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A Case of Juvenile Form Pompe's Disease Manifested as Chronic Alveolar Hypoventilation

Dong Gyu Kim, M.D., Kisuck Jung, M.D., Myung Koo Lee, M.D., In Gyu Hyun, M.D., Hwa Jung Lim, M.D., Hong Gi Song, M.D.*, Je G. Chi, M.D.**

Departments of Internal Medicine and Neurology, Hallym University College of Medicine, Seoul, Korea; Department of Pathology, Seoul National University College of Medicine, Seoul, Korea***

We describe a case of the juvenile form of Pompe's disease that presented as primary alveolar hypoventilation due to respiratory muscle involvement. This 17-year-old girl had been asymptomatic until this admission, although she had a delayed puberty. Arterial blood gas analysis, pulmonary function test as well as physical findings were compatible with chronic alveolar hypoventilation syndrome. Since she had lower extremity muscle weakness and pseudomyotonic discharge on electromyography a muscle biopsy was done, which revealed glycogen storage disease. The patient was managed successfully with nasal intermittent positive pressure ventilation.

Key Words: *Pompe's disease, nasal intermittent positive pressure ventilation (NIPPV), alveolar hypoventilation.*

INTRODUCTION

Generalized glycogenosis, or Pompe's disease, has usually been recognized in infancy; early cardiac death is a clinical hallmark (Pompe., 1932). In recent years, other forms of this disorder have been described, which show predominant muscular wasting and weakness with or without cardiac complication (Egel., 1970). There are three clinical presentations; infantile, juvenile and adult form. Family studies suggest autosomal recessive inheritance. The incidence is not known exactly but may exceed 1 in 100,000. We report a patient who has a juvenile form of Pompe's disease which was initially manifested as chronic alveolar hypoventilation syndrome.

CASE REPORT

A 17-year-old girl was admitted to a neighboring hospital because of a mild fever and cough which had developed three days before admission. She was born without any congenital problems and had been healthy until this admission except for a delayed puberty. Chest radiograph revealed hazy infiltration in the right lower lobe. Arterial blood gas analysis on admission was as follows; pH 7.23, $PaCO_2$ 101mmHg, PaO_2 31.7 mmHg and HCO_3 42.9 mEq/L. After voluntary hyperventilation, $PaCO_2$ and PaO_2 were 37.1 mmHg and 89.1 mmHg, respectively. Pulmonary function test revealed very severe restrictive and mild obstructive patterns. Echocardiography revealed normal findings. She was diagnosed as primary alveolar hypoventilation with pneumonia initially due to daytime somnolence, insomnia, lethargy, no evidence of dyspnea and normalization of hypercapnea after voluntary hyperventilation.

After administration of antibiotics, the infiltrative lesion on the chest radiograph was cleared and the fever subsided. She was discharged with clinical improvement, only to be readmitted to the same hospital two weeks later due to dyspnea and peripheral cyanosis.

Seven days after the second admission, she was transferred to Kang Dong Sacred Heart Hospital with the endotracheal tube in situ. On admission, she was alert, but looked anxious. The vital signs were as follows; body temperature 36.5°C, respiration rate 28 per min, pulse rate 124 per min and blood pressure 120/80 mmHg. She was not complaining of dyspnea

Address for correspondence: *Kisuck Jung, Department of Internal Medicine, Kang Dong Sacred Heart Hospital, 445 Gil-Dong, Kangdong-Gu, Seoul, 134-011, Korea. Tel: 488-0111 (220)*

despite a rapid respiration rate and hypercapnea.

Physical examination revealed decreased breathing sound in both lungs with coarse inspiratory crackles in the right lower lung. Lips were cyanotic. Motor weakness was evident to the degree of difficulty in elevating the lower extremities against gravity without any sensory change. There was scoliosis in the lumbar spine and mild degree of eqinovarus.

Laboratory data were as follows; WBC 15000/mm^3, hemoglobin 11.9 g/dL, hematocrit 36%, SGOT 42 IU/L, SGPT 48 IU/L, alkaline phosphatase 112 IU/L, sodium 134 mEq/L, potassium 4.2 mEq/L. Fasting blood sugar was 100 mg/dL, two hours postprandial sugar 164 mg/dL, creatine phosphokinase 132 IU/L (38-160), LDH 558 IU/L (240-460). Creatine kinase and LDH isoenzyme patterns were normal.

Tensilon test was negative. Electrocariography was normal. Electromyography revealed moderately increased insertional activities in the upper and lower extremity muscles and pseudomyotonic discharges. There was no evidence of denervation potential.

She underwent a muscle biopsy of the vastus lateralis. The muscle biopsy showed vacuoles of varying size in most fibers. Some of them were very large and contained a basophilic substance (Fig. 1, 2) which stained as acid mucopolysaccharide. An increased quantity of glycogen was demonstrated by D-PAS staining. The remaining sarcoplasm and interstitium were unremarkable. Under electron microscopy, the vacuoles were membrane bound and glycogen particle were found both free in the cytoplasm and within lysosomes together with degradation products. She was diagnosed as having a Pompe's disease considering above pathologic findings although α-glucosidase deficiency was not proved biochemically.

A mechanical ventilator was applied in SIMV mode, FIO_2 0.21 and respiratory rate 10 per min. Arterial blood gas under mechanical ventilation were; $PaCO_2$ 54.9 mmHg, PaO_2 72.5 mmHg. After weaning on the 7th hospital day, blood gas data were maintained at a similar level, until the systolic murmur was heard at the pulmonic area (Grade 3/6) on the 12th hospital day. Echocardiography revealed pulmonic hypertension without valvular abnormality. Lower extremity and respiratory muscle weakness gradually progressed, and adequate ventilation couldn't be achieved without additional ventilatory assistance. Nasal intermittent positive pressure ventilation (NIPPV) was adopted to avoid endotracheal intubation and subsequent tracheostomy (Fig. 3).

NIPPV was applied to her in CMV mode, FIO_2 0.21, tidal volume 700 mL, and respiratory rate 17 per min. It provided adequate ventilation while concomittantly allowing for a significant reduction in spontaneous inspiratory effort. It resulted in sustained improvement

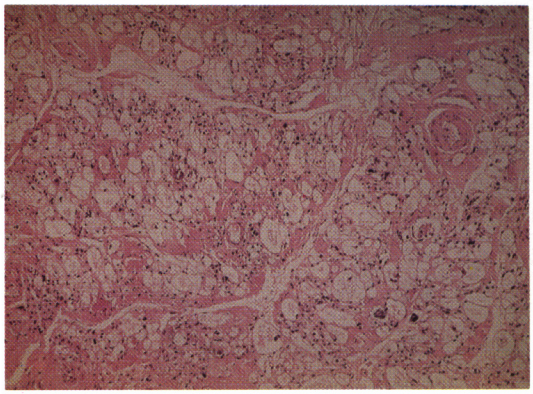

Fig. 1. Muscle biopsy shows vacuolization of muscle fiber and glycogen storage (H&E ×100).

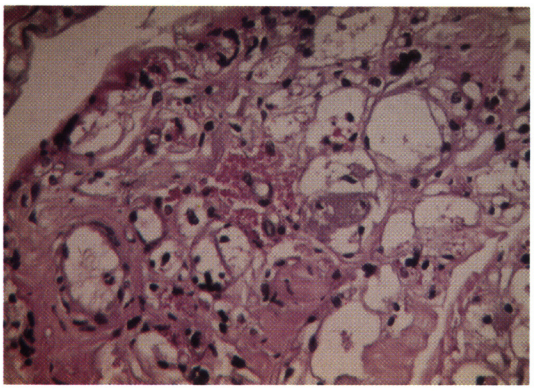

Fig. 2. Increased quantity of stored glycogen in muscle fiber (D-PAS ×400).

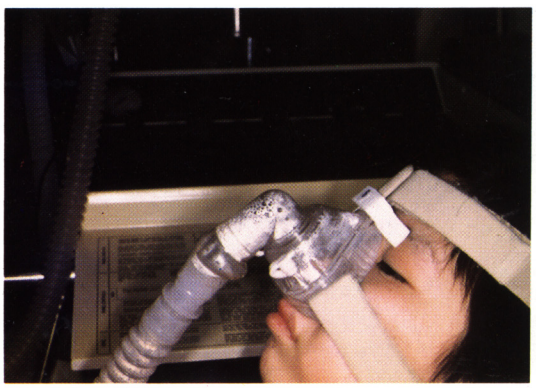

Fig. 3. Application of nasal intermittent positive pressure ventilation (NIPPV) with home ventilator.

in $PaCO_2$ and PaO_2 as well as increased exercise tolerance (Gerald et al., 1987; Zev et al., 1990). She could avoid tracheostomy by using the nasal mask. Duration of mechanical ventilation as a whole was shortened day by day. She finally required mechanical ventilation only during sleep. Blood gas data under mechanical ventilation via nasal mask were; $PaCO_2$ 35.4 mmHg and PaO_2 121.1 mmHg. The pulmonic systolic murmur subsided. She could maintain a normal blood gas level until the time of discharge.

After discharge she has continued NIPPV at home only during sleep without any significant problem.

DISCUSSION

Pompe's disease or alpha-glucosidase deficiency, is a lysosomal storage disease (Hers., 1965). This enzyme has widespread distribution in tissue, but its deficiency affects primarily skeletal and cardiac muscle (Martin., 1973).

The disorder is not associated with hypoglycemia, ketosis, or other abnormalities of intermediary metabolism. The infantile form presents within the first 6 months of life and may be manifested at birth. Clinical features include skeletal muscle hypotonia and weakness, massive cardiac enlargement, enlargement of the tongue, but the liver is usually normal size prior to cardiac decompensation. Muscle enzymes such as creatine phosphokinase and aldolase are usually elevated, and the ECG may show large QRS complexes and a shortened PR interval (Gillette et al., 1974; Hwang et al., 1985).

Motor weakness and developmental delay may be present. Death occurs in the first year in most cases due to the cardiac involvement, pneumonia or aspiration. Electromyography reveals pseudomyotonic discharge, fibrillation, and high frequency discharges in all clinical forms (Lenard et al., 1974).

The juvenile form has features suggestive of a progressive form of muscular dystrophy. These patients have gait abnormalities but no cardiac symptoms (Engel et al., 1973; Tanaka et al., 1979). Plasma creatine phosphokinase and aldolase are elevated, and the length of survival is variable but no patient has survived beyond 19 years (Gembetti et al., 1971).

An even milder adult form presents as skeletal muscle weakness from third to fifth decade. Three types of skeletal muscle weakness can be distinguished from each other (Horstmann., 1990). The first one is characterized by an involvement of the limb-girdle muscles only. The second type shows the same pattern with additional progressive insufficiency of the respiratory muscles.

The third type presents with weakness of the respiratory muscles without any other severe muscle involvement.

The primary complaint is muscle weakness, but some patients have acute respiratory failure due to involvement of the muscles of respiration (Rosenow et al., 1978). The disease is slowly progressive and is often misdiagnosed as having some form of muscular dystrophy (Engel., 1970; Martin et al., 1976; DiMauro et al., 1978).

The muscle biopsy shows vacuoles of varying size in most muscle fibers. Some of them are very large and containe a basophilic substance which stain as acid mucopolysaccharide. An increased quantity of glycogen is demonstrated by D-PAS staining. Excessive glycogen is also found in other tissues including the liver and central nervous system, particularly in the anterior horn cells of the spinal cord (Gembettiet al., 1971). Specific diagnosis is made by enzyme assay of biopsy material from muscle or liver or in cultured skin fibroblasts (Bienvenu et al., 1981; Ninomiya., 1984). In general, some residual enzyme activity is present in patients with the adult form of the disease, but the exact level is not of prognostic significance. Prenatal diagnosis is reliable and has been used extensively for the infantile form (Buttrworth et al., 1977; Lin et al., 1987). To dates, specific effective treatment is not known. Various forms of enzyme infusion therapy have been tried but were ineffective (Denick et al., 1976). The myopathy with adult form Pompe's disease can be manifested as an early or isolated respiratory involvement, and hence the underlying problem is often not suspected because disorders of respiratory muscle involvement such as postpolio syndrome and idiopathic diaphragmatic paralysis are confused.

Our case was diagnosed as acute and chronic respiratory failure of the juvenile form of Pompe's disease which was initially confused with primary alveolar hypoventilation because the respiratory and lower extremity muscle involvement did not develop as an early manifestation. By the time the patient was transferred to our hospital, respiratory and lower extremity muscle involvement was evident though. It was considered that the pulmonary hypertension might be developed as a secondary change to chronic hypoxemia and hypercapnea.

We applied NIPPV to avoid tracheostomy. The application of NIPPV is a simple, noninvasive method for supporting chronic intermittent ventilation through a tightly fitted nasal mask (Lifecare, USA). Robert et al reported that the results of 1 year of nocturnal home ventilation via nasal mask appeared to be similar to

the results obtained from noctural home ventilation via tracheostomy in terms of adequate ventilation (Robert et al., 1983). NIPPV is far better than ventilation via tracheostomy site if adequate ventilation is provided. Colonization of large airway and subsequent infection are major complicating problems with tracheostomy, but we can expect much lower incidence of pulmonary infection with NIPPV. NIPPV can also decrease duration and frequency of daytime oxygen desaturation episodes. This continued correction permits the patient to participate in daytime activities without respiratory assistance. NIPPV is also a safe and effective alternative to ventilation via tracheosomy in early chronic failure and to be effective in patients with restrictive defects resulting from chest wall and parenchymal disease as well as neuromuscular weakness (Leger et al., 1989). Since she has been doing well with NIPPV, we suggest it could replace conventional mechanical ventilation via the tracheostomy site and avoid associated complications.

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