severe pain in hands and feet with fever but without swelling or redness of joints; isolated proteinuria, premature stroke, and cornea verticillata	Alpha-galactosidase activity in serum and/or lymphocytes; genotyping, slit lamp investigation of the eye, and tissue biopsy (skin, kidney, and heart)
Mucopolysaccharidosis I	Hurler disease, Scheie disease, and compound Hurler/Scheie disease	Incidence: 1:80,000; Autosomal recessive	Scheie disease: skeletal abnormalities, stiffened joints, carpal tunnel syndrome, heart (valvular) disease, and corneal clouding. Hurler patients show facial dysmorphism and mental retardation	Contractures, carpal tunnel syndrome, and/or dysostosis multiplex/hip dysplasia in connection with diffuse corneal clouding and/or thickening of heart valves	Alpha-iduronidase activity in leukocytes GAG excretion in urine X-ray (dysostosis multiplex)

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