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A Case of Congenital Glycogen Storage Disease Type IV With a Novel *GBE1* Mutation

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Glycogen storage disease type IV (Andersen disease) is a rare metabolic disorder characterized by deficient glycogen branching enzyme activity resulting in abnormal, amylopectin-like glycogen deposition in multiple organs. This article reports on an infant with the congenital neuromuscular subtype of glycogen storage disease type IV who presented with polyhydramnios, hydrops fetalis, bilateral ankle contractures, biventricular cardiac dysfunction, and severe facial and extremity weakness. A muscle biopsy showed the presence of material with histochemical and ultrastructural characteristics consistent with amylopectin. Biochemical analysis demonstrated severely reduced branching enzyme activity in muscle tissue and fibroblasts. Genetic analysis demonstrated a novel deletion of exon 16 within *GBE1*, the gene associated with glycogen storage disease type IV. Continued genetic characterization of glycogen storage disease type IV patients may aid in predicting clinical outcomes in these patients and may also help in identifying treatment strategies for this potentially devastating metabolic disorder.

Keywords: glycogen storage disease type IV; *GBE1*; glycogen branching enzyme

Glycogen storage disease type IV, also known as Andersen disease, is a rare autosomal recessive disorder characterized by a deficiency in glycogen branching enzyme activity. This severe metabolic disorder results in abnormal deposition of a relatively insoluble glycogen with long, unbranched outer chains in various tissues such as liver, muscle, heart, and nervous system. Although the classic presentation is hepatosplenomegaly, failure to thrive, and progressive liver cirrhosis, glycogen storage disease type IV is a heterogeneous disorder with variable age of onset, pattern of organ involvement, and severity that is partly related to the degree of accumulation of abnormal glycogen in different tissues.[1,2] The diagnosis of glycogen storage disease type IV has traditionally been made using biochemical approaches to measure glycogen branching enzymes in individual tissues.[3] Glycogen storage disease type IV has been associated with mutations in *GBE1*, which encodes the glycogen branching enzyme.[4] Since then, several groups have identified different types of *GBE1* mutations, including nonsense, missense, deletion, insertion, and splice-site mutations, and have attempted to establish genotype–phenotype correlations.[5]

In addition to the classic presentation and milder nonprogressive variants affecting liver and cardiac function, an extremely rare and severe congenital neuromuscular variant of glycogen storage disease type IV has been described in fewer than 20 reported cases.[6-14] Furthermore, only a subset of these patients have their causative mutations identified. We report on an infant with the severe congenital neuromuscular subtype of glycogen storage disease type IV whose diagnosis was confirmed by histochemical, biochemical, and mutation analysis.

Case Report

A male infant was born at 36 weeks gestational age to consanguineous parents of Chinese ancestry with no family history for metabolic or genetic disease. A fetal ultrasound at 17

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weeks gestation demonstrated a slightly larger right than left ventricle with the heart more midline in position. A follow-up ultrasound at 35 weeks gestation suggested polyhydramnios and showed liver congestion with a thickened gall bladder. No ascites or pleural effusions were noted, but a small pericardial effusion was seen. A third ultrasound at 36 weeks gestation revealed more anasarca and a significant pericardial effusion prompting delivery by Cesarean section with vacuum assistance. Apgars were 3, 6, and 7 at 1, 5, and 10 minutes, respectively. The infant had severe hypotonia and muscle weakness requiring intubation and significant cardiorespiratory support.

At birth, his head circumference was 37 cm (>95th percentile), weight was 2600 g (50th percentile), and length was 45.5 cm (between 25 and 50th percentile). He had severe edema consistent with hydrops fetalis and multiple petechiae on the chest and upper arms. He had a slightly flattened face with very small palpebral fissures, borderline low set ears, and micrognathia. No macroglossia was evident. A dilated ophthalmologic examination was normal. There was no palpable hepatosplenomegaly. He had a single transverse palmar crease on the right hand. He had normal descended testes bilaterally. On neurological exam, he had severe bilateral facial weakness, severe hypotonia, and minimal spontaneous movement. His distal extremities responded only minimally to noxious stimulus. He had very weak palmar and plantar reflexes with poor suck and diminished deep tendon reflexes. There were bilateral equivarus deformities of the feet.

The patient required significant cardiorespiratory support for severe biventricular cardiac dysfunction. At the parents' request, ventilator support was withdrawn and the patient died shortly thereafter at 37 days postnatal age. The parents declined a postmortem examination.

Magnetic resonance imaging of the brain showed mild extra-axial fluid bifrontally, but otherwise was normal. An electroencephelogram demonstrated a low amplitude, 2 to 4 Hz delta frequency background and normal sleep architecture with no epileptiform features. Nerve conduction studies demonstrated normal sensory nerve action potentials and low amplitude compound action potentials with normal velocity. Needle electromyography revealed markedly abnormal spontaneous activity with abundant fibrillations and positive sharp waves. There were only rare motor units observed; thus a recruitment pattern could not be assessed.

Complete blood counts, serum electrolytes, and liver function tests were initially normal. The liver function tests gradually increased from an initial aspartate aminotransferase level of 64 IU/L and an alanine aminotransferase level of 9 IU/L to 249 IU/L and 177 IU/L, respectively (normal ranges: aspartate aminotransferase 0 to 40 IU/L, alanine aminotransferase 0 to 40 IU/L). Creatine kinase levels were initially elevated at 570 IU/L (normal range 38 to 174 IU/L). Cerebrospinal fluid analysis and culture were normal. Serum amino acids, urine organic acids, plasma acylcarnitine panel, urine acylglycine panel, very long chain fatty acids levels, and carbohydrate deficient transferrin testing were normal. Genetic testing revealed a normal 46,XY karyotype, no deletion of exon 7 within *SMN1* (the gene associated with spinal muscular atrophy), and no triplet repeat expansion in *DMPK* (the gene associated with myotonic dystrophy).

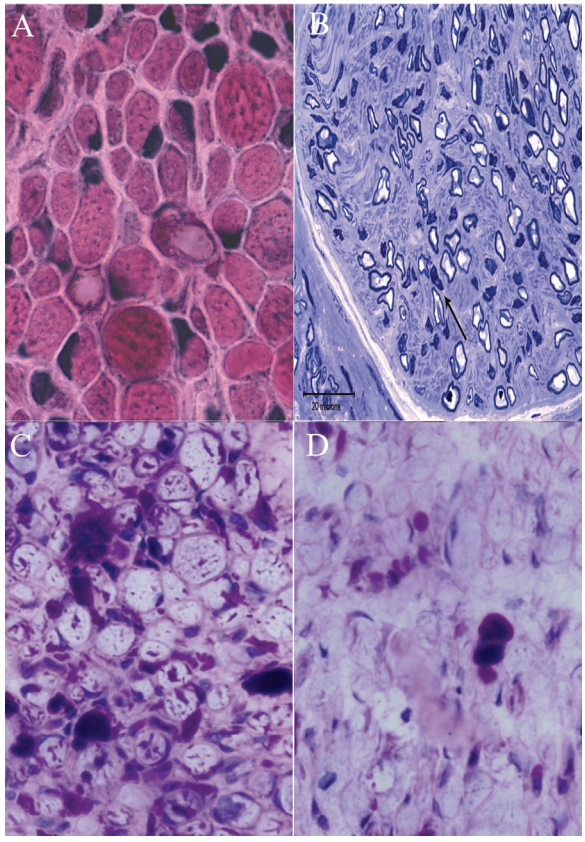

Figure 1. Immunohistological analysis of quadriceps muscle and sural nerve tissue. A, Hematoxylin and eosin stain shows basophilic deposits within muscle tissue. B, Toluidine blue stain demonstrates dense inclusions (arrow) in sural nerve sections. Bar indicates 20 μm. C, Periodic acid-Schiff shows strong positive staining within the cytoplasm of quadriceps muscle fibers, which is partially diastase resistant (D).

Biopsies of the quadriceps muscle and sural nerve were performed. Hematoxylin and eosin staining demonstrated basophilic deposits within the muscle fibers (Figure 1A). Periodic acid-Schiff staining showed excessive storage and positive staining for intracytoplasmic intrasarcolemmal inclusions that were partially resistant to diastase digestion (Figure 1C,D). Toluidine blue stained plastic sections of sural nerve demonstrated inclusions (Figure 1B). Ultrastructural studies showed intracytoplasmic inclusions of various sizes in both muscle and nerve cells (Figure 2). Within muscle, the inclusions distended myofibrils in many areas. Two types of glycogen were seen on electron microscopy, one granular and

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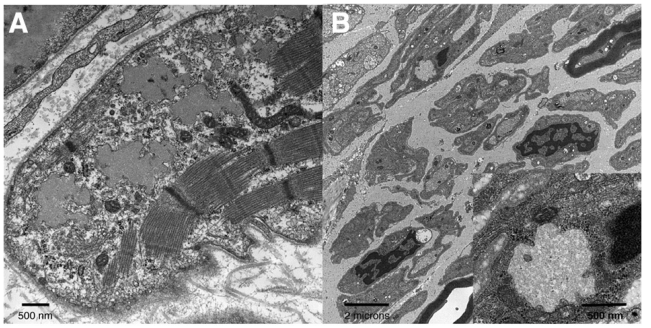

Figure 2. Electron micrographs of muscle and nerve tissue. A, Quadriceps muscle fiber with amorphous membrane bound, nonmembrane bound, and intracytoplasmic inclusions. B, Sural nerve plastic section shows intracytoplamic inclusions of abnormal glycogen in a Schwann cell. Inset shows abnormal glycogen inclusions at higher magnification.

irregularly membrane bound (Figure 2A), and the other amorphous and smoothly bound, possibly reflecting the diastase sensitive and diastase resistant forms. Biochemical analysis was performed and demonstrated severely reduced branching enzyme activity in muscle tissue (1 µmol/min/g tissue; range 32 ± 10 µmol/min/g) and fibroblasts (146 nmol/min/mg protein; range 1300 ± 396 nmol/min/mg protein), confirming the diagnosis of glycogen storage disease type IV.

Genomic polymerase chain reaction analysis of the infant's DNA demonstrated a deletion of exon 16 within *GBE1* (gGBE-f-GTGAGACTGCGTCATGCCTA/gGBE-r-TTAGCCAGGAAAGCAAAATG). This was confirmed by real-time polymerase chain reaction analysis of mRNA from the patient's skin fibroblasts using specific primers (cGBE-ex12-ATAAGTCGCTGGCATTTTGG/cGBE-ex16-GGATCTGCCGAATTGA) for exon 12 to exon 16 which showed a lack of amplification through exon 16 of *GBE1*. However, DNA analysis from blood obtained from the infant's parents showed that the exon 16 region of *GBE1* could be amplified from both parents. This could be due to heterozygous carrier status in both parents. This particular mutation was not identified in any other glycogen storage disease type IV patient or normal controls (n = 30).

Discussion

Glycogenoses are a group of heterogeneous genetic disorders characterized by specific defects in glycogen metabolism. In general, there is variable involvement of muscle, cardiac, hepatic, and/or neural tissue as well as variable age of onset depending on the particular glycogen storage disease. Of the 14 glycogenoses which can affect the nervous system, only glycogen storage disease type II (acid maltase deficiency, Pompe disease), glycogen storage disease type VII (phosphofructokinase deficiency, Tarui disease), and glycogen storage disease type IV (glycogen branching enzyme deficiency, Andersen disease) typically have infantile manifestations. Infants typically present with hypotonia and multiorgan involvement in contrast to older children and adults who usually have milder symptoms such as nonprogressive liver or cardiac involvement or a mild myopathy.

The congenital neuromuscular variant of glycogen storage disease type IV was first described by Zellweger in 1972, and since then, fewer than 20 cases have been reported in the literature.[15] Similar to our patient, many of the reported cases have common shared clinical characteristics, among which are a history of decreased fetal movements, polyhydramanios, fetal hydrops, cervical cystic hygroma, and severe hypotonia at birth or death in the neonatal period. In addition, a fetal akinesia deformation sequence has also been described, resulting in arthrogryposis and pulmonary hypoplasia that are likely secondary to the decreased fetal movements and profound hypotonia and weakness.

The diagnosis of glycogen storage disease type IV is made by documenting periodic acid-Schiff positive, diastase resistant material consistent with abnormal glycogen which accumulates intracytoplasmically as well as documenting reduced glycogen branching enzyme activity in affected tissue such as liver, muscle, or fibroblasts. Affected patients demonstrate approximately 1% to 10% of the glycogen-branching enzyme activity compared to controls; however, patients with the severe congenital neuromuscular variant typically have less than 5% of normal glycogen branching enzyme activity.

All forms of glycogen storage disease type IV result from molecular defects in *GBE1*, located on chromosome 3p12. *GBE1* mutation analysis of a variety of patients suggests a genotype–phenotype correlation, with null mutations such as deletions, insertions, or nonsense mutations being associated with a more severe clinical phenotype.[4,5,9] The extremely low level of glycogen branching enzyme activity in muscle tissue (<5% normal range) correlates with the severe clinical phenotype seen in our patient. However, a patient with a nonlethal mild form of congenital glycogen storage disease type IV was recently reported.[16] This patient had no detectable glycogen branching enzyme activity in muscle and 2 compound heterozygous missense mutations.

The diagnosis of glycogen storage disease type IV should be considered when severe, unexplained dysfunction of cardiac or skeletal muscle or liver is present, and biopsy of an appropriate tissue is crucial to establishing the diagnosis. Furthermore, the presence of fetal akinesia deformation sequence and/or the other shared clinical characteristics (i.e., polyhydramnios, fetal hydrops, or cystic hygroma with a normal karyotype) as well as the presence of abundant fibrillations on neonatal electromyography should also raise the

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possibility of glycogen storage disease type IV. Prenatal diagnosis can be made by assaying the levels of glycogen-branching enzyme activity in cultured amniocytes and chorionic villi or by DNA mutation analysis of *GBE1* if the family mutations are already known.[17,18] Further mutation analysis of *GBE1* in clinically, enzymatically, and histochemically diagnosed glycogen storage disease type IV patients will aid in understanding the genotype–phenotype correlations in this heterogeneous and rarely fatal disorder.

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