

Infantile Pompe disease: A case report and review of the Chinese literature

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Abstract. Pompe disease, also known as glycogen storage disease type II, is caused by acid maltase deficiency, and can lead to lysosomal glycogen storage. The primal manifestations may be observed in children and adults, and also in infants. In general, the clinical spectrum in infants is more progressive and lethal than that in older patients. This case report describes the case of a newborn who was found to have cardiac hypertrophy, hepatomegaly and elevated serum enzyme levels, which was characterized by an aspartate aminotransferase level of 95 U/l, lactate dehydrogenase level of 778 U/l and creatine kinase level of 1,299 U/l. On the basis of the clinical signs and laboratory results, dried blood spots from the baby were tested to determine the acid α -glucosidase (GAA) activity, and the result confirmed that the GAA activity was only 0.10 pmol/punch/h (normal reference range, 2.88-89.02 pmol/punch/h) at pH 3.8, which was clearly lower than the normal range, leading to a diagnosis of Pompe disease. Pompe disease is incurable, and before the introduction of enzyme replacement therapy (ERT), pain relief was the main treatment. Recognizing this disease earlier and starting ERT in infants prior to the development of clinical symptoms is likely to improve the quality of life of patients.

Introduction

Pompe disease (OMIM 232300), a rare autosomal recessive disorder, is caused by mutation in the gene encoding acid α -1,4-glucosidase (GAA, OMIM 606800), which maps on chromosome 17, and results in glycogen storage in many tissues. The incidence of Pompe disease appears to vary according to ethnicity. Its estimated frequency is 1/50,000 in

Taiwan (1), 1/138,000 in the Caucasian population and 1/31,000 in individuals of African ancestry (2). The onset symptoms can appear at any time of life, ranging from 0 to 71 years of age (3). Infantile Pompe disease (IPD), also known as classic Pompe disease, presents with cardiomegaly as the most common symptom. Patients often succumb to cardio-respiratory failure caused by muscle weakness and hypotonia in the first year of life (4). The classic form occurs soon after birth, excluding cardiomyopathy. Patients with this disorder also exhibit muscle weakness, hypotonia, respiratory distress, feeding problems and other symptoms. This study describes a case that was unexpectedly identified, having cardiomegaly and hepatomegaly without progressive motor symptoms or feeding problems, and was diagnosed from the GAA activity following dried blood spot (DBS) testing. IPD has a better response to enzyme replacement therapy (ERT) than non-classic Pompe disease, and the earlier the ERT treatment is initiated, the better the prognosis. The condition of the patient accepting the therapy is considered to be more important than the age of the patient to the outcome (5). ERT was not accepted in the present case because of a poor prognosis and other considerations of her parents.

Case report

In December 28, 2013, a 12-h-old newborn girl, the first child of non-consanguineous parents was admitted to Nanjing Children's Hospital (Nanjing, China) with a hoarse voice after birth. The baby was born at term with a birth weight of 3,500 g. Following rupture of the membranes 21 h earlier, the mother delivered the baby at 38 weeks in a delivery room. Prenatal examinations and assays were performed in a timely manner and identified no abnormalities. A general physical examination of the baby was conducted, and the liver edge ~3 cm below the rib was palpated. No dysmorphic features were identified in the examination. A cardiac ultrasound was ordered to examine the heart, which indicated the presence of cardiac hypertrophy. Serum muscle enzymes, including aspartate aminotransferase, lactate dehydrogenase and creatine kinase were found to be elevated (examination and assay results are listed in Table I). No feeding problems, macroglossia, hypotonia or muscle weakness were exhibited. The blood GAA activity was screened to eliminate Pompe disease. DBSs were sent to Shanghai Institute for Pediatric Research, Xinhua Hospital,

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Table I. Symptoms, examination and assay results of the case.

Symptoms and diagnosis	Assay and examination results
Cardiac hypertrophy	AST, 95 U/l; LDH, 778 U/l; CK, 1,299 U/l
Hepatomegaly	Echocardiography: left ventricular posterior wall slightly thickened and ventricular septal thickening; patent ductus arteriosus 2 mm in diameter; atrial septal defect 3.5 mm in diameter; no left ventricular outflow tract obstruction
Infantile Pompe disease	GAA, 0.1 pmol/punch/h ^a

^aNormal reference range 2.88-89.02 pmol/punch/h at pH 3.8. AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; GAA, acid α -glucosidase.

Table II. Signs and symptoms of Pompe disease in reviewed cases (age <1 year old).

Signs and symptoms	No. (%)
Feeding or swallowing problems	17 (51.5)
Dysphagia or respiratory problems	17 (51.5)
Hypotonia and weakness or rapidly progressive disease course	21 (63.6)
Delayed motor milestones	19 (57.5)
Cardiomegaly and cardiomyopathy and/or cardiac failure	25 (75.7)
Moderate hepatomegaly	22 (66.7)
Macroglossia	15 (45.4)

Table III. Laboratory assays and examinations of the reviewed cases (n).

Assay/examination	Performed	Abnormal
CK	28	26
Transaminasemia	20	20
LDH	14	13
Electromyogram	7	7
Electrocardiogram	25	25
Muscle biopsy	11	10
Cardiac ultrasonography	23	23
GAA activity		
Skin fibroblast	6	6
DBS or leukocyte/lymphocyte	16	16
Genetic analysis	23	23

CK, creatine kinase; LDH, lactate dehydrogenase; GAA, acid α -glucosidase.

Shanghai Jiaotong University Medical School (Shanghai, China). A month later, the results were obtained and revealed that the GAA activity was 0.1 pmol/punch/h (normal reference range, 2.88-89.02 pmol/punch/h) at pH 3.8, significantly lower than the normal prescribed minimum, which indicated IPD. Although the family members had no history of this disorder,

Table IV. Mutations in the reviewed cases and whether previously reported or newly identified.

Status	Mutations	Chromosome exon numbers
Known	p.G689K, p.G576S	(10,14)
	p.P266S	(15,16)
	p.P361L, p.R437C, p.R600C, p.W746S, p.W746*	(16)
Novel	p.W738X	(10,14)
	p.A702H, p.T711A, p.V723M	(15)
	p.R168P, p.E521V, p.R594H	(16)

they were advised to undergo genetic testing. When the child was 3.5 months old, telephone follow-up was conducted, and it was found that the child had no feeding problems and was gaining weight. Her muscle tone was normal. Written informed consent was obtained from the patient's parents.

Discussion

The Wanfang, VIP Chinese Science and Technology Periodicals Database, SinoMed, Duxiu Knowledge Search Database and China National Knowledge Infrastructure databases were searched to identify reports concerning IPD published in Chinese journals. A total of 33 cases from the years 1984 to 2012 were identified, excluding a case from the same hospital. The symptoms of these cases are presented in Table II, and the laboratory and examination results are presented in Table III.

The reviewed cases were not completely investigated by the full range of assays and examinations. In particular, the electromyogram and skin fibroblast testing of GAA activity were infrequently conducted. It is possible that some of the reviewed cases did not report the results of all the tests and examinations that were conducted.

The methods for diagnosing Pompe disease include muscle biopsy, fibroblast GAA testing, gene analysis and peripheral blood GAA activity testing. The GAA assay in muscle or skin fibroblasts remains the gold standard as it can provide a definite diagnosis of Pompe disease (4). In comparison with other methods, peripheral blood GAA activity testing is more

acceptable because of its feasibility, lack of suffering and for economic reasons. In 2010, Qiu *et al* reported that DBSs were particularly suitable for the screening of newborns for GAA activity, and that leukocyte GAA activity can also be used in the diagnosis of Pompe disease in newborns and high-risk individuals (6). In 2008, Chien *et al* confirmed that the early detection of Pompe disease by newborn screening is feasible, by conducting a large-scale newborn screening pilot program in which GAA activity was measured in dried blood spots; the newborn screening resulted in an earlier diagnosis of Pompe disease (at <1 month old compared with 3-6 months old in the unscreened control group) (7). In the USA, several pilot programs that are currently ongoing or in the planning stages should provide the data necessary to recommend universal newborn screening for Pompe disease for all infants (8).

In 2005, Kishnani *et al* reviewed 168 cases of IPD in Israel, Taiwan, North America and Europe, and found that among the cases, 97.6% were confirmed by GAA activity assay; in only 10 cases (6.0%) was GAA mutation analysis pursued (2). In the reviewed cases in mainland China, ~33% of the cases had muscle biopsy, 69.7% had undergone genetic analysis, 16.2% underwent skin fibroblast testing of GAA activity, and 48.5% underwent DBS or leukocyte/lymphocyte testing of GAA activity. The skin fibroblast testing of GAA activity and genetic analysis were mostly reported in Beijing, while the DBS or leukocyte/lymphocyte testing of GAA activity was reported in Shanghai.

Pompe disease is essentially caused by encoding gene mutations that are located in chromosome 17q25.2-q25.3 and contain 19 coding exons. At present, >200 different mutations have been reported. The mutations exhibit regional differences; c.-32-13T is the most frequent mutation in late-onset Pompe disease (5), c.1935C>A (p.Asp645Glu) is very frequent in Taiwan (9), and it is also common along the coast of China (10), but there are no reports of the common mutations in mainland China. Only 69.7% of the reviewed cases had undergone genetic analysis and identified to have mutations; some of the mutations had been reported previously in other countries, and some were new identified (Table IV).

Prenatal examinations are also important for IPD. One of the reviewed cases had been found to have cardiac hypertrophy by routine prenatal ultrasonography at 38 weeks. In 2011, Swarr *et al* reported a case who had an unusual cardiac 'mass' and biventricular hypertrophy identified by prenatal ultrasound at 30 weeks, which was consistent with the diagnosis of infantile Pompe disease by the detection of GAA activity from a blood spot (11). Following the diagnosis of a patient, it may be necessary for the family to undergo genotype testing and have a genetic consultation with professional geneticists. Zeng *et al* reported the case of a pregnant woman who already had two baby girls diagnosed with the disease (12). GAA activity was tested in the fetal amniotic fluid and genetic diagnosis was conducted, which confirmed IPD prior to birth (12). If a family has an affected child or siblings, prenatal diagnosis is necessary and it can be confirmed by enzyme analysis of uncultured chorionic villus cells, or by gene analysis through chorionic villus samples or amniocentesis (4,13). Preimplantation genetic diagnosis (PGD), may be available for families in which the disease-causing mutations have been identified (13).

Prior to the emergence of ERT, there was no effective therapy for Pompe disease. No treatment other than supportive care was available to manage the symptoms of patients. In 2006, recombinant human GAA (rhGAA) was approved by the Food and Drug Administration of the USA. The treatment of the disease then changed from symptomatic management to therapeutic intervention. Previous studies reporting the effects of ERT on animals and in clinical trials have demonstrated that ERT has outstanding effects on cardiac hypertrophy and function, and some infants who initiated ERT achieved motor milestones (5). Del Rizzo *et al* (14) conducted a 26-month follow up of a baby girl who was diagnosed with Pompe disease at the age of 3 days. The child was confirmed to have ventricular hypertrophy by cardiac ultrasound, and ERT was initiated at the age of 20 days. After being treated with ERT for 24 months, the size and function of the child's heart were normal, and growth and motor development were also normal. ERT can greatly modify or moderate the phenotype and progression of the disease (15,16). The effect on muscle function is not as satisfactory as that on the heart because of variability in the skeletal muscle response (16). Early treatment of children with IPD, prior to clinical diagnosis, is of benefit in prolonging survival and improving cardiac and motor function (8), but is not a cure; however, gene therapy may be a therapeutic option (16). The outcome of ERT is likely to be more promising if treatment starts early during the course of the disease. Therefore, the initiation of screening programs for Pompe disease is recommended. Genetic consulting in pregnancy for those with affected children or siblings may be the best method of reducing the incidence or morbidity of the disease.

IPD is fatal and difficult to cure. There maybe no clinical symptoms before the heart, liver or muscles are involved. Early diagnosis is important, as once the patient has respiratory and circulatory failure, there is no cure, although symptomatic treatment may be conducted to alleviate suffering. Following the introduction of ERT, patients are able to have a better quality of life and longer lifetime. However, while ERT only help to slow the progression of the disease, gene therapy may be a promising approach a provide a cure.

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