Childhood neuromuscular disease with rimmed vacuoles

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Abstract. A 5-year-old boy suffered from a slowly progressive non-familial neuromuscular disease, clinically marked by generalised muscle weakness, atrophy and hypotonia, a “myopathic” EMG and mildly elevated CK values. His gastrocnemius muscle showed marked myopathy, type I fibre predominance, and numerous “rimmed” vacuoles. This boy’s condition is regarded as a childhood neuromuscular disease with rimmed vacuoles.

Key words: Rimmed vacuoles – Childhood – Myopathy – Ultrastructure

Introduction

Congenital myopathies, usually occurring in early childhood, but infrequently also in adolescence and even in adulthood, are marked by morphological abnormalities in skeletal muscle, such as nemaline bodies, central cores or abnormal distribution and size of muscle fibres and their types as in congenital fibre type disproportion. “Rimmed vacuoles” [3] represent another pathological feature in skeletal muscle, seen in a variety of neuromuscular disorders. We want to present clinical and morphological findings in a young boy afflicted with a neuromuscular disorder since early childhood that was morphologically marked by numerous “rimmed vacuoles”.

Clinical data

This 5-year-old boy was born several days before term without complications after a pregnancy complicated by bleeding that required hormone therapy and by iron-deficient anaemia of his mother. She had had two previous abortions. Neither of the parents nor a younger brother have any neurological or neuromuscular diseases, but two or three siblings of both his grandfathers (exact number and sex of siblings is not known) died of unidentified causes in their early childhood.

Psychomotor development was grossly normal except for a slightly delay in speech development with first words at 16 months (normal pronunciation) and mildly delayed motor development treated with physiotherapy during his first year of life. He walked at 14 months. Psychointellectually he was normal at the age of 5 years (IQ of 105 on the Raven-CM Test; performance at age level on the drawing test; normal visuo-motor abilities, but poor fine-motor-performance on the Bender-Gestalt Test). A language development test was normal except for pronunciation.

Muscle weakness was first noted at the age of 2½ years when he refused to climb stairs and complained of leg pain in the evening. Then, gradually, swallowing difficulties developed and his speech became dysarthric.

When he was 4 years old, he had bilateral paresis of the glossopharyngeal nerve, slightly more severe on the right, and a peripheral facial nerve palsy on the left, as well as slightly diminished deep tendon reflexes. An electroneurogram of both fibular nerves was reported normal without further details available, as were cranial computer tomogram and acoustic-evoked potentials.

At the age of 5 years, he showed generalised muscle weakness of proximal and distal limb muscles, an inability to lift his head from a lying position, and to climb stairs without assistance. Occasional leg pain after exercise persisted, but did not increase in proportion to the developing muscle weakness. He fell frequently and was unable to run fast. He showed Gowers’ phenomenon and mild generalised muscle atrophy. In comparison to his right calf, his left calf was smaller in circumference by 1 cm and its skin temperature was lower. He had no sensory deficits; however, he exhibited reduced general body awareness. There was mild generalised muscle hypotonia except for mild bilateral extensor spasticity of his feet. His deep tendon reflexes appeared diminished; he had spontaneous bilateral Babinski signs, positive Gordon and Oppenheim signs. In addition to prominent muscle weakness, there were signs of minimal cerebral palsy such as eversion and hyperextension of his left extremities and flexion and inversion of his right extremities. Both feet showed inversion.

Poor fine-motor performance was regarded as secondary to muscle weakness. There were neither cerebellar signs, fasciculations nor fibrillations. Except for the impaired cranial nerve VII and IX functions, resulting in pronounced swallowing difficulties and dysarthric speech, examination of the cranial nerves, including audiologic tests, did not reveal any abnormalities.

Brain CT was normal. His EEG revealed single, sharp theta transients shifting from right to left in the occipitoparietal area, more pronounced on the left. Due to the child’s lack of co-operation, hyperventilation and photic stimulation could not be carried out. Occipital alpha rhythms were present.

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Electromyography of the anterior tibialis, rectus femoris, biceps brachii, and deltoid muscles revealed small action potentials reduced in amplitude without abnormal activity and regular interference patterns, which were interpreted as myopathic while electromyography of the levator labii and of the orbicularis oris muscles disclosed insufficient innervation and brief small action potentials, which were regarded as non-diagnostic.

The erythrocyte sedimentation rate was 3/9 for the first 2 h. Aldolase was 9.1 U/l (normal up to 7.5 U/l). Creatine kinase values were 46.3 U/l in December of 1982, 63 U/l and 124 U/l in May of 1983 (normal up to 80 U/l). Acid maltase activity was 0.633 mU/mg protein (96% of normal) in his leucocytes. Cell morphology and the chemistry of his cerebro-spinal fluid were normal. There was no evidence of hypothyroidism or myasthenia gravis.

He died at the age of 5 years and 10 months at home, 3 months after he was last seen at our hospital. No autopsy was performed.

Material and methods

A gastrocnemius muscle biopsy was obtained and unfixed frozen in isopentane in liquid nitrogen, after mounting of cross-sectioned muscle fascicles. Cryostat sections 10 μm thick were submitted to numerous histological and enzyme-histochemical preparations as previously outlined [3, 6]. A separate piece of muscle tissue was clamped in situ, excised and fixed in buffered glutaraldehyde still within the clamp, osmicated and washed in increasing concentrations of alcohol, followed by embedding in Epon. Toluidine blue and paraphenylene diamine stained sections 1 μm thick served to select suitable areas for ultra-thin sectioning to be studied by electron microscopy.

Results

By light microscopy, the muscle revealed a myopathic spectrum of atrophic and hypertrophic muscle fibres arranged at random. Internal nuclei were frequent as was endomydial fibrosis. No inflammatory infiltrates were present. Necrosis, phagocytosis, and basophilia of single muscle fibres occurred. Numerous muscle fibres contained “rimmed” vacuoles that often occupied considerable parts of a cross-sectioned muscle fibre (Fig. 1). Acid phosphatase was active within interstitial cells, in macrophages inside necrotic muscle fibres and scantily in “rimmed” vacuoles (Fig. 2), while the vacuoles had a considerable bluish content in the myoadenylate deaminase preparation (Fig. 3). In oxidative (NADH, MAG) and ATPase preparations after alkaline and acid pre-incubations these “rimmed” vacuoles appeared largely empty. In certain areas of the muscle specimen “rimmed” vacuoles were absent. In addition, the enzyme-histochemical preparations showed a rather uniform activity of the respective enzymes, light in the MAG preparation (Fig. 4), strong in the NADH preparation, but intermediate in the ATPase preparations after alkaline and acid pre-incubations, indicating that the majority of large and normal sized muscle fibres were actually of type I (Fig. 4).

Small angular fibres reacting strongly in the MAG preparation (Fig. 4) were scattered throughout the muscle biopsy. The amounts of lipid droplets and glycogen were within normal limits.

Discussion

“Rimmed” vacuoles had originally been observed in oculopharyngeal dystrophy [3], but were later consistently seen also in inclusion body myositis [2], thus representing a non-specific morphological feature present also in other well-defined neuromuscular entities [4] and listed in Table 1. Clinical and morphological findings in our patient eliminated certain neuromuscular conditions from this list as the cause of our patient’s neuromuscular signs and symptoms, such as oculocraniosomatic syndrome, inclusion body myositis, distal myopathy, spinal muscular atrophy, type II glycogenosis, or oculopharyngeal muscular dystrophy [9]. Numerous “rimmed” vacuoles were observed in a “familial granulovacuolar lobular myopathy with electrical myotonia” [7], but our patient lacked lobulated muscle fibres as well as myotonia as shown by electrophysiological examination.

In a recent paper [1], a familial and possibly neurogenic neuromuscular disorder of apparently autosomal dominant inheritance revealed “rimmed” vacuoles in severely affected distal (gastrocnemius and tibialis anterior) muscles but not in less affected proximal (quadriceps and deltoid) muscles, thus indicating that “rimmed” vacuoles may not be a feature occurring early in whatever the basic muscle disease might be but rather late, and possibly also more often in distal than in proximal limb muscles. Numerical increase of “rimmed” vacuoles with time was also observed in two brothers afflicted with a possible X-linked inherited myopathy [8].

Occasional membrane-bound glycogen, possibly within the lysosomal compartment also suggested type II glycogenosis, but this condition was ruled out by normal acid maltase activity in our patient’s leucocytes, and membrane-bound glycogen was scarce in myofibres and not present in mural cells of intramuscular vessels, where it is regularly encountered in type II glycogenosis. However, membrane-bound glycogen may be a rare and scant and thus non-specific finding in neuromuscular disorders and has also been described together with “rimmed” vacuoles in another congenital myopathy [5].

Clinical findings, onset of neuromuscular signs and symptoms in early childhood, as well as predominance of type I fibres in our patient’s muscle biopsy suggested a congenital myopathy. Another congenital myopathy previously reported