Nemaline myopathy in a newborn infant: a rare muscle disorder

Miopatia nemalinowa u noworodka – opis rzadkiej choroby

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Abstract

Nemaline myopathy (NM) is a genetically and clinically heterogeneous muscle disorder, defined by the presence of characteristic nemaline bodies on muscle biopsy. The disease has a wide spectrum of phenotypes, ranging from forms with neonatal onset and fatal outcome to asymptomatic forms. The neonatal form is severe and usually fatal. The clinical variability, with differing age of onset and severity of symptoms makes the diagnosis difficult during infancy. There is no curative treatment. L-tyrosine may prevent aspiration by reducing pharyngeal secretions and drooling. Most of the patients die from respiratory and cardiac failure.
This article discusses a newborn infant who presented with generalized weakness and respiratory failure. Partial response to L-tyrosine treatment was noted. The case is worth presenting to remind clinicians of congenital myopathies in the differential diagnosis of floppy infant during neonatal period and to emphasize the importance of muscle biopsy in diagnosis.

Key words: congenital, myopathy, nemaline body, floppy, infant.

Streszczenie

Miopatia nemalinowa jest schorzeniem mięśni, niejednorodnym pod względem genetycznym i klinicznym. Chorobę cechuje obecność charakterystycznych struktur nemalinowych w bioptacie mięśnia. Fenotyp jest bardzo zróżnicowany i obejmuje zarówno postacie noworodkowe prowadzące do zgonu, jak i postacie bezobjawowe. Postać noworodkowa przebiega ciężko i zwykle kończy się śmiercią. Zmienność kliniczna, łącznie ze zróżnicowanym wiekiem w chwili wystąpienia objawów i z różnym ich nasileniem, może utrudniać rozpoznanie w wieku niemowlęcym. Choroba jest nieuleczalna. Podawanie L-tyrozyny może zapobiec zachłyśnięciu poprzez zmniejszenie produkcji wydzieliny w gardle i śliny. Większość chorych umiera z powodu niewydolności oddechowej i krążenia.
W artykule omówiono przypadek noworodka z uogólnionym niedowładem i niewydolnością oddechową. Reakcja na podawanie L-tyrozyny była częściowa. Przedstawiony opis przypadku ma na celu przypomnienie klinicystom o miopatiach wrodzonych, które należy uwzględniać w rozpoznaniu różnicowym zespołu wiotkiego dziecka w okresie noworodkowym, oraz podkreślenie znaczenia biopsji mięśnia w ustalaniu rozpoznania.

Słowa kluczowe: wrodzona, miopatia, struktury nemalinowe, wiotkie, niemowlę.

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Introduction

Nemaline myopathy (NM) is a rare and heterogenous form of congenital myopathy which usually presents in infancy or early childhood with hypotonia, slowly progressive weakness of the facial, bulbar, proximal limb and respiratory muscles, lax ligaments, areflexia and skeletal deformities. Bulbar dysfunction causes swallowing difficulties and drooling, and may predispose to aspiration of oral secretions [1].

The clinical variability, with differing age of onset and severity of symptoms makes the diagnosis difficult in some cases [2]. Up till now, six different forms have been described [3]. Type of inheritance may be autosomal dominant, autosomal recessive and X-linked dominant.

Muscle enzymes are usually normal, but may be mildly elevated in some cases. Electromyography (EMG) is nonspecific. Muscle imaging is useful in distinguishing between neuropathic and myopathic processes. Muscle biopsy is diagnostic. Biopsy specimens show numerous threads like inclusions on modified Gomori trichrome staining [4].

Treatment is supportive. L-tyrosine may prevent aspiration by reducing pharyngeal secretions and drooling [5]. Pneumonia due to aspiration occurs frequently. Most of the patients die from respiratory and cardiac failure during infancy.

Here we report a newborn baby who was admitted to our neonatal intensive care unit (NICU) with severe respiratory failure and generalized muscle weakness and diagnosed as NM on muscle biopsy. The case was found worth presenting in order to remind clinicians of neonatal muscle disorders in the differential diagnosis of severe hypotonia during neonatal period.

Case report

A newborn baby who was born from the first pregnancy of a 29-year-old mother by vaginal delivery on the 36th gestational week was admitted to our NICU because of severe respiratory failure soon after birth. His family history did not reveal any significance in terms of neuromuscular disesases and there was no consanguinity between his parents. His antenatal screening tests were normal. However, fetal movements in the third trimester of pregnancy felt by his mother and observed by the obstetrician on the fetal ultrasonography were decreased and marked polyhydramnios had emerged after the 32nd week of pregnancy. At 36 weeks vaginal delivery had to be induced because of the onset of membra rupture and fetal distress.

Although the mother had not received any medication before or during delivery, the neonate had generalized hypotonia, severe dyspnea, bradycardia and central cyanosis at birth. The Apgar scores at 1 and 5 minutes were 2 and 6, respectively. He required immediate face mask/bag resuscitation in the delivery room. On admission to our NICU, weak chest and diaphragmatic movements, central cyanosis and generalized muscle weakness were identified. The infant lied in a frog-like position with abduction of the hips and an abnormal extension of the limbs. When pulled to sitting position, there was a remarkable head lag. In vertical suspension his arms and legs were extended and on horizontal suspension his head and limbs hung loosely. Except his eye movements, he did not have any spontaneous movements. Deep tendon reflexes were absent and neonatal reflexes including sucking and swallowing were decreased. No abnormal primitive reflex could be detected. Assessment of sensation did not reveal any pathology. He did not have any dysmorphic features or congenital defects. His karyotype was 46, XY. Widespread fine crackles were auscultated over both lungs. Because of severe respiratory failure, an endotracheal tube was placed and he was started on mechanical ventilation. Chest radiography revealed bilateral reticulogranular pattern and decreased lung ventilation. His blood gases were compatible with respiratory acidosis. He received single dose of surfactant and he was started on dual antibiotherapy with ampicillin and netilmicin. Routine haematological and biochemical examinations were completely normal. Serial transfontanel ultrasonographic examinations performed in consideration of birth asphyxia on the first, third, seventh and fourteenth days of life were assessed to be normal. No pathology could be seen on his electroencephalographic examination either. Echocardiography revealed restrictive patent ductus arteriosus, patent foramen ovale and mild pulmonary hypertension. Because of his ongoing severe hypotonia, weak cry and no effort to breath, muscle enzymes and screening tests for congenital metabolic disorders were performed and they were found to be completely normal. EMG or cerebrospinal magnetic resonance imaging (MRI) could not be performed because of his dependency on mechanical ventilation. Eventually, in order to exclude congenital neuromuscular disorders, a muscle biopsy was performed from gastrocnemius at age 8 weeks and the diagnosis of NM was established.

Microscopic examination revealed the intracellular accumulation of thread-like structures. The rods were not visible on hematoxylin-eosin staining, but appeared as red or purple structures against the blue-green myofibrillar background with the modified Gomori trichrome stain (Fig. 1). The distribution of rods within myofibers showed a tendency to cluster around nuclei. Furthermore an increased oxidative enzyme activity with cytochrome oxidase enzyme stain was also demonstrated (Fig. 2). Immunohistochemical stainings were done by streptavidin-biotin immunoperoxidase complex method using antibody against sarcomeric actin, smooth muscle actin, desmin and vimentin. Only focal desmin positivity could be demonstrated on these rods (Fig. 3). There was diffuse positivity in all muscle fibers with the antibody against myosin heavy chain neonatal. Genetic analysis for specific gene mutations could not be performed. Diagnosis was based on clinical findings and the observation of characteristic rod-shaped structures (nemaline bodies) on muscle biopsy.

Although he had received daily physiotherapy, he developed generalized muscle atrophy on follow up. He had profuse sialorrhoea from birth and required frequent suctioning. He experienced 8 aspiration pneumonitis attacks and he developed permanent atelectasis on his right lung. Despite of many extubation attempts he could not tolerate spontaneous respiration and he was kept on intermittent positive-pressure ventilation until his death. He was also dependent on orogastric feeding and parenteral nutrition throughout his hospital stay. Treatment of L-tyrosine was begun at 3 months of age (250 mg daily) and resulted in a marked improvement in his oral secretions and muscle strength. Unfortunately, he passed away because of a sudden cardiorespiratory failure after an attack of aspiration at 4 months of age.

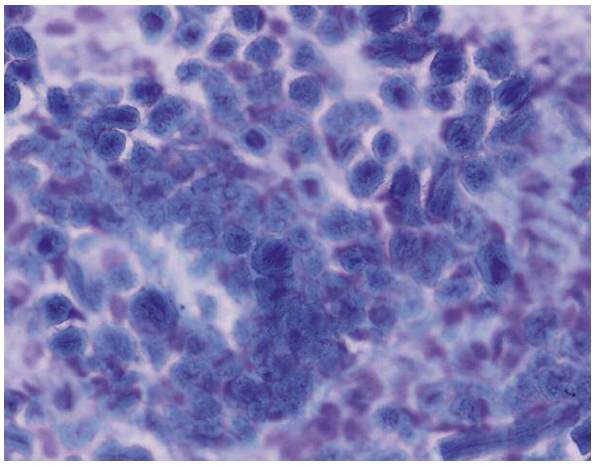

Fig. 1. Modified Gomori trichrome stain showed characteristic purple-colored rods in the perinuclear region

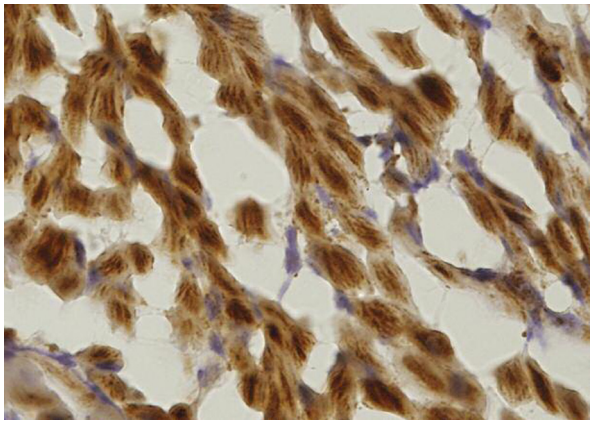

Fig. 2. Increased oxidative enzyme activity with cytochrome oxidase enzyme stain

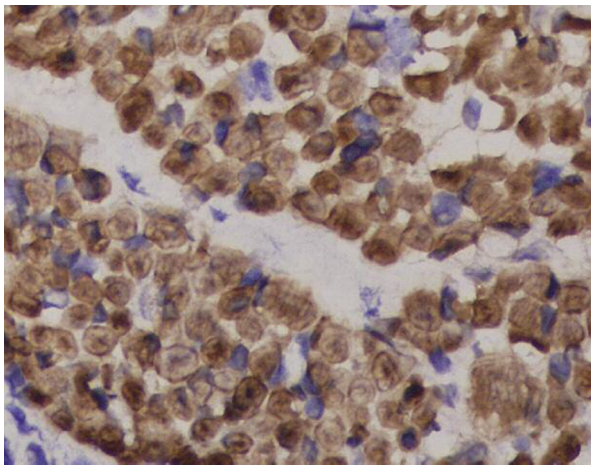

Fig. 3. Focal desmin positivity on immunohistochemical staining (streptavidin-biotin immunoperoxidase complex method)

Discussion

Almost any condition that affects the central or peripheral nervous system of a newborn can be expressed by hypotonia. Furthermore, most acute or multisystem illnesses in neonates are accompanied by some degree of hypotonia. Therefore clinicians must consider whether the infant is acutely ill from sepsis, organ failure, metabolic dysfunction, or other systemic illness. If these illnesses are not present as so in our case, the next step is to consider whether a primary disorder of the central or peripheral nervous system is the cause.

The differential diagnosis between a primary central nervous system disorder and a neonatal muscle disorder requires a methodical approach including a detailed family, obstetric and delivery history and a careful examination. Clues to the presence of a neuromuscular disorder include polyhydramnios, decreased fetal movements and malpresentation. Physical findings such as respiratory failure with decreased or absent diaphragmatic movements, typical frog-like body posture, decreased or absent spontaneous extremity movements, absence of abnormal primitive reflexes, absence of deep tendon reflexes, findings of bulbar dysfunction such as weak cry, poor suck and swallow reflexes, pooling of secretions and aspiration can all be interpreted in favour of a congenital muscle disorder. Afterwards, a muscle biopsy should be performed to prove the diagnosis. Most of these above mentioned clues and physical findings were present in our patient. Therefore we performed a muscle biopsy from gastrocnemius at age 8 weeks and diagnosed NM.

Nemaline myopathy is a genetically and clinically heterogenous muscle disorder which is characterized by severe muscle weakness and nemaline rod bodies in skeletal muscle fibers. The term "nemaline" was first used by Shy and his colleagues in 1963 who reported a new type of nonprogressive myopathy characterized by numerous thread-like structures within the muscle fibers [6].

Clinically, six different forms of NM have been described until today [3,4,7]. A classic/typical congenital form (46%) may appear as a floppy infant with additional facial and respiratory weakness. A severe congenital (neonatal) form (16%) is marked by lack of fetal movements and by respiratory insufficiency. Patients usually present at birth with severe muscle weakness, difficulties with sucking and swallowing. Contractures, fractures, arthrogryposis multiplex and dilated cardiomyopathy may also be associated. Most neonates suffer from hypoxia and usually require invasive ventilatory support. The intermediate congenital form (20%) with clinical severity apparent only later in the infantile period is characterized by generalized hypotonia, weakness and a very thin muscle mass. Muscles of the jaw may be too weak to hold it closed. Pooling of the oral secretions in the mouth is common and this may predispose to aspiration pneumonitis. Expressions of the other three forms (mild childhood or adolescent-onset form [13%], adult-onset [late-onset] form [4%] and the form with diverse features [< 1%]) are not apparent during the neonatal period. Our patient mostly met the criteria for the severe congenital form.

Dilated or hypertrophic cardiomyopathy is an uncommon complication of the disease [8-10]. Nemaline bodies clustered in the cardiac muscle can be demonstrated hystologically. Some authors have also described an unusual course of the disease with late onset scapulohumeral syndrome [11]. Our patient had undergone five echocardiographic examinations throughout his hospitalization and no associated cardiac involvement could be demonstrated.

Muscle enzymes are usually normal, but may be mildly elevated in some cases. EMG is nonspecific, showing similar abnormalities in all congenital myopathies. Especially before the age of 3 years, EMG usually shows mild abnormalities and a myopathic pattern can be found in only a few patients [12]. Muscle imaging is useful in distinguishing between neuropathic and myopathic processes, and can be used to identify an appropriate muscle to biopsy. Muscle MRI commonly reveals patchy, fatty degeneration of muscle tissue and variable involvement of different muscle groups [13]. Neither EMG, nor MRI are necessary for definite diagnosis. They are accepted as useful tools in making differential diagnosis. Repeated muscle enzymes, EMG and MRI (craniospinal) of our patient were completely normal.

Muscle biopsy is diagnostic. Biopsy specimens show numerous threads like inclusions on modified Gomori trichrome staining [4,14]. Based upon additional actin aggregates, three different histological subgroups of patients can be identified [4,15]. Intranuclear nemaline rods correlate with severe clinical manifestations and poor prognosis [16]. Similarly focal myofibrillar degeneration and increase in lysosomal enzymes may indicate poor prognosis. At this point, we should mention that myosin heavy chain has many isoforms which are specific for different muscle fibre types and some of which are developmentally regulated. Neonatal myosin has been described as one type of myosin heavy chain. It is known to be expressed in human striated muscles during the fetal period of human muscle development. Therefore expression of neonatal myosin in the postnatal period is accepted as an immaturity sign. In this respect, Fidziańska *et al.* [17] have described an infant with a neonatal form of nemaline myopathy showing ultrastructural features of muscle immaturity such as abnormal presence of myotubes, as well as cells in clusters within a common basement membrane and a great number of satellite cells adhering to very small muscle fibers. The muscle biopsy of our patient revealed intracellular clustered nemaline rods with apparently lacking

actin aggregates on trichrome stain and increased oxidative enzyme activity with COX. Immunohistochemical stainings demonstrated focal desmin positivity. We also detected diffuse neonatal myosin expression and accepted it as a sign of immaturity.

Genetically, causative mutations have been described in five genes encoding different skeletal muscle thin filament proteins. These filamental proteins and their encoding genes are: sarcomeric actin (*ACTA1*), alpha-tropomyosin (*TPM3*), beta-tropomyosin (*TPM2*), troponin T1 (*TNNT1*) and nebulin (*NEB*) [18,19]. Nebulin gene mutations are seen most commonly in autosomal recessive cases and these patients present as typical congenital NM [20,21]. Unfortunately we could not perform genetic analysis of our patient.

Therapeutic strategies for NM are symptomatic and empirical. Orogastric/nasogastric/nasojejunal tube feeding and gastrostomy may be needed for chronic dysphagia and sucking-swallowing difficulty. Pneumonia due to aspiration of oral secretions occurs frequently. Treatments for sialorrhoea, such as anticholinergic agents and salivary gland botulinum toxin injections, are often ineffective or associated with significant side effects [22]. Dietary L-tyrosine supplementation may improve bulbar functions and increase catecholamine-mediated sympathetic activity in the salivary glands [5]. By this way, it may reduce pharyngeal secretions and thus prevent drooling and aspiration. Our patient was dependent on orogastric feeding and parenteral nutrition throughout his hospital stay. Despite of many extubation attempts, he could not tolerate spontaneous respiration and he was dependent on intermittent positive-pressure ventilation. He experienced 8 attacks of aspiration pneumonitis until L-tyrosine treatment (250 mg daily) was started on at 3 months of age. L-tyrosine treatment resulted in a marked improvement in his oral secretions and muscle strength. However it could not detain him from developing upper right lung atelectasis due to previous aspirations.

Many of the patients die from respiratory and cardiac failure during infancy [23]. Unfortunately, there is no curative treatment modality. In conclusion, keeping in mind NM in the differential diagnosis of floppy infant and offering genetic counselling to families for consequent pregnancies seems to be the only way to prevent this genetic disorder at present.

Disclosure

Authors report no conflict of interest.

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