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Newborn Screening for Lysosomal Storage Diseases in Taiwan

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Lysosomal storage diseases (LSDs) are a group of rare inherited metabolic disorders caused by the deficiency of specific lysosomal enzymes and subsequent accumulation of substrates. Enzyme deficiency leads to progressive intra-lysosomal accumulation of the incompletely degraded substances, which cause dysfunction and destruction of the cell and eventually multiple organ damage. Patients have a broad spectrum of clinical phenotypes which are generally not specific for some LSDs, leading to missed or delayed diagnosis. Due to the availability of treatment including enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation for some LSDs, early diagnosis is important. ERT products have been approved with optimal outcomes for some LSDs in the recent decades, including Gaucher, Fabry, mucopolysaccharidosis (MPS) I, Pompe, MPS VI, MPS II, and MPS IVA diseases. ERT can stabilize the clinical condition, prevent disease progression, and improve the long-term outcome of these diseases, especially if started prior to irreversible organ damage. Based on the availability of therapy and suitable screening methods in the recent years, some LSDs, including Pompe, Fabry, Gaucher, MPS I, MPS II, and MPS VI diseases have been incorporated into nationwide newborn screening panels in Taiwan.

Keywords: Enzyme replacement therapy, Fluorimetry, Hematopoietic stem cell transplantation, Lysosomal storage disease, Newborn screening, Tandem mass spectrometry

Introduction

Lysosomal storage diseases (LSDs) are a group of rare inherited metabolic disorders caused by the deficiency of specific lysosomal enzymes and subsequent accumulation of substrates. More than 50 LSDs are known with a collective incidence of approximately 1 in 7,000–8,000 live births. Enzyme deficiency leads to progressive intra-lysosomal accumulation of the non-degraded substances, which cause cell destruction and eventually multiple organ damage. Individual LSD has its specific signs and symptoms due to different type of lysosomal substrate accumulation, varied organ(s) involved, and the immune or inflammatory responses. Patients have a broad spectrum of clinical phenotypes which are generally not specific for some LSDs, leading to missed or delayed diagnosis. Even within single LSD, there can be significantly varied impacts on different onset ages, severity of symptoms, and central nervous system involvement. Due to the availability of treatment including enzyme replacement therapy (ERT), substrate reduction therapy, and hematopoietic stem cell transplantation (HSCT) for some LSDs, early diagnosis is important. The US Food and Drug Administration has approved ERT products for some LSDs in the recent decades, including Gaucher, Fabry, mucopolysaccharidosis (MPS) I, Pompe, MPS VI, MPS II, and MPS IVA diseases. ERT can stabilize the clinical condition, prevent disease progression, and improve the long-term outcome of these diseases, especially if started prior to irreversible organ damage[1-3]. Based on the availability of therapy and suitable screening methods in the recent years, some LSDs,

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including Pompe, Fabry, Gaucher, MPS I, MPS II, and MPS VI diseases have been incorporated into nationwide newborn screening panels in Taiwan.

Newborn screening in Taiwan was initiated as a pilot program in 1981. The coverage rate increased to 90% in 1990, and is currently more than 99%. Screening services are coordinated and centralized in three national newborn screening centers, including Chinese Foundation of Health, Taipei Institute of Pathology, and National Taiwan University Hospital. Each center is responsible for one third of the designated area of Taiwan (estimated 60,000–70,000 cases per year, about ~33.3% of all newborns) in executing newborn screening programs[4]. Here, we review the current status of newborn screening for LSDs in Taiwan.

Selected Lysosomal Storage Disorders

1. Pompe disease

Pompe disease, also known as glycogen storage disease type II, is an autosomal-recessive lysosomal storage disorder characterized by the deficiency of acid α-glucosidase (GAA) activity, which leads to progressive accumulation of glycogen in all tissues, particularly in skeletal muscles and heart. The clinical phenotypes and the rate of worsening resulted from the disease can vary markedly, ranging from the severe, rapidly progressive infantile-onset Pompe disease (IOPD) to the attenuated, later-onset Pompe disease (LOPD)[5].

Chien et al.[6] reported the initiation of a pilot newborn screening program for Pompe disease at Newborn Screening Center of National Taiwan University Hospital in 2005, measuring GAA activity in dried blood spots (DBSs) via a fluorescence assay. Up until the end of 2011, more than 470,000 newborns were screened, and nine IOPD newborns received their first ERT prior to the age of 1 month. Yang et al.[7] reported another nationwide program of 669,797 newborns screening for Pompe disease in Taiwan. Fourteen newborns were diagnosed with IOPD. After 2010, the mean age at first ERT was 11.9 days. Yang et al.[7] described that their patients had better physical and developmental outcomes and lower anti-rh GAA antibodies after 2 years of treatment, even compared with the former group that started the ERT just 10 days later than their cohort. They suggested that ERT for IOPD patients should be started as early as possible before irreversible organ damage occurs. In Taiwan, relying on the performance of effective newborn screening system and accurate diagnostic protocol, IOPD cases could be detected more quickly and the application of the first-time ERT even a few days earlier may lead to better outcomes[6-13].

2. Fabry disease

Fabry disease is an X-linked inherited disorder resulted from the absence or reduction of α-galactosidase A activity in lysosomes, leading to a progressive accumulation of globotriaosylceramide (Gb3) and other neutral glycosphingolipids in lysosomes of all cells in the body. It is a complex, multisystemic disorder characterized clinically by acroparesthesias, hypohydrosis, angiokeratomas, corneal opacities, cardiomyopathy, gastrointestinal disturbances, progressive renal impairment and cerebrovascular lesions[14].

Lin et al.[15] screened ~57,000 newborn boys and found various Fabry mutations in ~1 in 1,400, and 82% of them had the cardiac variant mutation IVS4+919G>A with a very high incidence of 1 in 1,600. They reported an unexpected high prevalence of the cardiac variant Fabry mutation IVS4+919G>A among both newborns (~1 in 1600 males) and patients with idiopathic hypertrophic cardiomyopathy in the Taiwanese population. Hwu et al.[16] screened ~90,000 baby boys and found that the incidence of Fabry mutations was in ~1 in 1,250, in those 86% had the IVS4+919G>A mutation, with an incidence of 1 in 1,500. ERT appears be beneficial and safe for Taiwanese patients with cardiac-type Fabry disease, as well as for those with the classic type. The early identification of undiagnosed patients allows timely therapeutic intervention providing a better clinical outcome[17-19].

3. MPS I, MPS II, and MPS VI

MPSs are a group of rare inherited metabolic disorders caused by deficiencies of specific lysosomal enzymes involved in the sequential degradation of glycosaminoglycans (GAGs), leading to substrate accumulation in various cells and tissues, and progressive multiple organ dysfunction. Patients with MPS generally manifest unaffected at birth, but may appear multiple clinical symptoms after several months or years, such as coarse facial features, corneal clouding, hearing impairment, hepatomegaly, valvular heart disease, cardiac hypertrophy, skeletal deformities, poor joint range of motion, profound growth retardation and variable degree of central nervous system involvement. Eleven distinct types of MPS diseases (I, II, IIIA, IIIB, IIIC, IIID, IVA, IVB, VI, VII, and IX) have been reported. All MPS diseases are autosomal recessive inherited except MPS II, which is an X-linked trait and occurs mainly in males. Broad clinical heterogeneity exists in all MPS types with subjects ranging from attenu-

ated to severe forms[20]. A retrospective epidemiological survey revealed that from 1984 to 2004, the collective birth incidence of all MPS patients in Taiwan was 2.04 per 100,000 live births. MPS II had the highest calculated birth incidence (52% of all MPS cases diagnosed) in Taiwan, followed by MPS III (19%), MPS IV (16%), MPS VI (7%), and MPS I (6%)[21].

Lin et al.[22] conducted a pilot newborn screening program for MPS I from 2008 to 2013. α-iduronidase (IDUA) activity was measured in DBSs from 35,285 newborns using a fluorometric assay. Two subjects were identified with deficient leukocyte IDUA activity as well as confirmation by molecular DNA analyses. The incidence of MPS I in Taiwan estimated from this study is about 1/17,643 live births.

Newborn screening for MPS I, MPS II, and MPS VI has been executed in Taiwan since August, 2015. The suspicious infants who failed on the recalled checking were referred to the reference center at Mackay Memorial Hospital for detailed confirmative diagnostic procedures including urine GAGs qualitative and quantitative analyses, leukocyte enzyme activity assays, molecular analysis, echocardiography, X-ray checkups, and physical examinations. A total of 93,063 infants had joined the MPS I, MPS II, and MPS VI newborn screening program by the end of December, 2016. Three MPS I and one MPS II infants were identified. Urine GAG quantification, two-dimensional electrophoresis, and tandem mass spectrometry (MS/MS) for predominant disaccharide units of urinary GAGs were performed[23,24]. Leukocyte pellet was isolated from EDTA blood and used for fluorescent enzymatic assay of IDUA, iduronate-2-sulfatase (IDS), or arylsulfatase B (ASB) enzymatic assay. In addition, DNA was extracted and DNA sequencing analysis was performed on the babies and their parents[25]. ERT for MPS I, MPS II, and MPS VI have become available with optimal outcomes associated with early diagnosis and timely treatment which can be achieved by newborn screening[26-30].

4. Gaucher disease

Gaucher disease is an autosomal recessive lysosomal storage disease caused by the deficiency of the enzyme β-glucocerebrosidase (GBA). The deficient GBA activity leads to the accumulation of glucosylceramide in cells and particular tissues with subsequent devastating dysfunction of multiple organ systems. It is a multisystem storage disorder manifested by anemia, thrombocytopenia, hepatosplenomegaly, and bone dysplasia. Primary involvement of the central nervous system occurs in a minority of patients[31].

For the national newborn screening program of Gaucher disease in Taiwan, Lin et al.[32] reported that from 2011 to 2015, a total of 304,583 DBSs were screened. The most common mutation was c.1448T>C (p.Leu483Pro, previously known as Leu444Pro). One boy had compound heterozygous mutations, c.509G>A (p.Arg131His) and c.1448T>C (p.Leu483Pro), as well as the lowest GBA enzyme activity among all subjects. The boy had typical symptom with hepatosplenomegaly after two years' follow up and received ERT since then with prompt response. ERT has been shown positive effects in improving the Gaucher disease burden[33]. It is important to diagnose the disease earlier and to start effective therapy timely before irreversible damage occurs. Newborn screening for Gaucher disease is appropriate for early diagnosis and the results of DNA analysis is useful for genetic counseling.

Functional Detection of Enzymatic Products by Using the MS/MS Method

In recent years, Gelb et al.[34] have demonstrated high-throughput MS/MS proven to be a sensitive technology for large-scale screening of several LSDs, including Pompe, Fabry, Gaucher, MPS I, Niemann-Pick A/B, and Krabbe diseases[1]. The Chinese Foundation of Health was the first newborn screening center in Asia-Pacific region that has used MS/MS technology of large scale multiplexed screening for LSDs since 2010[4]. Liao et al.[35] reported a pilot study of large scale newborn screening for Fabry, Pompe, and Gaucher diseases by using the MS/MS method in Taiwan and compared the performance of the MS/MS with fluorescence (4-MU) method. Among the consecutive collection of more than 100,000 DBSs, sixty-four newborns were identified with confirmed Fabry mutations, 16 with infantile or late-onset Pompe disease, and one with Gaucher disease. The positive predictive value increased from 4.0% to 7.1% in the Pompe study, and from 61.0% to 95.5% in the Fabry study by the MS/MS compared with 4-MU assay. They concluded that the MS/MS method was a more specific, powerful and efficient tool than the 4-MU assay, as well as providing a multiplex solution of newborn screening for LSDs. Liao et al.[36] also delineated that MS/MS instead of fluorometry distinguished affected and pseudodeficiency patients in newborn screening for Pompe disease. In their study, the relatively large analytical range of MS/MS GAA assay (96%) winning over the fluorometric assay (<10%) in separation of the pseudodeficiencies from the IOPD/LOPD groups provided a robust approach to reduce the number of referrals.

In addition to newborn screening for LSDs, the researchers

in Taiwan also discovered some biomarkers for following up these diseases, such as globotriaosylsphingosine (lyso-Gb3) and globotriaosylceramide (Gb3) for Fabry disease[18,19,37,38], glucose tetrasaccharide (Glc4) for Pompe disease[39], CCL18 and chitotriosidase for Gaucher disease[33], and GAG (dermatan sulfate/heparin sulfate/keratan sulfate/chondroitin sulfate) for MPS[23]. The quantification of these biomarkers revealed better performance and discrimination in evaluation of the clinical course and follow up for the subjects with LSDs[4].

Conclusions

The performance of newborn screening and the confirmatory diagnosis for LSDs in Taiwan are quite remarkable and well-done. Early confirmatory diagnosis offers these subjects with timely opportunity to receive appropriate medical care, including ERT and HSCT, that leads to better clinical outcome. Newborn screening is a major public health achievement which has improved the morbidity and mortality of individuals with inborn errors of metabolism. Without a positive family history, presymptomatic detection of LSD could only be achieved by a newborn screening program. However, the detection and diagnosis in neonatal stage with late-onset LSDs, especially those with an onset in adulthood, may raise ethical issues. Major challenges include the cost and efficacy of the currently available treatments for LSDs and follow up of subjects who are predicted to develop late-onset LSDs. Before the era of newborn screening for LSDs, we could only diagnose LSDs by their pathologic manifestations. Now we can detect specific enzyme activity and gene mutations before the pathology is manifested. So how do we define the disease? It is a critical issue for us, particularly in the situation when there appears to be a disease with incomplete penetrance. It remains a question if some neonates with specific lysosomal enzyme deficiency and novel mutations left to be confirmed with having specific LSDs. Is an LSD the resulting symptomatic manifestation solely of the correlated enzyme deficiency? Obviously the availability of enzyme assays and genetic analysis have complicated the issue. Further comprehensive family studies and long-term follow up for identified individuals with probably pathogenic mutations could help us better understand which forms of LSDs need treatment as well as allow us to determine whether and when to start therapeutic interventions for these subjects.

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