Current status of diagnosis and treatment of lysosomal storage diseases in China

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Lysosomal storage diseases (LSDs) are a group of inherited disorders caused by deficiency of lysosomal enzymes or structural components. LSDs have been models of molecular and cellular therapies for inherited metabolic diseases. Enzyme replacement therapy (ERT), bone marrow transplantation and substrate reduction therapy (SRT) have been shown to be effective for many of the LSDs. Early diagnosis and treatment have best chance for a positive outcome. We reviewed the case reports, diagnosis and treatment of LSDs in China.

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Introduction

Lysosomes are cytoplasmic organelles that contain enzymes (especially acid hydrolases), which can degrade proteins, lipids, polysaccharides and many other kinds of macromolecules from extracellular environment through phagocytosis and endocytosis, or from cytosol via autophagy. Increasing evidence suggests that lysosomes and/or lysosome-like organelles may not only be a site for terminal degradation, but also involved in specialized functions, such as antigen presentation, blood clotting, bone remodeling and the regulation of growth factors and hormones.[1]

Lysosomal storage diseases (LSDs) are a group of inherited disorders with defects in lysosomal function, which is due to gene mutation of enzymes or structural components that play a role in the life cycle of lysosome. The incidence of LSDs is estimated to be 1 in 2500-5000 live births, which makes it one of the most prevalent groups of genetic diseases in humans.[2,3] Patients with LSDs are generally normal at birth, but symptoms appear progressively through the first few months or early years of life. These symptoms may include changes in facial appearance, bone deformities, joint stiffness and pain, loss of skills such as speech and learning, respiratory and cardiac problems, behavior problems and mental retardation, sight and hearing difficulties, enlargement of the spleen and liver.

In the last decade, LSDs have been models of molecular and cellular therapies for inherited metabolic diseases. Preclinical studies on *in vitro* systems and animal models allowed the successful development of bone marrow transplantation, substrate deprivation, enzyme replacement and gene transfer as therapeutic options for several LSDs.

With many inherited defects of metabolism, classification of LSDs began with eponyms, later reflected primary storage material, and finally focused on enzyme deficiency. Since different genetic mutations may cause various degrees of the deficiency of a specific hydrolase, variants of a particular biochemical form of disease may occur. These variants are subclassified according to clinical background with descriptive terms such as early or late onset, type I/II, type A/B, etc., or with precise molecular defect. At present, there are more than 40 lysosomal storage disorders, which can be categorized broadly into four classes by the nature of the primary storage material involved: disorders of glycoprotein degradation, disorders of lipid and splingolipid degradation, disorders of mucopolysaccharide degradation and other lysosomal storage diseases.

China pays lots of attention to LSDs in order to improve the population quality. In this article, we have reviewed the current progress of diagnosis and treatment

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of LSDs in China.

Disorders of glycoprotein degradation

Glycoproteins are characterized by various branched oligosaccharides containing a common core structure of mannose and two molecules of N-acetylglucosamine linked to asparagine of proteins. Cleavage of oligosaccharide from protein is followed by its sequential catabolism from the nonreducing end by specific glycosidases. Deficiency of one of these enzymes results in accumulation of intermediate products of catabolism.

α-mannosidosis

α-mannosidosis is due to deficiency of lysosomal α-mannosidase, an enzyme that normally catabolizes various oligosaccharide moieties of glycoproteins. As a consequence, a variety of mannose-containing oligosaccharides derived from high-mannose, complex, and hybrid oligosaccharides accumulate in lysosomes.[4] Two Chinese cases, a 2-year-old boy and a 5-year-old girl, were reported.[5] The α-mannosidase activity in their peripheral leukocytes was markedly decreased, along with other clinical and pathological manifestation, such as recurrent infections, coarsening of facial features, psychomotor retardation and dysostosis.

β-mannosidosis

A deficiency of β-mannosidase results in the accumulation of a disaccharide and trisaccharide with a terminal mannose β-linked to N-acetyl-glucosamine.[4] No case has been reported in China or in the Chinese elsewhere.

Fucosidosis

Fucose occurs as a sugar in some sphingolipids and oligosaccharide moieties of glycoproteins. Glycolipids and oligosaccharides containing this sugar accumulate in lysosomes associated with a deficiency of lysosomal α-fucosidase.[4] Fucosidosis exhibits a wide clinical spectrum. An early infantile form with severe neurological deterioration and growth retardation leads to death in the first decade of the patients. The more attenuated form is manifested by facial dysmorphia, dysostosis multiplex, angiokeratoma, cardiomegaly, hepatosplenomegaly, and seizures. Neurological deterioration progresses more slowly than that in the severe form. The survival is into middle age. There are three clinical cases reported respectively in Hong Kong (a 6-year-old boy with an intermediate form of fucosidosis),[6] Taipei (a 5-year-old girl)[7] and the mainland of China (a 15-year-old boy).[8]

Aspartylglucosaminuria

This disease is caused by the deficiency of aspartylglucosaminidase which results in lysosomal accumulation of the abnormal degradation products (mainly aspartylglucosamine) in patients' cells and tissues. The diagnosis of aspartylglucosaminuria has so far been based on the detection of abnormal metabolites in urine and decreased enzyme activity in the cultured fibroblasts or isolated lymphocytes.[9] Although pan-ethnic, aspartylglucosaminuria is most prevalent in the Finnish population. No case has been reported in the Chinese population.

Mucolipidosis I

Mucolipidosis I (MLI) is due to isolated neuraminidase deficiency and exhibits two major phenotypes: type I (also known as cherry-red spot myoclonus syndrome) and type II (symptoms include facial dysmorphia, hepatosplenomegaly, developmental delay, skeletal abnormalities, hypotonia, myoclonus, ataxia and intellectual impairment). No case has been reported in the Chinese population.

Galactosialidosis

This disease is caused by the deficiency of protective protein (cathepsin A) and consequently lack of beta-galactosidase and neuraminidase. Galactosialidosis can be classified into early infantile form, late infantile form, and juvenile/adult form, by clinical characteristics.[10] Although there are many cases reported in Japan, no case has been reported in the Chinese population.

Schindler disease

The clinical and pathological features of Schindler disease result from the deficient activity of lysosomal alpha-N-acetylgalactosaminidase. Schindler disease can be classified into type I (early infantile form) and type II (adult-onset form).[4,11] No case has been reported in the Chinese population.

Disorders of lipid and sphingolipid degradation

Lipids are a class of hydrocarbon-containing organic compounds essential for the structure and function of living cells. Sphingolipids are a class of lipids derived from the aliphatic amino alcohol sphingosine. There are three main types of sphingolipids: ceramides, sphingomyelins, and glycosphingolipids. Sphingolipids are often found in neural tissue, and play an important role in both signal transmission and cell recognition. Different disorders of lipid and sphingolipid degradation

are caused by different types and degree of hydrolytic enzyme deficiency.

Gangliosidosis

Ganglioside is a compound composed of a glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids (AKA N-acetylneuraminic acid) linked on the sugar chain. It is a component of the cell plasma membrane which modulates cell signal transduction events. It has recently been found to be of great importance in immunology.[12]

GM1 gangliosidosis, characterized by the accumulation of GM1 ganglioside (the "prototype" ganglioside) and galactose-rich glycoprotein fragments, are caused by a deficiency of beta-galactosidase, with resulting abnormal storage of acidic lipid materials in cells of the central and peripheral nervous systems, particularly in the nerve cells. GM1 has three forms: early infantile, late infantile, and adult. Qian et al[13] reported a 1.5-year-old girl with early infantile GM1 gangliosidosis died as a result of pneumonia and respiratory hypoxia. She had psychomotor disorder from neonatal period and low β-galactosidase activity of peripheral blood leukocytes.

GM2-gangliosidosis, a group of recessive disorders characterized by accumulation of GM2 ganglioside in neuronal cells, has three types: type I, type II and AB variant. GM2-gangliosidosis type I, also known as Tay-Sachs disease, is caused by a deficiency in the enzyme beta-hexosaminidase A. It can also be classified into variant forms (Infantile, Juvenile, Adult/Late) based on the time of onset of neurological symptoms. Patients with this desease are characterized by a "cherry-red" spot in their retina. In 1987, Shi et al[14] reported the first case of successful prenatal diagnosis of GM2-gangliosidosis type I by determining the activities of relevant lysosomal hydrolases in cultured amniotic cells. Akalin et al[15] found two new mutations of beta-hexosaminidase A gene (HEXA) in Chinese: one is an insertion of an A after nt 547 which generates an early termination codon 6 bp downstream from the insertion site, the other is a T>C transition at nt 1453 with the corresponding amino acid substitution W485R. Clinical features and pathological changes have helped the diagnosis of many cases in the Chinese population, but rarely been confirmed by enzyme activity or DNA test.[16,17]

Fabry disease

Fabry disease is an X-linked inherited LSD, caused by deficiency of lysosomal alpha-galactosidase A due to mutations in the Gal gene at Xq22, and consequently the intralysosomal accumulation of glycosphingolipids. Pathological symptoms may include skin lesions, episodes of fever, and eratopathy. Death in early adulthood is usually due to renal failure.[18] In China, most patients with Fabry disease were diagnosed by clinical features and pathological changes, and partly confirmed by DNA or enzyme activity test.[19-21] Some new alpha-galactosidase A mutations were identified, including a G to C transversion in the last nucleotide of exon 1, a point mutation S65T, a C to A transversion resulting in an early termination Y222X, an A to G transition with the corresponding amino acid substitution T410A and a G to C transition causing the corresponding amino acid substitution A292P.[22-26] Clinical trial of enzyme replacement therapy has not been applied in Chinese patients.

Gaucher disease

Gaucher disease is caused by impaired activity of glucocerebrosidase, resulting in the accumulation of glucocerebroside. Symptoms may include hepatosplenomegaly, liver malfunction, skeletal disorders, severe neurologic complications, swelling of lymph nodes, distended abdomen, a brownish tint to the skin, anemia, low blood platelets and yellow fatty deposits on the sclera. Gaucher disease has three common clinical subtypes: type 1 (nonneuropathic type) is the most common form; type 2 (acute infantile neuropathic type) typically begins within 6 months from birth; type 3 (chronic neuronopathic form) can begin at any time in childhood or even in adulthood.[27]

As the most common lysosomal storage disorder, Gaucher disease was given much attention in China. Most patients with Gaucher disease were diagnosed by clinical features and pathological changes, and some of them were confirmed by DNA or enzyme test. Wang et al[28] established the prenatal diagnosis by testing β-glucosidase in chorionic villi. In the past decade, many new mutations of Chinese patients have been reported.[29-36] By studying the relationship between genotype and phenotype in 10 Chinese cases of Gaucher's disease, Shi et al[37] found that L444P mutation is commonly found in either neuropathic or nonneuropathic type of the disease, whereas F213I, D409H and G202R mutations are only closely related to the neuropathic type. Currently, enzyme replacement therapy is being taken in Chinese patients with Gaucher disease.

Metachromatic leukodystrophy

It is caused by the deficiency of arylsulfatase A, causing the storage of the sphingolipid sulfatide. The disease is characterized by progressive demyelination, which results in severe, finally lethal, neurologic symptoms.[38] Genetically, the disease is heterogeneous. Most mutant alleles are private, and thus no common mutation has

been found in Chinese.[39,40] In China, most patients with metachromatic leukodystrophy disease were diagnosed by clinical features and pathological changes, and some of them were confirmed by enzyme test.[41,42] The activity of arylsulfatase A in various tissues was tested among ten postnatally and five prenatally diagnosed cases.[3,43]

Niemann-Pick diseases

Niemann-Pick diseases can be classified into four types according to the genetic causes and the symptoms exhibited by the patient. Both type A and B are caused by mutations in the SMPD1 gene, which encodes acid sphingomyelinase. Type C1 is caused by mutations in the NPC1 gene, whose protein product is involved in the movement of cholesterol and lipids within cells. Type C2 is caused by mutations in the NPC2 gene whose protein product binds to and transports cholesterol.

Zhang et al[44] reported four prenatal diagnosed cases of type B Niemann-Pick disease. Fang et al[45] employed [^{14}C] sphingomyelin as the substrate and assess the activity of sphingomyelinase in a prenatal case. Clinical features and pathological changes helped to diagnose many Niemann-Pick cases in Chinese, but only some of them were confirmed by enzyme activity test.[46]

Lyu et al[47] reported the first case of Niemann-Pick type C in the Chinese population, which had specific clinical characteristics, typical pathologic and histochemical manifestations, and normal activities of sphingomyelinase. Niemann-Pick disease type C1 is also heterogeneous. Yang et al[48] found six novel NPC1 mutations (N968S, G1015V, G1034R, V1212L, S738Stop and I635fs) in Chinese patients.

Farber lipogranulomatosis

It is caused by the accumulation of ceramide because of the deficiency of acid ceramidase. Farber disease presents in the first few weeks of life with irritability, hoarse crying, hepatosplenomegaly, nodular swellings of the joints, severe mental and motor retardation and recurrent respiratory infections. Death usually occurs within 2 years of age. No case has been reported in the Chinese population.

Cholesterol ester storage disease

Cholesterol ester storage disease, also known as Wolman disease, is caused by accumulation of cholesterol esters and triglycerides because of the deficiency of acid lipase. Wolman disease presents in the first weeks of life with hepatosplenomegaly, failure to thrive, diarrhoea and vomiting. The adrenal glands become calcified and foam cells develop in bone marrow and other tissues. Death usually occurs within a few months of life. Only one Chinese case in Taiwan was reported.[49]

Disorders of mucopolysaccharide degradation

Mucopolysaccharides (or glycosaminoglycans, GAGs) are long unbranched polysaccharides consisting of a repeating disaccharide unit. Members of the mucopolysaccharide family vary in the types of hexosamine, hexose or hexuronic acid unit. They also vary in the geometry of glycosidic linkage. Mucopolysaccharides form an important component of connective tissues.

Mucopolysaccharidosis (MPS)

Mucopolysaccharidosis is a group of inherited metabolic diseases caused by the absence or malfunctioning of lysosomal enzymes essential to breaking down mucopolysaccharides. Characterized by the accumulation of dermatan sulfate and heparan sulfate, mucopolysaccharidosis is classified into 7 clinical types (type I, II, III, IV, VI, VII and IX) and numerous subtypes (such as type IH, IS, IH/S, IIIA, IIIB, IIIC, IIID, IVA and IVB).

MPS I, known as Hurler syndrome (MPS IH), Scheie syndrome (MPS IS) and Hurler-Scheie syndrome (MSP IH/S), is caused by deficiency of α-L-iduronidase. MPS II, known as Hunter syndrome, is caused by deficiency of iduronate-2-sulfatase. MPS III, known as Sanfilippo syndrome, is caused by deficiency of heparan N-sulfatase (MPS IIIA), α-N-acetylglucosaminidase (MPS IIIB), acetylCoA N-acetyltransferase (MPS IIIC) and N-acetylglucosamine 6-sulphatase (MPS IIID), respectively. MPS IV, known as Morquio syndrome, is caused by deficiency of galactose 6-sulfatase (MPS IVA) and β-galactosidase (MPS IVB). MPS VI, known as Maroteaux-Lamy syndrome, is caused by deficiency of N-acetylgalactosamine 4-sulfatase (MPS VIA) or arylsulfatase B (MPS VIB). MPS VII, known as Sly syndrome, is caused by deficiency of β-glucuronidase. MPS IX is caused by deficiency of hyaluronidase.

Molecular mutation studies revealed many novel mutations in respectively genes of Chinese patients of MPS I,[50,51] MPS II,[52,53] MPS III,[54] MPS IV[55] and MPS VI.[56,57] Clinical features and pathological changes helped the diagnosis of many MPS patients in Chinese,[58] and some of them were confirmed by DNA testing.[59,60] Protocols were developed to test the activity of α-L-iduronidase, galactose 6-sulfatase, and arylsulfatase B. Prenatal diagnosis of nine MPS cases were reported.[3,61]

Multiple sulfatase deficiency (MSD)

Multiple sulfatase deficiency, characterized by impaired activity of all known sulfatases, is caused by deficiency of SUMF1 gene product that is responsible for post-

translational modification of a cysteine residue, which is essential to the activity of sulfatases. Less than 30 MSD patients have been reported up to now and 23 different mutations in the SUMF1 gene have been identified.[62] No case has been reported in the Chinese population.

Other lysosomal storage diseases

Neuronal ceroid-lipofuscinoses (NCL)

Neuronal ceroid-lipofuscinoses, known as Batten disease, are a group of severe neurodegenerative disorders characterized clinically by visual loss, seizures and psychomotor degeneration, and pathologically by loss of neurons and lysosomal accumulation of autofluorescent storage material resembling aging pigment. Until now, eight genetic loci have been identified (CLN1-8). Four CLN genes have been isolated (CLN1, CLN2, CLN3 and CLN5) and their gene products have been characterized. The product of CLN1 is a lysosomal palmitoyl-protein thioesterase (PPT1) and CLN2 is a lysosomal pepstatin-insensitive peptidase. CLN3 and CLN5 are proteins with multiple membrane-spanning regions and have no homologies to other proteins that would suggest their function. The CLN3 protein is associated with lysosomal membranes and the intracellular location of the CLN5 protein is unknown. Therefore, there is ample evidence that the neuronal ceroid-lipofuscinoses represent a new class of lysosomal storage disorders.[63] Zhong et al[64] used allele specific primer extension (ASPE) in prenatal diagnostic test for infantile and late-infantile NCL. In China, three cases of late-infantile and one case of juvenile NCL were reported without confirmation by DNA or enzyme test.[65-67]

Glycogen storage disease type II

Glycogen storage disease type II, known as Pompe disease, is caused by the deficiency of acidic α-glucosidase. It is characterized by the intra-lysosomal accumulation of glycogen and consequent progressive skeletal and heart muscle dysfunction. Genetic studies revealed some novel mutations in Chinese Pompe patients,[68,69] and the C1935A is the most common mutant in the Chinese population.[70] Clinical features and pathological changes helped in diagnosis of some patients with Pompe disease in China, but few of them were confirmed by enzyme or DNA test.

Glycogen storage disease type II B

Glycogen storage disease type II B, known as Danon disease, is caused by the deficiency of lysosomal-associated membrane protein 2, LAMP-2. Danon disease typically presents in the second decade in males, or later in affected females. It is characterized by severe cardiomyopathy, skeletal muscle weakness and varied mental retardation.[71] As an extremely rare disease, no case has been reported in the Chinese population.

Mucolipidosis II

Mucolipidosis II, known as inclusion-cell (I-cell) disease, mucolipidosis IIIA and mucolipidosis IIIC are caused by the deficiency of N-acetylglucosamine-1-phosphotransferase. Clinical symptoms include hypotonia, facial dysmorphia, gingival hypertrophy, hepatomegaly, skeletal dysplasia, frequent upper respiratory tract infections, hernias and cardiac complications. Zhang et al[72] have established a method to test the activity of N-acetylglucosamine-1-phosphotransferase in various tissues, and reported one prenatal diagnosed case of this disease.

Other lysosomal storage diseases, such as mucolipidosis IV, pycnodysostosis, adult nonnephropathic type cystinosis, infantile nephropathic type cystinosis, cystinosis juvenile or adolescent nephropathic, infantile sialic acid storage disorder and saposin deficiencies, are rare and no case has been reported in the Chinese population.

Perspectives

Nowadays treatments for some LSDs are available, such as enzyme replacement therapy for Gaucher disease, Fibry disease, Pompe disease (clinical trial), Hurler syndrome (clinical trial) and Niemann-Pick disease type A/B (preclinical), substrate reduction therapy for type 3 Gaucher disease, Niemann-Pick disease type C and GM2 gangliosidosis.[73] There is a growing consensus on the development of newborn-screening methods to detect these disorders before the onset of clinical symptoms so that therapeutic interventions can be initiated. Quantification of metabolites and enzyme reaction product in dried blood spots (DBS) by mass spectrometry and high sensitivity fluorescent methods is rapidly advancing.

As currently there is no cured prognosis for many LSDs, combination of the methods of molecular genetics, cytogenetics and biochemical genetics is urgently expected to facilitate prenatal diagnosis of LSDs to reduce the risk of newborn patients and thus lighten the burden of families.

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