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Congenital nemaline myopathy: two patients with consanguineous parents, one with a progressive course

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Summary. Clinical, morphological and genetic data are presented on two unrelated children with congenital nemaline myopathy. In one of these, the weakness and hypotonia were progressive. The parents of both children were second cousins. These cases together with those already published suggest that the frequency of consanguineous marriages in parents of children with nemaline myopathy is increased. This is a further argument in favour of an autosomal recessive type of congenital nemaline myopathy in addition to the autosomal dominant variety.

Key words: Nemaline myopathy – Autosomal recessive inheritance

Zusammenfassung. Es werden zwei miteinander nicht verwandte Kinder mit kongenitaler Nemaline Myopathy aus klinischer, morphologischer und genetischer Sicht beschrieben. Zu einem der Fälle waren die Muskelschwäche und die Hypotonie progredient. In beiden Fällen waren die Eltern der Kinder Vettern 1. Grades. Dies sowie die entsprechenden Angaben aus der Literatur weisen darauf hin, daß Konsanguinität bei den Eltern von Kindern mit Nemaline Myopathy gehäuft vorkommt. Es scheint dies ein Argument dafür zu sein, daß neben dem autosomal dominanten Typus auch eine autosomal rezessive Form der kongenitalen Nemaline Myopathy existiert.

Introduction

Since its initial description [18], congenital nemaline myopathy has generally been considered to be a non-progressive disease. So far, death has been ascribed

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to intercurrent complications, and clear evidence for progression of the disease has not been found. Autosomal dominant inheritance with variable expression has been proved in a number of families [1, 7, 8, 13]. However, the possibility of autosomal recessive inheritance has also been raised [1, 15]. Because of this implied genetic heterogeneity, the need for investigation of apparently healthy parents and other family members has been stressed [1, 3].

We describe here two unrelated cases of congenital nemaline myopathy, one with unequivocal progression of the weakness before her final illness. Both children were born from consanguineous marriages, suggesting autosomal recessive inheritance in these cases.

Case reports

Case 1

This girl was born after an uneventful pregnancy with reportedly normal foetal movements. The birth weight was 3000 g. On the 4th day of life, feeding and swallowing difficulty became apparent, necessitating feeding via a nasogastric tube. She showed motor restlessness with jittery movements. The muscle tone was slightly diminished. Her condition improved during the following days and at age 3 weeks she was discharged, without apparent neurological problems. At age 6 weeks, the child was hospitalized again with bronchopneumonia. Physical examination revealed the child to have a dolichocephalic skull, a normally arched palate, a pigeon chest and long, slender extremities. She was moderately hypotonic and unable to swallow her saliva. Coughing was weak. The external ocular and facial muscles appeared to function normally, but the mouth was constantly open. The sucking and rooting reflexes were weak. At age 4.5 months, spontaneous movements of the arms and legs had ceased except for slight movements of the hands and fingers. The traction response and head balance were absent, the head lag was extreme. There was marked weakness of the shoulder girdle with a positive sliding-through phenomenon and winged scapulae. The legs hung loose, without movements on horizontal and vertical suspension. There was generalized areflexia. At the age of 5 months, the child died as a result of acute aspiration. The following laboratory investigations gave normal results or were negative: a complete blood count, serum electrolytes, serum enzymes, including creatine kinase, serum ammonia and lactate, serological reactions for congenital infections, a 24-h urine screening for abnormal excretion of amino acids, organic acids and mucopolysaccharides, an ECG, a CT scan of the head, an EEG, and nerve conduction velocities. An EMG showed no denervation phenomena at rest; voluntary potentials could not be obtained.

She was the sixth child of healthy Pakistani parents, whose maternal grandmothers were sisters. Both parents had had a normal motor development. They had never had any complaints of muscular weakness, fatiguability or cramps. At school, the father had excelled at sports. They were both tall, normally built persons with normal muscle strength and volume. The deep tendon reflexes were normal. There was no percussion myotonia. No other relatives could be

examined, but anamnestic data of a number of them were available. One brother of the index case had died from pneumonia before the age of 1 year. According to the parents, he had not been a floppy infant. The other sibs of the index case were healthy. A brother of the father also married a second cousin; the child of this couple was said to have been unable to move or make eye contact. However, her appearance had been different from that of the proband. Later, she showed many involuntary extension movements and died before the age of 2 years. Five paternal uncles of the proband had all died before the age of 11 years; it was impossible to obtain any detailed information about the causes of death. Reportedly, none had been weak or floppy.

Case 2

This Dutch boy was born after an uncomplicated pregnancy, with, however, sparse foetal movements. The birth weight was 4000 g. He was floppy from birth. At age 4 months, his mother noticed for the first time that he had problems with swallowing. His motor development was retarded: rolling over at age 14 months, sitting with support at age 12 months, walking unaided at age 2.5 years. When standing up, he always had to support his body with his hands on his knees. His mental development was normal. On examination, at age 3 years and 10 months, his length was at the 90th percentile, and his weight at the 10th percentile for length. He had a pigeon chest, but no other skeletal deformity. Eye closure was weak, but the other facial muscles functioned normally, as did the tongue and pharyngeal muscles. The flexors of the neck were weak, as were the muscles of the shoulder and the pelvic girdle. He had a waddling gait and could neither walk on his heels nor run. Gowers' sign was positive. The deep tendon reflexes were normal. There were no fasciculations and no percussion myotonia. The following laboratory investigations gave normal results or were negative: a complete blood count, serum electrolytes, serum enzymes, including creatine kinase, serum lactate and acid-base balance, serum carnitine, serological reactions for congenital infections, a 24-h urine screening for abnormal excretion of amino acids, organic acids, oligosaccharides and indoles, radiographs of the skull and the thorax, an ECG and an EEG. An EMG was not performed. This boy was the first of two children; his brother was examined 2 years later at the age of 3 years. His appearance was the same as that of his brother, and he had evident proximal weakness, too. A muscle biopsy was not permitted. The parents were second cousins. The father had died from a brain tumour a few months before we first saw case 2. He was reported to have had a normal motor development and normal muscle strength. Physical and neurological examination of the mother revealed no abnormalities.

Material and methods

A biopsy specimen of the vastus lateralis muscle was taken from case 1 when she was aged 4 months, from case 2 when he was aged 3 years and 10 months. Biopsy specimens were also taken from the deltoid muscle of both parents of case 1. A

muscle biopsy of the mother of case 2 was not performed. At the autopsy of case 1, performed 24 h after death, specimens were taken of the iliopsoas, the biceps brachii, the vastus medialis and the rectus abdominis muscles, the diaphragm and an intercostal muscle. All muscle tissue was processed according to standard histological, histochemical, enzyme-histochemical and electron-microscopic procedures. Examination of the CNS was not permitted.

Results

Case 1

The autopsy showed the following gross findings: the lungs were oedematous and badly aerated, with infiltrations and aspirated milk in the lower airways. The heart showed some interstitial oedema, but no other abnormalities.

The examination of the muscle biopsy specimen and of the muscle tissue obtained at autopsy showed the following abnormalities. In all cryostat sections stained with the modified trichrome technique, abundant rods were found in all type-I fibres, but not in the type-II fibres (Fig. 1). Many muscle spindles were seen in the autopsy material; they did not contain rods. No ragged-red fibres or other structural abnormalities were noted. The muscles generally contained two populations of fibres: small type-I and large, even hypertrophic type-II fibres, mostly in a fairly even distribution. However, the samples from the iliopsoas and rectus abdominis muscles contained only type-I fibres. In the biceps brachii and an intercostal muscle, areas with only type-I fibres intermingled with areas with a disproportion of fibre-types (Fig. 2). Investigation by electron microscopy was performed only on autopsy tissue; the presence of rods was confirmed according to the criteria set forth by Engel [4].

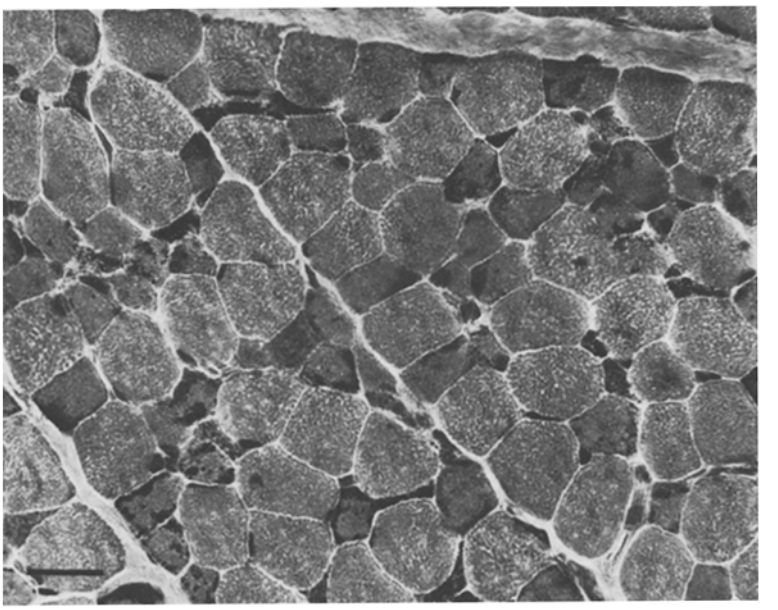
The father's muscle biopsy showed a slightly increased number of fibres with internal nuclei (8%, normally less than 3%). No rods were found in serial cryostat sections of two tissue blocks (50 sections each), nor in semi-thin sections of Epon-embedded material, stained with toluidine blue, nor in ultrathin sections studied by electron microscope. The mother's biopsy, studied by the same techniques, was completely normal.

Case 2

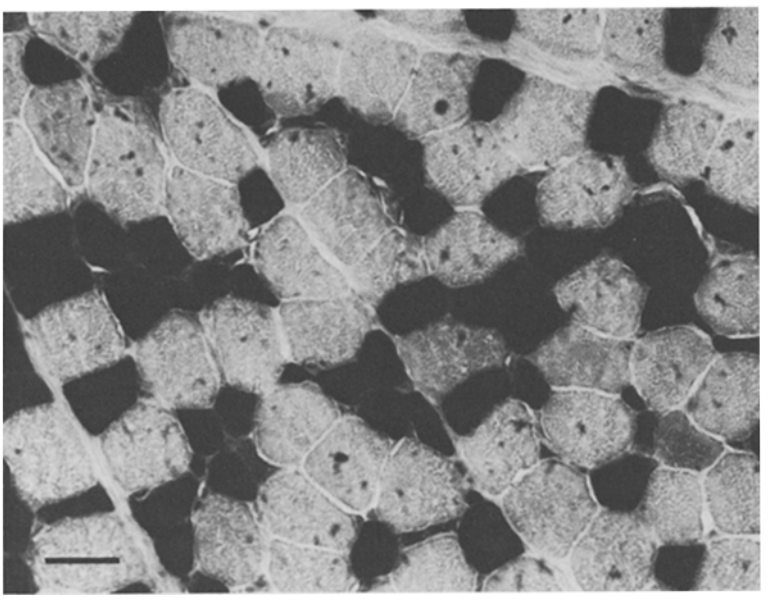
The muscle biopsy contained almost exclusively fibres which corresponded enzyme-histochemically to type-I fibres. Small type-II fibres were found only sporadically. Rods were found in a large number of type-I fibres, but not in the type-II fibres. No other abnormalities were present. At electron microscopy, the presence of rods was confirmed (Fig. 3).

Discussion

On the basis of the clinical and morphological data, a diagnosis of congenital nemaline myopathy can be made in both cases. Both patients showed some



a



b

Fig. 1a and b. Serial cryostat sections of biopsy specimen of quadriceps muscle of case 1. Rods are present in type-I fibres only. **a** Modified trichrome stain; **b** Ca-ATPase at pH 4.2. Bar = 20 μm

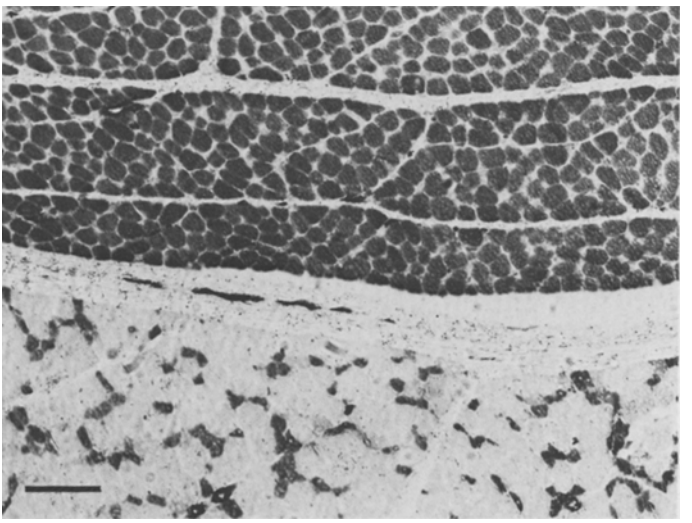


Fig. 2. Cryostat section of biceps muscle of case 1, obtained at autopsy. Ca-ATPase at pH 4.2. Areas with only type-I fibres and with an appearance of fibre-type disproportion are seen. Bar = 80 μm

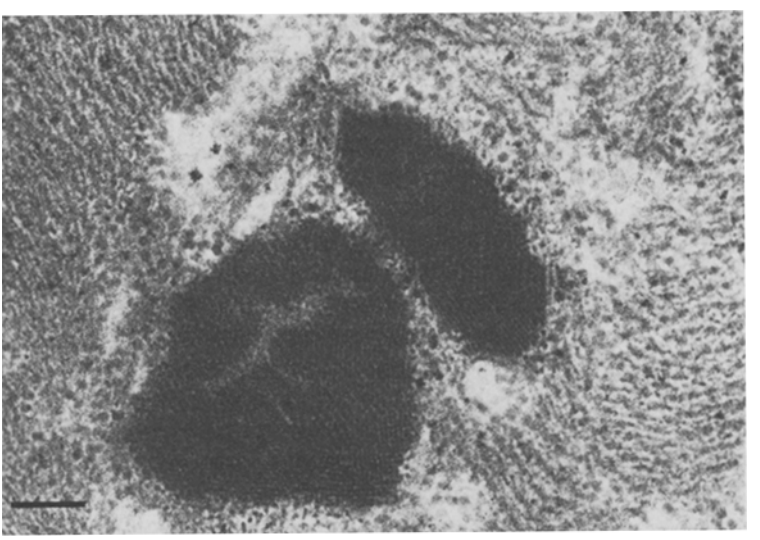


Fig. 3. Electron-microscopic appearance of two cross-sectioned rods of case 2, showing a lattice-like structure. Bar = 0.2 μm

remarkable features. Congenital nemaline myopathy is generally considered to be a non-progressive disease. There are a few reports of slow progression of the muscular weakness [5, 8, 12, 20]; none of these patients is known to have died from his weakness. Many of the patients who died [1, 14, 17] were extremely floppy from birth with severe weakness of limb and pharyngeal muscles. They died before the age of 1 year from pneumonia or acute aspiration. Clinical deteriora-

tion may have been present, but impossible to document in some of these children. In this study, case 1 showed only minimal muscle hypotonia during the first month of life and was able to swallow milk until that age. Thereafter, her strength progressively deteriorated, following an intercurrent pneumonia, and declined further after recovery from the infection. Such a progressive clinical deterioration has apparently not been documented before in congenital nemaline myopathy.

The enzyme-histochemical findings in the muscle tissue obtained at the autopsy of case 1 illustrate once more that type-II fibre paucity is an important feature in congenital nemaline myopathy, as it is in other congenital myopathies. Areas with type-I fibres only were found between fascicles with a pattern resembling fibre-type disproportion (Fig. 2). Such findings might suggest reinnervation or an abnormality of fibre-type differentiation during the foetal period. Simple denervation is almost certainly not present in congenital nemaline myopathy [2], but the role of a neurogenic factor in foetal fibre-type differentiation is well established [10, 11]. This could imply that a neurogenic factor is involved in the pathogenesis of congenital nemaline myopathy [9]. However, definite proof of a neurogenic involvement has so far been lacking. The number of motoneurons in the spinal cord of children with congenital nemaline myopathy has been reported to be normal [16].

Both cases are compatible with autosomal recessive inheritance. Autosomal dominant inheritance of nemaline myophaty is well established [1, 7, 8, 13, 19]. The possibility of recessive inheritance was first raised by Peterson and Munsat [15], while Arts et al. [1] found evidence of autosomal recessive inheritance in four families. In the latter study, it was possible to identify a number of heterozygote carriers for the recessive type. Some heterozygotes had a small number of fibres with rods in the muscle biopsy. The presence of an increased number of fibres with internal nuclei was considered to be aspecific evidence in favour of heterozygosity. However, not all heterozygotes could be recognized in this way [1]. The parents of both patients presented here were second cousins; the father of case 1 had an increased number of fibres with internal nuclei, the biopsy specimen of her mother was normal. A biopsy specimen could not be taken from the mother of case 2.

Consanguinity of parents of children with nemaline myopathy has been reported previously. Two cases have appeared in the Japanese literature and were summarized by Kondo and Yuasa [13]; another case was published recently [6]. The proportion of consanguineous marriages among all cases of congenital nemaline myopathy with possible autosomal recessive inheritance published so far (including the two cases presented here but excluding families with patients in two or more generations) is 5/43. This high ratio strongly suggests an autosomal recessive type of congenital nemaline myopathy in addition to the well-established autosomal dominant type, and confirms earlier findings [1]. In the absence of known clinical and biochemical differences between the autosomal dominant and the autosomal recessive variety, adequate genetic counselling cannot be given without evaluating both possibilities by means of an extensive family investigation.

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