LATE INFANTILE ACID MALTASE DEFICIENCY*
A Case Report

*Mine Çalışkan MD***, Yüksel Yılmaz MD****, Piraye Serdaroğlu MD*****
*Nur Aydınlı MD****, Meral Özmen MD******

SUMMARY: Çalışkan M, Yılmaz Y, Serdaroğlu P, Aydınlı N, Özmen M. (Division of Pediatric Neurology, Department of Pediatrics, and Department of Neurology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey). Late infantile acid maltase deficiency: a case report. Turk J Pediatr 1999; 41: 121-125.

A five-year-old boy with late-infantile (juvenile) form of acid maltase deficiency is presented. His symptoms were restricted to skeletal muscle. There is commonly a correlation between the amount of residual acid maltase activity and the severity of the clinical picture. Although the residual enzyme level was very low in our patient, no progression of his neurological findings have been observed during the follow-up period of two years. *Key words: acid maltase deficiency, glycogen storage diseases, late-infantile form.*

Glycogenosis type II is an autosomal recessively inherited disorder caused by defects in lysosomal acid maltase (acid alpha-glucosidase). Acid maltase deficiency (AMD), a clinically heterogeneous disorder, can be divided into three clinical forms: infantile, late-infantile (childhood/juvenile) and adult, based on the extent of organ involvement, age of onset and rate of progression. The fatal infantile-onset form is characterized by massive accumulation of glycogen in all tissues, including cardiac and skeletal muscle. In the late-onset forms, symptoms begin in childhood or adult life, the course is usually slow and the clinical picture is mostly restricted to skeletal muscle[1-3].

We present a five-year-old boy with delayed motor development and muscle weakness who was diagnosed as AMD by muscle biopsy. The dignosis was confirmed by enzyme deficiency in skin fibroblast culture.

Case Report

A five-year-old boy was admitted to the Pediatric Neurology Unit because of difficulties in walking and muscular weakness. He was the only child of healthy first-degree consanguineous parents; there was no history of neuromuscular disease in the family. His pre-, peri- and postnatal histories were unremarkable with the exception of his premature birth weight of 1900 g. He had head control at four months, sat without support at nine months and walked unaided at 18 months. He had been suffering from recurrent upper respiratory infections.

* From the Division of Pediatric Neurology, Department of Pediatrics, and Department of Neurology, İstanbul University İstanbul Faculty of Medicine, İstanbul.

** Associate Professor of Pediatrics, İstanbul University İstanbul Faculty of Medicine.

*** Pediatrician, İstanbul University İstanbul Faculty of Medicine.

**** Associate Professor of Neurology, İstanbul University İstanbul Faculty of Medicine.

***** Professor of Pediatrics, İstanbul University İstanbul Faculty of Medicine.

Clinical examination revealed a mentally normal boy with a body weight of 14 kg (10^{th} percentile), height of 100 cm (20^{th} percentile), and head circumference of 48.5 cm (10^{th} percentile) (Fig. 1). He had generalized hypotonia. Muscle strength was diminished more in the proximal than distal extremities. When lying in a supine position, he could not raise his head; however, most muscles moved against gravity. He rose from the floor manifesting a prominent Gowers' sign and walked unaided. There was marked lordosis of the lumbar spine and bilateral contractures of the Achilles tendons. Tendon reflexes were hypoactive. Examination of other systems including heart did not reveal any abnormal findings. During the follow-up period of two years, there was no progression in his neurological findings.

Laboratory findings: The serum creatine kinase (CK) was elevated to 2409 U/L (N: 30-200), SGOT was 352 U/L and SGPT 224 U/L. The electrocardiogram, chest x-ray and cardiac ECHO were normal. Pulmonary function tests could not be performed due to lack of cooperation.

Fig. 1: Five-year-old boy with acide maltase deficiency.

Motor nerve conduction velocity was normal. On the needle electromyography the motor unit potentials were of short duration, mostly polyphasic and low voltage. Occasional myotonic-like bursts of activity were recorded. Cranial MRI performed at age of seven years was normal.

Muscle biopsy was characterized by vacuolar myopathy. Most of the fibers contained large and usually multiple vacuoles. Most vacuoles contained periodic acid-Schiff (PAS) positive material, some of which persisted after diastase digestion, as well as acid phosphatase reactivity (Figs. 2, 3).

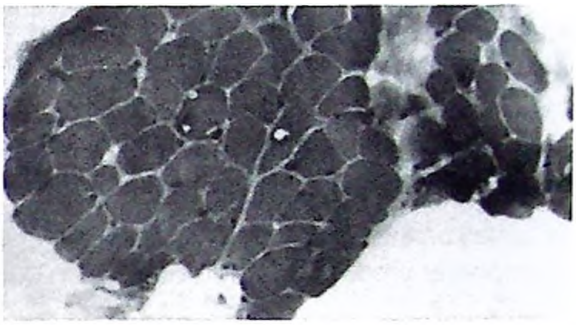
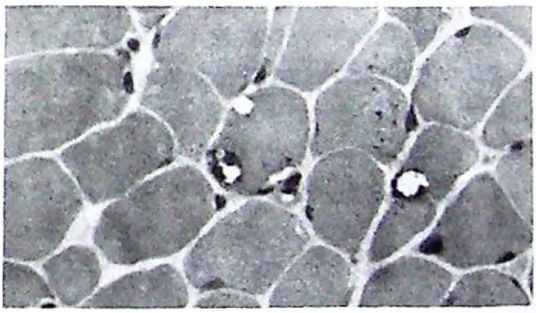


Fig. 2. Hematoxylin and eosin preparation (44X) demonstrating the variability in fiber size and vacuolation in two fibers.



(a)

(b)

Fig. 3: Modified Gomori trichrome preparation [88 X (a) and 176 X (b)] demonstrating vacuolation of some fibers.

Skin fibroblast culture (Mainz-Germany) revealed a markedly decreased alpha-glucosidase level of 0.059 mU/mg (N: 1.41-5.83).

Discussion

In 1965 Zellweger et al.[4] reported a mild "abortive" form of AMD in two brothers aged 15 and $4^1/_2$ years with a mild myopathy. Since then clinically heterogeneous forms of the disease have been described, often resembling a limb girdle or Duchenne muscular dystrophy. In these patients symptoms usually become apparent in the first decade of life. Although in some cases there has been evidence of associated cardiac involvement, other systems do not appear to have been significantly involved[3, 5, 6]. The symptoms of our patient were also restricted to skeletal muscle. This type of case stresses once again the importance of muscle biopsy in apparently typical "muscular dystrophy" with a raised CK level and myopathic electromyographic changes.

A definitive diagnosis is based on the biochemical demonstration of decreased alpha-glucosidase activity in peripheral lymphocytes, in muscle or in cultured fibroblasts[1, 2].

The cause of the clinical heterogeneity remains obscure. Reuser et al.[2] showed a logical correlation between the level of residual activity and the course of the disease in 25 adult, four juvenile and 46 infantile forms. But the relatively mild clinical phenotype of some adult patients with an exceptionally low residual activity remained unexplained. The very low level of acid maltase in our patient correlated with the moderate-severe form of the disease. However, during the two year follow-up period, we have not observed any progression in the neurological findings. The family has also been informed about the availability of prenatal diagnosis. A second pregnancy was terminated because of low level of alpha-glucosidase in the amniotic cell culture. Although the course of the late-infantile form is usually slowly progressive, the sudden onset of respiratory failure might be life threatening and is usually fatal before the third decade. In many cases, nightly ventilatory support is ultimately needed, and was also planned for in our case[2, 3].

In some rare cases, storage of glycogen in vascular smooth muscle cells leading to an aneurysm of the basilar artery has been described. This was complicated by fatal rupture in two patients[11]. Cranial MRI performed at the age of seven years was normal in our case.

The gene for acid maltase has been mapped to chromosome 17 q 21-23. In most reported families all affected members are afflicted with the same disease variant. However, there are some reports about intrafamilial clinical heterogeneity. In one of them, three siblings had infantile AMD and their paternal grandfather had adult-onset AMD. Allelic diversity with various combinations of homo- ("severe" allele) and heteroallelic (a "severe" and a "mild" allele) mutant genotypes has been suggested as the basis for the clinical and biochemical heterogeneity of AMD[8-10].

Early trials of enzyme therapy failed because of insufficient quality and quantity of the administered enzyme. In a more realistic animal model, preparations of human placental and bovine testis alpha-glucosidase were administered to healthy mice and found to be taken up by heart and skeletal muscle, the major target organs. Although these results are promising, the ultimate effect of enzyme therapy in AMD can only be tested in clinical trails in humans[12].

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REFERENCES

1. Swaiman KF. Diseases associated with primary abnormalities in carbohydrate metabolism. In: Pediatric Neurology (2nd ed) St. Louis: Mosby; 1994: 1258-1261.
2. Reuser AJ, Kroos MA, Hermans MM. Glycogenosis type II (acid maltase deficiency). Muscle Nerve 1995; 3: (Suppl) 61-69.
3. Engel AG, Gomez MR, Seybould ME, et al. The spectrum and diagnosis of acid maltase deficiency. Neurology 1973; 23: 95-106.
4. Zellweger H, Brown BJ, McCormick WF, et al. A mild form of muscular glycogenosis in two brothers with alpha-1,4-glucosidase deficiency. Ann Paediatr 1965; 205: 413-437.
5. Smith J, Zellweger H, Afifi AK. Muscular form of glycogenosis, type II (Pompe). Neurology 1967; 17: 537-544.
6. Swaiman KF, Kennedy WR, Sauls HS. Late infantile acid maltase deficiency. Arch Neurol 1968; 18: 642-648.
7. Mehler M, DiMauro S. Residual acid maltase activity in late-onset acid maltase deficiency. Neurology 1977; 27: 178-184.
8. Raben N, Nichols RC, Boerkoel C, Plotz P. Genetic defects in patients with glycogenosis type II (acid maltase deficiency). Muscle Nerve 1995; (Suppl) 3: S70-74.
9. Barohn RJ, McVey AL, DiMauro S. Adult acid maltase deficiency. Muscle Nerve 1993; 16: 672-676.
10. Hoefsloot LH, van der Ploeg AT, Kroos MA, et al. Adult and infantile glycogenosis type II in one family, explained by allelic diversity. Am J Hum Genet 1990; 46: 45-52.
11. Makos MM, McComb RD, Hart MN, Bennett DR. Alpha-glucosidase deficiency and basilar aretry aneurysm: report of a sibship. Ann Neurol 1987; 22: 629-633.
12. Van der Ploeg AT, Kroos MA, Willemsen R, Brons NH, Reuser AJ. Intravenous administration of phosphorylated acid alpha-glucosidase leads to uptake of enzyme in heart and skeletal muscle of mice. J Clin Invest 1991; 87: 513-518.