CASE REPORT

An unusual cause of hypertrophic cardiomyopathy in an infant: A case report and brief literature review

Une cause inhabituelle de cardiomyopathie hypertrophique chez un nourrisson : Un rapport de cas et une brève revue de littérature

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Abstract

Introduction: Nemaline myopathy (NM), also known as Nemalinosis, is a rare congenital muscle disease with an incidence of 1 in 50000. It is characterized by nemaline rods in muscle fibers, leading to muscle weakness. We reported a case of NM revealed by cardiac involvement, and we highlighted the challenges in diagnosing this condition as well as its poor prognosis.

Observation: The patient is a 7.5-month-old infant from a consanguineous marriage, with a history of bronchiolitis and psychomotor retardation. The infant was admitted to the paediatric intensive care unit due to respiratory distress, which necessitated intubation and mechanical ventilation. A chest X-ray revealed cardiomegaly and bilateral bronchial syndrome, while an electrocardiogram showed left ventricle hypertrophy. Emergency echocardiography revealed biventricular hypertrophy. Laboratory tests indicated significant rhabdomyolysis, hepatic cytolysis, microcytic hypochromic anemia, negative troponins, and respiratory acidosis. The enzymatic activity of acid alpha-glucosidase was inconclusive. Genetic analysis for mutations in exon 2 associated with Pompe disease and congenital muscular dystrophy, the most common differential diagnoses, returned negative results. Given the presence of rhabdomyolysis, the emergence of tongue fasciculations, and pronounced axial and peripheral hypotonia, a muscle biopsy was performed. This revealed the presence of nemaline rods, confirming the diagnosis of NM. The patient's condition deteriorated, marked by extubating failure due to severe muscle weakness. The infant passed away after 50 days of hospitalization.

Conclusion: This case underscores the severity and complexity of NM revealed by hypertrophic cardiomyopathy, emphasizing the importance of early diagnosis and prenatal genetic counseling.

Key words: Case report, Congenital, Nemaline myopathy, Mutation

Résumé

Introduction: La Myopathie à Némaline (MN), également connue sous le nom de Nemalinose, est une maladie musculaire congénitale rare dont l'incidence est de 1 sur 50000. Nous avons rapporté un cas de MN, révélé par une atteinte cardiaque sous forme d'hypertrophie ventriculaire et nous avons discuté les difficultés de diagnostic de cette maladie ainsi que son mauvais pronostic.

Observation: Il s'agissait d'un nourrisson âgé de 7 mois et demi, issu d'un mariage consanguin, avec des antécédents de bronchiolite à répétition et de retard psychomoteur. Il a été admis en unité de soins intensifs pédiatrique en raison d'une détresse respiratoire qui a nécessité une ventilation mécanique. La radiographie du thorax a révélé une cardiomégalie et un syndrome bronchique bilatéral, tandis que l'électrocardiogramme a révélé une hypertrophie du ventricule gauche. L'échocardiographie a révélé une hypertrophie biventriculaire. Les tests biologiques ont révélé une rhabdomyolyse importante, une cytolyse hépatique, une anémie hypochrome microcytaire, des troponines négatives et une acidose respiratoire. L'activité enzymatique de l'alpha-glucosidase n'était pas concluante. L'analyse génétique des mutations de l'exon 2 associées à la maladie de Pompe et à la dystrophie musculaire congénitale étaient négatifs. La biopsie musculaire a révélé la présence de bâtonnets de Némaline , confirmant le diagnostic de MN avec atteinte cardiaque. L'état du nourrisson était marqué par l'échec de l'extubation en raison d'une faiblesse musculaire sévère et le décès à 50 jours d'hospitalisation.

Conclusion: Ce cas met en évidence la gravité et la complexité de l'atteinte cardiaque associée à la MN, soulignant l'importance d'un diagnostic précoce et d'un conseil génétique prénatal.

Mots clés : Cas rapporté, Congénitale, Myopathie à Némaline, Mutation

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Introduction

Nemaline myopathy (NM), also known as nemalinosis, is a rare congenital muscle disorder with an incidence of approximately 1 in 50,000 births (1). First described by Shy and Conen in 1963, it is characterized by the presence of nemaline rods in skeletal muscle fibers, which leads to muscle weakness (2–4). Symptoms can appear at any age, from infancy to adulthood, with significant variability in severity (3). Prenatal diagnosis is possible through genetic analysis, which can detect mutations associated with the condition (2). However, cardiac involvement in NM patients is rarely reported, with hypertrophic cardiomyopathy (HCM) identified in fewer than 10 cases in the literature and a lack of correlation between cardiac involvement and genetic mutations (5).
We presented a case report of NM revealed by HCM in an infant, along with a literature review, particularly focusing on this entity's genetic variability and associated diagnostic challenges.

Case report

Our patient was a 7.5-month-old male infant, born to consanguineous parents, with a history of two episodes of bronchiolitis and psychomotor delay (he was unable to sit). The mother had no history of diabetes mellitus and had not received prenatal care. The infant was brought to the emergency department with symptoms of dyspnea, nasal obstruction, and rhinorrhea, the oxygen saturation was 88%. He was admitted to the pediatric department with a diagnosis of a new episode of bronchiolitis and was treated with oxygen therapy through a nasal cannula, nasal Suctioning, β-2 agonists, and corticosteroid aerosols. However, his condition rapidly worsened within 24 hours, with significant deterioration in both respiratory and neurological function. The infant became drowsy, unresponsive, and exhibited labored breathing (arterial oxygen saturation of 60%), along with hemodynamic instability, prompting immediate transfer to the pediatric intensive care unit. Due to the severity of his condition, he was intubated and mechanically ventilated from the outset. A chest X-ray revealed cardiomegaly and bilateral bronchial syndrome, while the electrocardiogram showed a right bundle branch block and left ventricular hypertrophy (Figure 1).

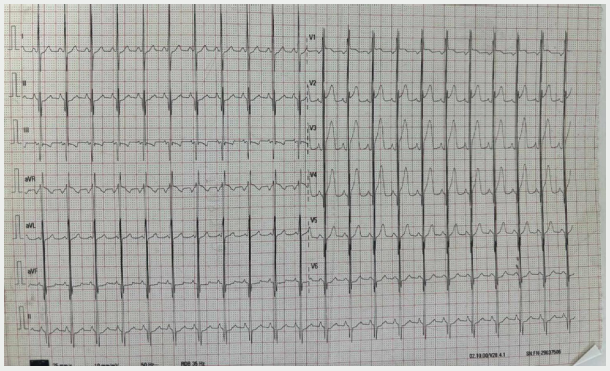

Figure 1. The electrocardiogram of the patient showed right bundle brunch and left ventricle hypertrophy

An emergency transthoracic echocardiography revealed biventricular hypertrophy without obstruction. Laboratory results indicated significant rhabdomyolysis, with creatine phosphokinase at 744 IU/l (normal range: 20-200) and lactate dehydrogenase at 1030 IU/L (normal below 500), hepatic cytolysis, microcytic hypochromic anemia (hemoglobin at 8.8 g/dL (normal range: 12-13)), negative troponin levels, respiratory acidosis, and an elevated C-reactive protein of 41 mg/L (normal below 5). Given the neurological distress, a brain computed tomography scan was performed but showed no abnormalities. A lumbar puncture revealed the presence of two white cells with normal biochemistry, and tests for herpes culture and polymerase chain reaction were negative. A cerebral magnetic resonance imaging with spectroscopy was conducted, revealing hypoplasia of the corpus callosum, which did not account for the clinical presentation.
A metabolic disorder was suspected due to the multi-organ involvement, but tests for ammonia and lactate levels, including the lactate-to-blood pyruvate ratio, were normal (lactate at 1.59 mmol/l (normal below 1.65)). Given the electrocardiogram findings suggestive of Pompe disease, an assessment of acid alpha-glucosidase activity was conducted, though the results were inconclusive. Genetic analysis for exon 2 mutations associated with Pompe disease and common congenital muscular dystrophies returned negative. The dosage of L carnitine was normal.
In the presence of rhabdomyolysis, tongue fasciculations, and significant axial and peripheral hypotonia, a muscle biopsy was performed, revealing the presence of nemaline rods in more than 60% of speciemn, which confirmed the diagnosis of NM with cardiomyopathy (Figure 2).

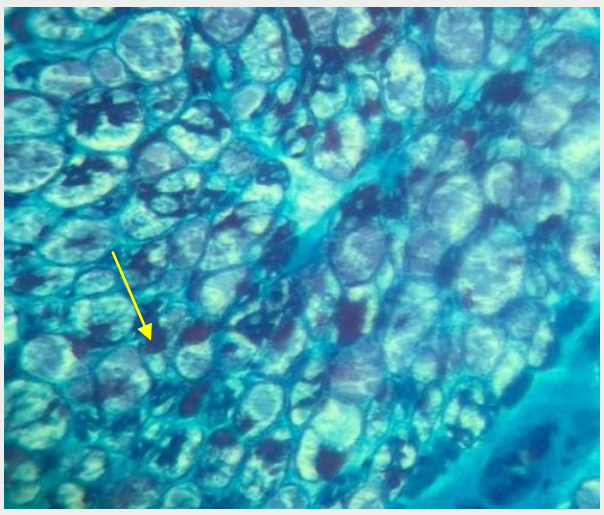

Figure 2. Muscle biopsy showing the presence and distribution of nemaline bodies inside myofibers (yellow arrow)

The patient was treated symptomatically with diuretics, β-blockers, invasive mechanical ventilation, and supportive care. The clinical course was complicated by failed extubating attempts due to respiratory exhaustion, right apical atelectasis, and recurrent bradycardia, along with progressive induration of the peripheral muscles. Unfortunately, the patient passed away on day 50 of

hospitalization. A post-mortem exome study genetic testing confirmed the presence of the following mutation: myopalladin gene mutation (MYPN). Genetic counseling was planned, but the father and mother missed the appointment.

Discussion

Our case highlights an extremely rare cause of neonatal HCM which is NM, an etiology of HCM that is seldom considered by pediatricians. The association between muscle weakness and cardiac hypertrophy should always be considered in such cases. Fewer than 10 cases have been reported in the literature (Table 1) (5–11). Most cardiomyopathies reported in patients with nemaline myopathy were of the dilated type (5). Our patient presented with a severe and fatal congenital form, featuring biventricular hypertrophy, posing a diagnostic challenge.

Faced with the association of neurological impairment and left ventricular hypertrophy in an infant, we considered several diseases, particularly metabolic conditions such as Pompe disease (also known as glycogen storage disease type II), L-carnitine deficiency, mitochondrial disorders, malformation syndromes or neurogenetic disease (12). However, biological tests and genetic analyses ruled out these diagnoses. Additionally, muscle biopsy revealed significant deposits of nemaline rods in 60% of the specimen. Another potential cause of HCM in newborns is a secondary HCM due to gestational diabetes in the mother (13), it was ruled out as the child's mother had no diabetes.

HCM is not necessarily correlated with NM, although it can occur as part of the disease's spectrum, particularly because both conditions involve muscle pathology. However, without an endomyocardial biopsy, it is challenging to establish a direct link between the two.

In our case, the HCM pattern could be either a manifestation of NM or simply a coincidental association. Unfortunately, we did not perform a cardiac biopsy.

Considering that cardiac biopsy was only reported in one case in the literature (9), and given the diagnostic value of such procedures, this distinction becomes critical. It would indeed be valuable to highlight this uncertainty in your manuscript, especially in the absence of histopathological confirmation of NM involvement in the heart muscle.

NM is a disease characterized by the presence of nemaline rods, which are abnormal structures that interfere with muscle contraction (14). This can lead to muscle weakness, hypotonia, a positive Gower sign, delayed motor development, and respiratory distress (3). The clinical phenotype of NM is highly heterogeneous (15). Some individuals may experience mild muscle weakness, while others may face severe respiratory difficulties, inability to move independently, or rare manifestations such as cardiomyopathy, ophthalmoplegia, or abnormal distribution of muscle weakness (15). The cardiac disease could be dilated cardiomyopathy or HCM.

A clinical classification of NM based on the pattern of weakness and age at onset has been described including severe congenital NM, intermediate congenital NM, typical congenital NM, childhood-onset NM, and adult-onset NM (16). The severe, intermediate, and typical congenital forms begin in infancy but have different prognoses. With the typical form of NM, children are born as floppy infants, gross motor activity is slow, but fine motor activity and intelligence are usually normal. The clinical presentation of our patient aligns with the severe congenital form of NM. The analysis of the different cases reported in the literature of HCM and NM did not show any correlations between the clinical presentation and the cardiac disease (Table I) (6,8–11,17).

The association of certain genetic mutations with cardiac involvement in cases of NM is not well clear. Some mutations have been identified in patients, such as ACTA1 mutation. In our case, genetic testing confirmed the presence of MYPN mutation. This genetic mutation is one typically found in patients with NM and does not appear to be linked to cardiac involvement. Advances in genetic testing have revealed that patients with NM and their families could benefit from genetic analysis for early diagnosis (15). At least 13 genetic mutations affecting the structure and function of muscle filaments are associated with NM, including mutations in the following genes: TPM3, NEB, ACTA1, TPM2, TNNT1, KBTBD13, CFL2, KLHL40, KLHL41, LMOD3, MYO18B, TNNT3, and MYPN(15). The myopalladin gene (MYPN) mutation identified in our patient is known to cause mildly progressive nemaline/cap myopathy but it was not correlated to cardiac involvement (18).

Treatment for NM primarily focuses on alleviating symptoms and enhancing the patient's quality of life. Management remains mainly supportive, and currently, there is no available curative treatment. This approach often includes physical therapy to maintain muscle strength and mobility, respiratory support devices to assist with breathing, and medications to manage pain and other symptoms. Ongoing researches aim to deepen our understanding of the disease and develop new treatment options. Some authors highlighted the emerging role of L-tyrosine in the supportive care of infants with nemaline rod myopathy (19,20). Heart transplantation could be the curative option for cardiac diseases.

Our patient did not get antenatal care, the diagnosis was made late and that is why we get poor outcomes. Prenatal ultrasound can provide important clues leading to the diagnosis of NM (14). In the first trimester, ultrasounds may appear normal or reveal abnormalities such as increased nuchal translucency (14). In the second trimester, abnormalities may include fetal akinesia and/or extremity abnormalities (14). By the third trimester, ultrasounds often show fetal akinesia, hydramnios, and are frequently associated with fetal growth retardation(14).

Our case report showed a few limitations. First, our findings are based on a single patient, which limits the generalizability of the results. The unique genetic mutation found in this patient may not be present in all cases of NM with cardiac involvement. Second, the case concludes with the infant's death after 50 days of hospitalization, limiting the discussion of long-term outcomes and management strategies for similar cases.

Table 1. Review of patients with nemaline myopathy (NM) associated to hypertrophic cardiomyopathy (HCM).

Reference	Age, sex	Symptoms/Treatment	TTE	Biopsies	Genetic examination	Therapy	Follow-up	Key messages
Case 1 Van Antwerpen et al. (10)	5.5 yrs Male	Respiratory failure Nocturnal hypoventilation	HCM: ventricular septum markedly thickened with a septum to left ventricular posterior wall ratio of 1.9	***Skeletal muscle***: electron-dense nemaline rods ***Myocardium***: not performed.	Not performed	NIPPV	N/A	First case published of association between HCM and NM in an infant. Cardiac involvement discovered at the age of 5 years while the NM discovered at the age of 2 months.
Case 2 Skyllouriotis et al. (9)	4 yrs Male	Respiratory distress Muscle hypotonia Psychomotor retardation	HCM: concentric, biventricular hypertrophy, with a septal/ freewall ratio of 1.7.	***Skeletal muscle:*** - rod bodies ++, -disorders of mitochondrial fatty acid oxidation ***Myocardium:*** -hypertrophic myocardial cells but no evidence of rod bodies or any indication of a storage disorder.	Chromosome analysis was normal	Non reported	Gradual improvement in both the cardiomyopathy and skeletal muscle conditions, but moderate muscle hypotonia persists	A combination of NM with HCM and metabolic disorder (a disorder of mitochondrial fatty acid oxidation).
Case 3 Damico et al. (8)	2 yrs Male	***Severe congenital NM*** -Generalized hypotonia predominantly involving axial and shoulder girdle muscles Heart murmur	HCM discovered before NM	***Skeletal muscle:*** rod bodies ++ ***Myocardium:*** not performed	ACTA1 (K336E mutation) raising the hypothesis that the K336E mutation possibly affects actin polymerization, and leading to Ca2+ dysregulation and perturbation of muscle contractility.	Non reported	Death at 3 yrs of age, suddenly during night-time sleep	First case in which a primary diagnosis of HCM has been linked to NM and a mutation in the ACTA1 gene
Case 4 Nakajima et al. (17)	Neonate: First day of life	Dyspnea, bradycardia, cyanosis, and generalized muscle hypotonia at birth	Asymmetric biventricular hypertrophy (hypertrophy of the septum and the left ventricular posterior wall.) with outflow obstruction	***Skeletal* muscle:** rod bodies ++ ***Myocardium:*** not performed	Not performed	NIPPV β-blockers, angiotensin converting enzyme inhibitors	Heart failure remains controlled with medication	Association between NM and HCM was discovered at birth as there is a common gene mutation.
Case 5 Kim et al. (7)	20 yrs Male	Diffuse limb muscle weakness and exertional dyspnea since childhood	Biventricular hypertrophic cardiomyopathy with right ventricular outflow tract obstruction;	***Skeletal* muscle:** nemaline rods on light and electron microscopy ***Myocardium:*** not performed	ACTA1 (E239Kmutation) E239 might belocated near the polymer contact site, and an amino acid change at 239 may be predicted to cause polymerization defects As a result, this novel mutation could produce similar effects on skeletal and cardiac muscles.	Non reported	NA	this case is Second report where HCM is associated with NM and a heterozygous mutation of ACTA1.
Case 6 Arshid et al. (2012) (6)	Neonate: First day of life	***Typical NM*** diffuse hypotonia, but no focal motor deficit	Severe biventricular hypertrophy, obstruction of the right and left ventricular outflow tracts	***Skeletal* muscle:** nemaline rods on light and electron microscopy ***Myocardium:*** not performed	Chromosome analysis was normal	Heart transplantation, continuous positive pressure ventilation, β-blockers	2 episodes of atrial and not ventricular arrhythmias at 3 months and 17 months of age Follow up until 19 months: normal	Earliest presentation of HCM reported in the literature in the setting of NM Youngest report of HCM in association with NM. It appears that the HCM associated with NM is present on the first day of life, as opposed to other forms of HCMs which may not be phenotypically present until later in life

NA: Not available. **NIPPV**: Non-invasive positive pressure ventilation. **TTE**: Transthoracic echocardiography, **yr**: years

Conclusion

This case highlights a newly reported association between hypertrophic cardiomyopathy and NM. We emphasize the challenges in establishing diagnosis and the critical role of comprehensive genetic testing.

References

1. Wang Q, Hu F. Nemaline myopathy with dilated cardiomyopathy and severe heart failure: A case report. World J Clin cases. 2021;9(11):2569–75.
2. Shy GM, Engel WK, Somers JE, Wanko T. Nemaline myopathy. A new congenital myopathy. Brain. 1963;86(4):793–810.
3. Sewry CA, Laitila JM, Wallgren-Pettersson C. Nemaline myopathies: a current view. J Muscle Res Cell Motil. 2019;40(2):111–26.
4. Conen Pe, Murphy Eg, Donohue Wl. Light and electron microscopic studies of "myogranules" in a child with hypotonia and muscle weakness. Can Med Assoc J. 1963;89:983–6.
5. Finsterer J, Stöllberger C. Review of cardiac disease in nemaline myopathy. Pediatr Neurol. 2015;53(6):473–7.
6. Mir A, Lemler M, Ramaciotti C, Blalock S, Ikemba C. Hypertrophic cardiomyopathy in a neonate associated with nemaline myopathy. Congenit Heart Dis. 2012;7(4):1–5.
7. Kim SY, Park YE, Kim HS, Lee CH, Yang DH, Kim DS. Nemaline myopathy and non-fatal hypertrophic cardiomyopathy caused by a novel ACTA1 E239K mutation. J Neurol Sci. 2011;307(1–2):171–3.
8. D'Amico A, Graziano C, Pacileo G, Petrini S, Nowak KJ, Boldrini R, et al. Fatal hypertrophic cardiomyopathy and nemaline myopathy associated with ACTA1 K336E mutation. Neuromuscul Disord. 2006;16(9–10):548–52.
9. Skyllouriotis ML, Marx M, Skyllouriotis P, Bittner R, Wimmer M. Nemaline myopathy and cardiomyopathy. Pediatr Neurol. 1999;20(4):319–21.
10. Lynn Van Antwerpen C, Gospe SM, Dentinger MP. Nemaline myopathy associated with hypertrophic cardiomyopathy. Pediatr Neurol. 1988;4(5):306–8.
11. Durling HJ, Reilich P, Müller-Höcker J, Mendel B, Pongratz D, Wallgren-Pettersson C, et al. De novo missense mutation in a constitutively expressed exon of the slow alpha-tropomyosin gene TPM3 associated with an atypical, sporadic case of nemaline myopathy. Neuromuscul Disord. 2002;12(10):947–51.
12. Colan SD. Hypertrophic cardiomyopathy in childhood. Heart Fail Clin. 2010;6(4):433–44.
13. Hammami R, Ouali S, Naffeti I, Hammas S, Kacem S, Gribaa R, et al. Neonatal hypertrophic cardiomyopathy of difficult etiologic diagnosis Pan Afr Med J. 2011;10 :1-5.
14. Yu QX, Zhen L, Lin XM, Wen YJ, Li DZ. Clinical and molecular analysis of nine fetal cases with clinically significant variants causing nemaline myopathy. Eur J Obstet Gynecol Reprod Biol. 2024;292:263–6.
15. Haghighi A, Alvandi Z, Nilipour Y, Haghighi A, Kornreich R, Nafissi S, et al. Nemaline myopathy: reclassification of previously reported variants according to ACMG guidelines, and report of novel genetic variants. Eur J Hum Genet. 2023;31(11):1237–50.
16. Wallgren-Pettersson C. Nemaline and myotubular myopathies. Semin Pediatr Neurol. 2002;9(2):132–44.
17. Mizue N, Yoshio S, Kentaro K and YF. An infant with congenital nemaline myopathy and hypertrophic cardiomyopathy. J Nippon Med Sch. 2008;75:350—353.
18. Polavarapu K, Bardhan M, Anjanappa RM, Vengalil S, Preethish-Kumar V, Shingavi L, et al. Nemaline rod/cap myopathy due to novel homozygous mypn mutations: The first report from south asia and comprehensive literature review. J Clin Neurol. 2021;17(3):409–18.
19. Suzan S, Mehmet Y O, Duygu B, Nilufer O, Beril T, Serife S O. Nemaline rod myopathy treated with L-tyrosine to relieve symptoms in a neonate. Arch Argent Pediatr. 2019;117(4).
20. Dalal N, Naranje K, Moriangthem A, Singh A. L-tyrosine for treatment of an infant with nemaline rod myopathy. BMJ Case Rep. 2024;17(6).