Neuromuscular Disorders 20 (2010) 783–790

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Branching enzyme deficiency/glycogenosis storage disease type IV presenting as a severe congenital hypotonia: Muscle biopsy and autopsy findings, biochemical and molecular genetic studies

A.L. Taratuto [a,*], H.O. Akman [b], M. Saccoliti [a], M. Riudavets [a], N. Arakaki [a], L. Mesa [d], G. Sevlever [a,c], H. Goebel [e], S. DiMauro [b]

[a] Department of Neuropathology, Institute for Neurological Research, FLENI, Buenos Aires, Argentina
[b] Department of Neurology, Columbia University Medical Center, New York, USA
[c] Department of Pathology, Bazterrica Institution, Buenos Aires, Argentina
[d] Department of Neurology, Favaloro Institution, Buenos Aires, Argentina
[e] Department of Neuropathology, Mainz University, Mainz, Germany

ARTICLE INFO

Article history:
Received 17 March 2010
Received in revised form 8 July 2010
Accepted 21 July 2010

Keywords:
GSD IV
Andersen disease
Branching enzyme
General autopsy
Brain

ABSTRACT

The fatal infantile neuromuscular presentation of branching enzyme deficiency (glycogen storage disease type IV) due to mutations in the gene encoding the glycogen branching enzyme, is a rare but probably underdiagnosed cause of congenital hypotonia. We report an infant girl with severe generalized hypotonia, born at 33 weeks gestation who required ventilatory assistance since birth. She had bilateral ptosis, mild knee and foot contractures and echocardiographic evidence of cardiomyopathy. A muscle biopsy at 1 month of age showed typical polyglucosan storage. The autopsy at 3.5 months of age showed frontal cortex polymicrogyria and polyglucosan bodies in neurons of basal ganglia, thalamus, substantia innominata, brain stem, and myenteric plexus, as well as liver involvement. Glycogen branching enzyme activity in muscle was virtually undetectable. Sequencing of the *GBE1* gene revealed a homozygous 28 base pair deletion and a single base insertion at the same site in exon 5. This case confirms previous observations that GBE deficiency ought to be included in the differential diagnosis of congenital hypotonia and that the phenotype correlates with the 'molecular severity' of the mutation.

1. Introduction

The spectrum of diseases associated with severe congenital hypotonia has recently been expanded to include newly described congenital entities, i.e., lamin A/C (LMNA) gene mutations [1], dynamin [2] and C-terminal titin deletions causing congenital hypotonia with childhood onset fatal dilated cardiomyopathy [3].

A rare or perhaps underdiagnosed disease is the fatal infantile neuromuscular presentation of glycogen storage disease type IV (GSD IV) or Andersen disease, an autosomal recessive disorder due to branching enzyme (GBE) deficiency and caused by mutations in the *GBE1* gene mapped to chromosome 3p12.3. Cases have been associated to polyhydramnios and decreased fetal movements [4–18]. GSD IV has a heterogeneous presentation which includes progressive lethal liver cirrhosis in childhood, severe cardiomyopathy, a neuromuscular form with variable onset and severity (perinatal, congenital, juvenile or adult) [8,12], and a rare autosomal recessive disorder affecting mainly but not exclusively Ashkenazi Jewish patients called late-onset adult polyglucosan body disease (APBD) [19].

In most cases of severe congenital hypotonia, muscle biopsy is performed and, in GSD IV, it reveals polyglucosan bodies within muscle fibers. The incidence of this disorder is probably as low as estimated in 1994, i.e., 1 in 760.000–960.000 births [7]. Here, we report a case of severe congenital GSD IV, including diagnostic muscle biopsy findings at 1 month of age and autopsy findings at 3 months 16 days of age.

2. Patient and methods

2.1. Patient

This girl, the first child of consanguineous parents, was born at 33 weeks of gestation by emergency cesarean section due to fetal bradycardia. She was unable to breathe, was intubated, and required mechanical ventilation and nasogastric feeding for the rest of her life. Birth weight was 2120 g, head circumference was

* Corresponding author. Address: Department of Neuropathology, Institute for Neurological Research-FLENI, Montañeses 2325, 3rd Floor, C1428AQK Buenos Aires, Argentina.
E-mail address: ataratuto@fleni.org.ar (A.L. Taratuto).

0960-8966/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.nmd.2010.07.275

34 cm, and body length 46 cm. Apgar scores were 2/5/7. She had severe generalized hypotonia, slight knee and ankle contractures and spontaneous movements were limited to the feet. There were bilateral ptosis and roving eye movements. Deep tendon reflexes were present. Echocardiogram showed cardiomyopathy with ventricular hypokinesia and markedly reduced ejection fraction (25%) requiring high doses of inotropic drugs. Brain and abdominal echograms were normal. CT brain scanning performed at 11 days of age showed bifrontal cephalohematoma and dilation of the pontocerebellar cistern, the Sylvian cisterns, and the subarachnoid cortical spaces (brain convexity), whereas the ventricles were normal. There were also bilateral hypodense periventricular and deep hemispheric areas consistent with hypoxic–ischemic insult. A muscle biopsy was performed at 1 month of age. At 2 months of age, auditory and visual evoked potentials and EEG were normal. EMG showed normal nerve conduction velocities and a few polyphasic motor neuron potentials of diminished amplitude (80–100 mV), suggestive of primary muscle involvement with no evidence of lower motor neuron involvement (LMN). Neurometabolic evaluation was normal. In particular, there was no evidence of a peroxisomal disease nor increased lactic acid, and the karyotype was normal. Serum creatine kinase (CK) was 810 IU/l. The activity of α-glucosidase in blood (filter paper) was normal by a fluorometric method. The neutral/acid maltase ratio was 0.3 (control: <30) and the percentage of inhibition of acid α-glucosidase was 75 (control: <90). She required tracheostomy because of recurrent respiratory infections. She died of cardiorespiratory failure at 3mo, 16 days of age and autopsy was performed.

2.2. Muscle biopsy, light and electron microscopy

A left biceps muscle biopsy specimen was frozen in liquid nitrogen-chilled isopentane. Cryostat sections were stained or reacted

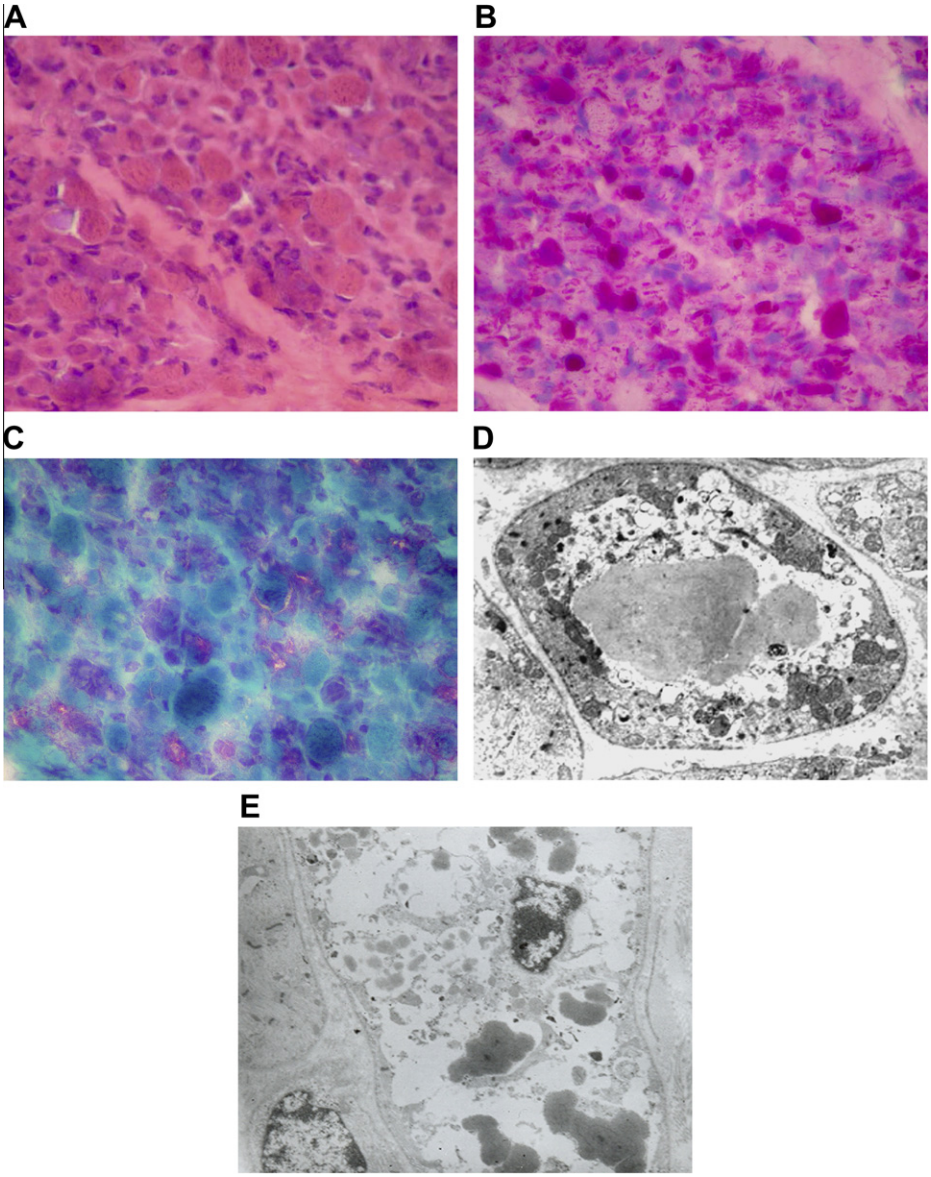

Fig. 1. Muscle biopsy. (A) Prominent perimysial fibrosis, rounded and angulated fibers with variation in sizes within the same fascicles (H&E 250×). (B) PAS-positive material within muscle fibers, most of which was resistant to diastase digestion (PAS-diastase 250×). (C) Abnormal reddish material within some vacuolated fibers (Gomori trichrome 250×). (D and E) Electron microscopy showed myofibrillar degeneration and intracytoplasmic inclusions of amorphous, homogeneous or slightly granular polyglucosan bodies, some of them with higher density (E) (8800× EM).