Glycogen Storage Disease Presenting as Fetal Hydrops: A Case Report

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Glycogen storage disease (GSD) is a group of heterogeneous disorders of glycogen metabolism that results in abnormal storage of glycogen in multiple organs. Clinical manifestations of GSD vary according to the basic enzyme defect. Only types II, IV, V or VII of GSD have been known to manifest in the infantile period. Of the 11 types of GSD, the congenital subtype of GSD type IV is characterized by severe neonatal hypotonia, multiple contractures, polyhydramnios, and fetal hydrops. We report a case of a patient born at a gestational age of 34 weeks and 3 days with fetal hydrops, joint contractures, and akinesia. Muscle biopsy results were highly indicative of GSD. This is the first case of suspected GSD in Korea presenting as fetal hydrops. The possibility of other disorders associated with glycogen metabolism should be considered in fatal fetal hydrops patients with severe hypotonia and arthrogryposis, and aggressive investigations such as muscle biopsy should be performed for early diagnosis.

Key Words: Glycogen storage disease, Fetal hydrops, Arthrogryposis

Case Report

A male infant was born at a gestational age of 34 weeks and 3 days to consanguineous parents with no family history of metabolic or genetic diseases. A fetal ultrasonography at 29 weeks’ gestation showed polyhydramnios, which persisted throughout the pregnancy.
A follow-up ultrasonography at 33 weeks' gestation demonstrated pleural effusion and skin edema, and the patient was suspected of having fetal hydrops. The mother was admitted to our hospital at 33 weeks and 2 days' gestation due to class A2 gestational diabetes mellitus with polyhydramnios and short cervical length. An elective Cesarean section was performed at 34 weeks and 3 days' gestation. The Apgar score was 2 at 1 minute and 3 at 5 minutes after birth. The infant showed no initial crying with a decreased heart rate of less than 100 beats per minute (bpm). Intubation was immediately performed in the operating room. The heart rate recovered to >100 bpm post intubation.

At birth, his head circumference was 34.5 cm (>90 percentile), weight was 1,968 g (25–50 percentile), and length was 45 cm (25–50 percentile). The patient had facial edema and whole body petechiae. He had a high arched palate and simian lines. He showed multiple joint contractures in both hips, knees, ankles, shoulders, elbows, wrists, and in all fingers and toes, with limited range of motion. Additionally, his hip joints were dislocated, and fixed in the abducted posture. Both testes were not palpable. His muscle tone was flaccid, and physiologic reflexes such as Moro reflex, rooting reflex and truncal incurvation reflexes were not evoked.

The patient's initial vital signs showed a blood pressure of 45/28 (mean BP 33), a pre ductal saturation of 81% and a post ductal saturation of 62%; his heart rate was checked at 140 bpm. High frequency ventilator mode and nitric oxide were provided. He was also suspected of having pneumothorax; thoracentesis was done and resulted in a massive drainage of air from the right chest tube and a drainage of air and pleural fluid from the left chest tube. His brain ultrasonography showed germinal matrix hemorrhage and widening of the extra axial cerebrospinal fluid space with the possibility of subdural fluid collection. The abdominal ultrasonography revealed bilateral pelviectasia with the suggestion of portal vein and parenchymal air in the liver. Four hours after birth, the patient presented with hypotension, bradycardia and desaturated to 47%. Cardiopulmonary resuscitation (CPR) was performed, and the patient continued to have repeated episodes of bradycardia. Congenital myopathy or a metabolic disorder was strongly suspected at the time, thus a muscle biopsy was performed with informed consent from the parents of the patient. At the parents' request, CPR was discontinued. The patient expired 8 hours after birth.

Screening for common metabolic diseases was negative, and major fetal infections (toxoplasmosis, rubella, cytomegalovirus, parvovirus and herpes simplex virus) were ruled out by serum antibody levels. Chromosome analysis showed a normal karyotype of 46, XY.

Pathologic examination of the muscle biopsy showed moderate sized variations of myofibers, many vacuolated myofibers and mild interstitial fibrosis (Fig. 1). Electron microscopic study revealed myofibrillar loss.
and subsarcolemmal and intermyofibrillar pools of glycogen particles (Fig. 2). Severe myofibrillar and Z-band disorganization was also observed. These pathologic findings were consistent with GSD, the non-lysosomal type. The clinical presentations and histological findings strongly suggest the fatal congenital subtype of GSD type IV. The mother is planning her next pregnancy and will be receiving genetic counseling.

**Discussion**

In the present case, congenital myopathy (such as Nemaline myopathy) was initially suspected, and a muscle biopsy was thus conducted. The pathologic results after the patient expired showed typical characteristics of GSD. As the patient expired 8 hours after birth and the parents refused autopsy, blood samples and body tissues for further investigation could not be obtained. Although we failed to discover the specific type of GSD in this patient, we found that only a few cases of GSD have been reported in the literature that presented as fetal hydrops. Alegria A et al. reported a female preterm infant who expired on the fourth day of life and was confirmed to have GSD type IV by necropsy and measuring branching enzyme activity in cultured fibroblasts. They speculated that fetal hydrops was caused by the accumulation of glycogen in the myocardium in utero, resulting in heart failure. This seems to be an example of an extreme manifestation of the fetal form of GSD type IV. The infant in the present report also showed edema, pleural effusion, ascites, severe hypotonia and arthrogryposis. Arthrogryposis is associated with fetal akinesia. This patient did not show hepatomegaly nor hypoglycemia.

In order to make a confirmative diagnosis of GSD type IV, determination of GBE enzymatic activity is required along with the typical histologic characteristics. Another approach to the etiology is genetical analysis, as GSD type IV is associated with mutations in the GBE1 gene located on chromosome 3p12. In our case, further evaluation could not be performed since the parents did not agree to postmortem examination. Although conclusive diagnosis was not possible, the clinical and histological findings of our case were highly suggestive of the congenital subtype of GSD type IV.

As GSD type IV is an autosomal recessive disease with decreased GBE1 activity, genetic counseling when planning the next pregnancy is important. Parental DNA tests are also helpful due to the fact that enzyme mutation is a key factor in the development of the disease. Also, enzyme activity measurement via chorionic villi sampling should be considered for the next pregnancy.

We report a case of suspected GSD presented as fetal hydrops, with the patient expiring after only 8 hours of life. The clinical and histological findings were strongly suggestive of the congenital subtype of GSD type IV. This is the first reported case in Korea. The possibility of disorders associated with glycogen metabolism should be considered in fatal fetal hydrops patients with severe hypotonia and arthrogryposis, and aggressive investigations such as liver biopsy and muscle biopsy should be performed for early diagnosis. In cases suspected of GSD IV, GBE activity assay should...
be performed to determine the enzymatic activity for confirmation and a gene study should be considered for further investigation and more conclusive diagnosis.

References


