

Infantile-Onset Glycogen Storage Disease Type II (Pompe Disease): Report of a Case with Genetic Diagnosis and Pathological Findings

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Glycogen storage disease type II (GSD-II), also known as Pompe disease, is a rare autosomal recessive disease due to deficiency of lysosomal acid α -glucosidase (GAA). The infantile-onset form is the most severe, and most patients present with hypotonia and cardiomyopathy in early infancy. We report on a typical case of Pompe disease in a patient who died at 8 months of age due to aspiration pneumonia and hypertrophic cardiomyopathy. Genetic studies showed deficient GAA activity and mutation of the GAA gene with Gly615Arg (exon 13, G1845A). On autopsy, glycogen had markedly accumulated in the liver, myocardium and skeletal muscle. The neurons of the anterior horn of the spinal cord and medulla were also involved, but the cortex was spared. These neurological-histologic findings may explain the clinical features of poor motor function, decreased deep tendon reflexes and lack of mental retardation. (*Chang Gung Med J* 2004;27:379-84)

Key words: pompe disease, autopsy, acid α -glucosidase.

Infantile-onset glycogen storage disease type II (GSD-II) is one of the causes of infantile sudden death.⁽¹⁾ Affected infants can appear normal at birth, but soon develop generalized muscle weakness, areflexia, macroglossia, hepatomegaly and massive cardiomegaly. Most patients die of cardiorespiratory failure prior to 2 years of age. GSD-II is an autosomal recessive disorder, caused by deficient activity of lysosomal acid α -glucosidase (acid maltase) (GAA). It is an enzyme responsible for the degradation of glycogen in lysosomes. GSD-II encompasses a wide range of clinical phenotypes, which correlate with residual GAA enzyme activity, and the most severe one is the infantile-onset form. In this report, we describe a case of infantile-onset Pompe disease with typical clinical appearance with genetic diagnosis and pathological findings.

CASE REPORT

A 5 month-old boy was born at full-term by a G2P2 mother. He had a birth body weight of 2750 gm. He had no perinatal insult and had a normal Apgar score 8-9. After birth, frequent respiratory distress, feeding difficulties and poor weight gain were noticed by his parents. He was sent to our hospital because of fever and respiratory distress. On examination, he had a high fever (up to 39°C), and dyspnea, and his blood pressure and pulse 109/84 mmHg and 170/min respectively. He was poorly-nourished with a body weight of 6.6 kg (25th percentile), acyanosis, weak crying, and protruding tongue. Chest examination revealed no significant heart murmur but he had coarse breathing sounds, and his precordial maximal impulse was shifted to left. There

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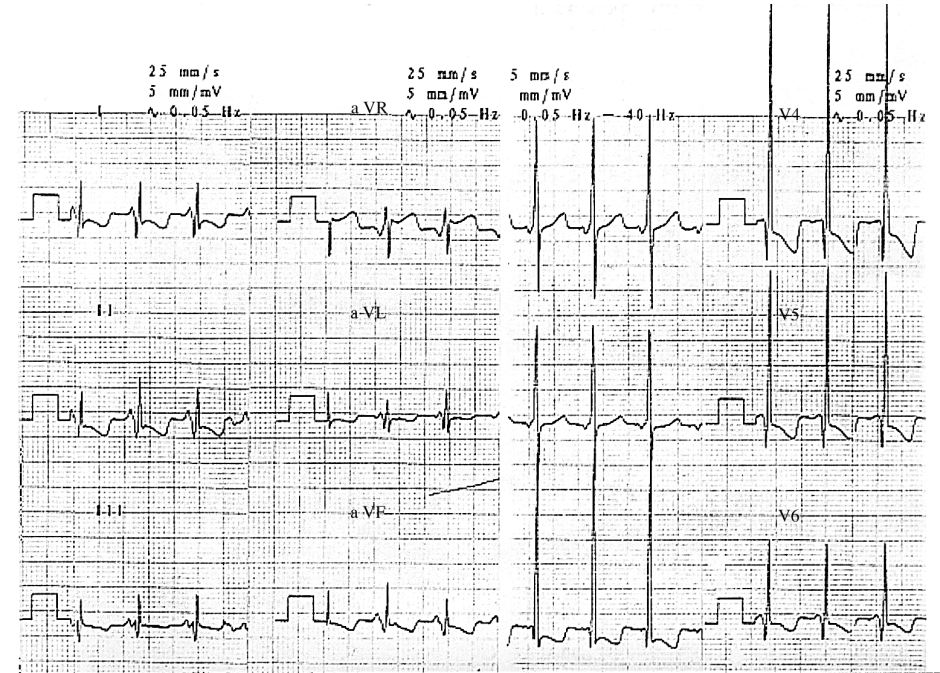


Fig. 1 ECG reveals a short PR interval, high QRS voltage, ST-T changes and prominent Q wave in the left precordial leads.

was marked hepatomegaly but no splenomegaly. Brachial and femoral pulses were normal. Neither nailbed cyanosis nor clubbing fingers were noted. Flaccid extremities with frog position and decreased deep tendon reflexes were found on neurological examination. Developmental milestones were delayed. His older brother died of hypertrophic cardiomyopathy with congestive heart failure at 5 months of age.

Chest films showed cardiomegaly with a cardiothoracic ratio of about 80% and hepatomegaly. An ECG (Fig. 1) revealed a short PR interval, high QRS voltage, ST-T changes and prominent Q wave in the left precordial leads. The echocardiogram (Fig. 2) demonstrated bi-ventricular and inter-ventricular hypertrophy but no left ventricular outflow tract obstruction. Pompe disease was confirmed by deficient activity of acid α -glucosidase (GAA) (0.283 units, control 1.203 units). This activity was also decreased in his parents (father 0.620 units, mother 0.412 units). The level of total/free carnitin, which were 19.13/15.62 nmol/mL, were mildly reduced, as compared with those in control patients ($46.3 \pm 9.9/39.8 \pm 8.6$ nmol/mL). Increased levels of glutamic oxaloacetic acid transferase (GOT)--- 377 U/L and

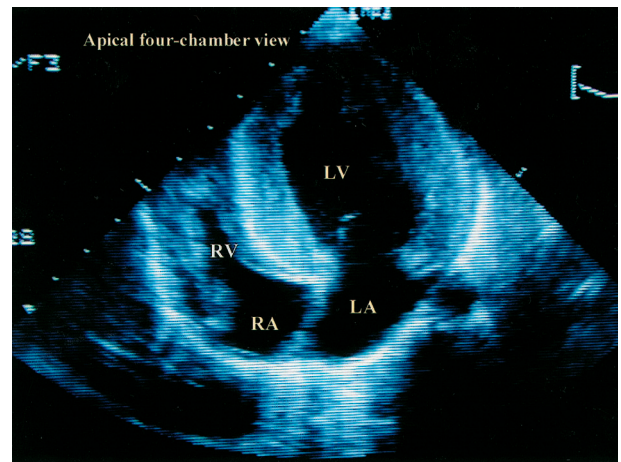


Fig. 2 Echocardiogram demonstrates bi-ventricular and inter-ventricular hypertrophy.

creatinine phosphokinase (CPK)--- 1262 U/L with CPK-MB 2.8% were also found. The levels of pyruvate and lactate (pyruvate/lactate 0.29/19.13 mg/dL) were within the normal range. There was no hypoglycemia. Genetic studies (Fig. 3) revealed point mutation on exon 13 with Gly615Arg. After improvement of his respiratory condition, he was

discharged under the medication of digoxin, lasix and carnitine. The patient had progressive cardiorespiratory deterioration despite medical treatment, and he was hospitalized several times because of bronchopneumonia and congestive heart failure. He died of cardiopulmonary failure, aspiration pneumonia and hypertrophic cardiomyopathy at 8 months of age.

On autopsy, histopathologic examination revealed vacuolar changes in all skeletal muscles and the myocardium (Fig. 4A), and marked ballooning changes in the neurons of the spinal cord (Fig. 4B) and medulla, but the cortex was spared. Periodic

acid-Schiff (PAS) stain of the neurons in the spinal cord (Fig. 4C) was strongly positive, and PAS with diesterase stain was negative, which confirmed abundant glycogen deposition. Electronic microscopic examination of hepatocytes revealed glycogen deposition in multiple membrane-bound nodules. The whole pictures were compatible with Type II glycogen storage disease (Pompe disease). Genetic studies of the myocardium and skeletal muscle also showed mutation of the specific gene for acid-maltase at exon 13. The lung showed mild multifocal bronchopneumonia, secondary to severe heart failure and poor motor function.

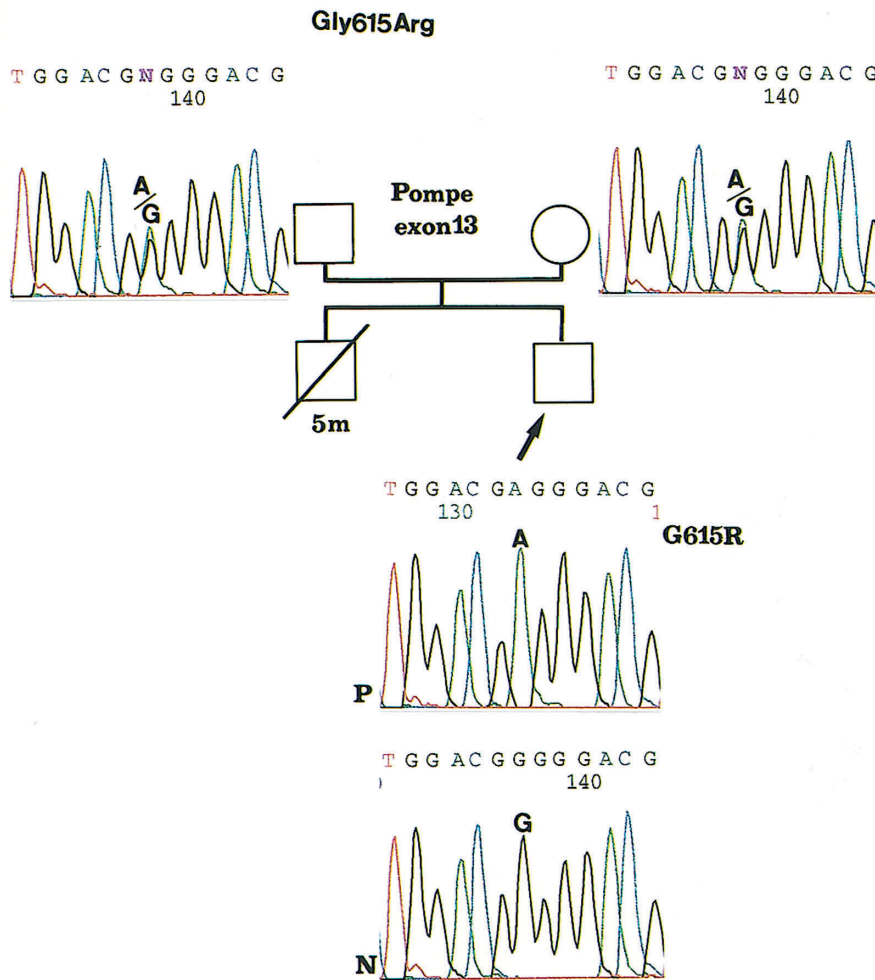


Fig. 3 DNA sequencing reveals point mutations on exon 13 of Gly615Arg.

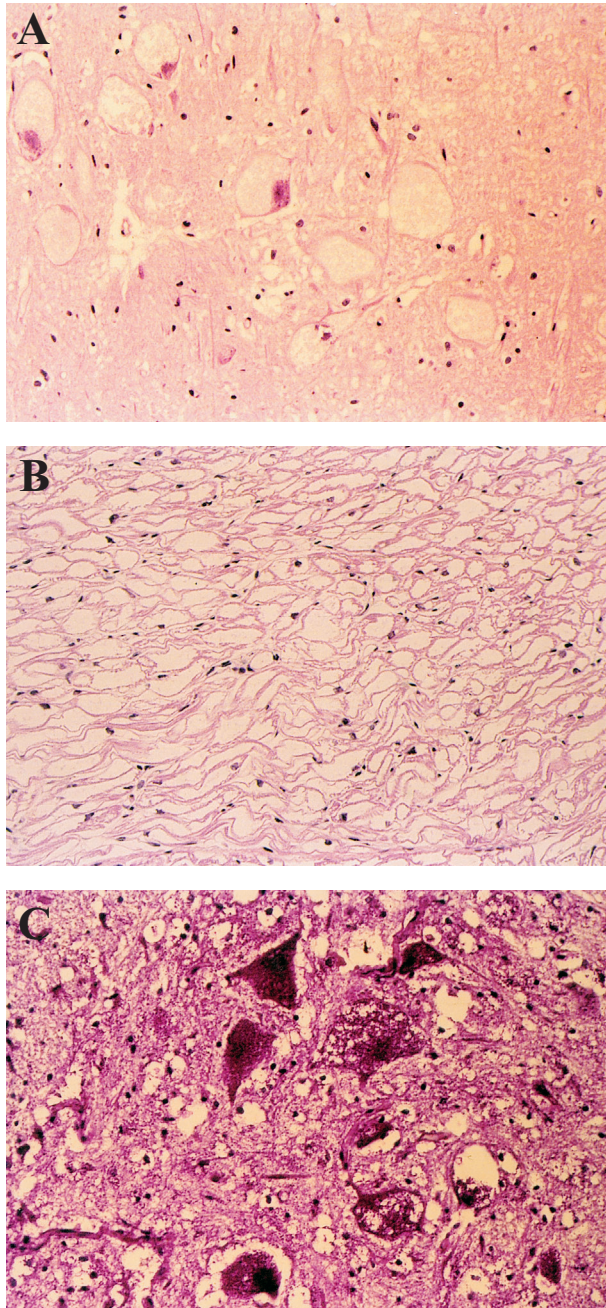


Fig. 4 Pathological examinations demonstrate vacuolar changes in the myocardium ((A) H & E stain, 100 \times) and ballooning changes in the motor neurons of the spinal cord ((B) H&E stain, 400 \times). PAS stain of the neurons ((C) 400 \times) is strongly positive.

DISCUSSION

The differential diagnosis of hypertrophic cardiomyopathy in an infant includes familial hypertrophic cardiomyopathy, corticosteroid or catecholamine excess, storage disorder, tumor infiltration, outflow tract obstruction from anatomical valvular or vascular lesions and mitochondrial respiratory chain enzyme abnormalities.^(2,3) Our patient appeared healthy at birth but gradually experienced macroglossia, hepatomegaly, massive cardiomegaly, and general muscle weakness with weak crying and feeding difficulties. His older brother died of hypertrophic cardiomyopathy with congestive heart failure at 5 months of age. The clinical features and family history were compatible with GSD-II, and genetic studies further confirmed the diagnosis.

The short PR interval on EKG may result from facilitating nerve conduction due to glycogen deposits. High QRS voltage is consistent with cardiomegaly. ST-T changes with a prominent Q in the left precordial leads may be signs of a "strain" pattern or ischemic changes.⁽³⁾

Pompe disease is caused by mutations in the GAA gene. Multiple types of mutations in the GAA gene (locus on 17q23) have been reported worldwide.⁽⁴⁾ The GAA genetic study in our patient demonstrated site mutation on exon 13, ie, Gly615Arg. The parents of our patient both carried the recessive gene. A child of two heterozygous parents has a 25% chance of being homozygous. Prenatal genetic diagnosis is done using amniocytes or chorionic villi,⁽⁵⁾ and genetic counseling for the family is necessary.

The histological findings in the nervous system of our patient showed marked deposition of glycogen on the neurons of the anterior horn of the spinal cord and medulla, but the cortex was spared. These may explain the clinical features of poor motor function, and decreased deep tendon reflexes and lack of mental retardation in this disease. The reason why the cerebral cortex was not involved is unknown, and has not been mentioned in previous articles.

Electron microscopic examination of hepatocytes reveals glycogen deposition in multiple membrane-bound nodules.⁽⁶⁾ Fat staining is focally positive. Lipid accumulation and mildly reduced concentrations of carnitine in infantile Pompe disease have

been reported.⁽⁷⁾ We prescribed carnitine for the patient to correct the deficiency, improve fatty acid metabolism and retard the rapid deterioration of cardiopulmonary function.

In this article, we reported on a patient with infantile-onset GSD-II. Comprehensive studies included a typical clinical appearance, chest roentgenogram, EKG, echocardiograms, genetic diagnosis and pathological findings. Carnitine supplements may be of benefit for the patient with infantile Pompe disease with carnitine deficiency until the safety and efficacy of rhGAA enzyme therapy has been well documented.

REFERENCES

1. Jordan DM, Ellen RE, Charles IB. An interesting case of infant sudden death: severe hypertrophic cardiomyopathy in Pompe's disease. *PACE* 1999;22:821-2.
2. Gottesman GS, Hoffmann JW, Vogler C, Chen SC. Hypertrophic cardiomyopathy in a newborn infant. *J of Pediatr* 1999;134:114-8.
3. Hugh DA, Howard PG, Edward BC, David JD. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents*. Lippincott Williams and Wilkins, 2001: 1167-86.
4. Ko TM, Hwu WL, Lin YW. Molecular genetic study of Pompe disease in Chinese patients in Taiwan. *Hum Mutat* 1999;13:380-4.
5. Kleijer WJ, van der Kraan M, Kroos MA. Prenatal diagnosis of glycogen storage disease type II: enzyme assay or mutation analysis? *Pediatr Res* 1995;38:103-6.
6. Griffin JL. Infantile acid maltase deficiency. III. Ultrastructure of metachromatic material and glycogen in muscle fibers. *Virchows Archiv B Cell Pathol Incl Mol Pathol* 1984;45:51-61.
7. Verity MA. Infantile Pompe's disease, lipid storage, and partial carnitine deficiency. *Muscle Nerve* 1991;14:435-40.

嬰孩發病之第二型肝醣貯積症 (龐貝氏症)

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肝醣貯積症第二型，也稱為龐貝氏症，是一種罕見的染色體隱性遺傳疾病。其病因是由於溶小體 (lysosome) 內之 acid α -glucosidase 缺乏。嬰孩發作型的病情最嚴重，大部份病患會在嬰兒時期即產生肌肉張力低下及心肌肥大的症狀。我們提出一典型之嬰孩發作型龐貝氏症。此病患在8個月大時因吸入性肺炎及肥厚性心病變而死亡。遺傳學檢驗發現 acid α -glucosidase 的活性降低，且在 acid α -glucosidase 之基因有突變現象。解剖後發現肝醣大量貯積於肝臟心肌及骨肌。另外在脊髓及延髓內也有肝醣貯積的情形，但大腦皮質並未受影響。這也許可以解釋此類病患運動功能不良和深腱反射降低，但是不會有智力退化的臨床現象。(長庚醫誌 2004;27:379-84)

關鍵字：龐貝氏症，解剖，acid α -glucosidase。

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