Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8314-21
Intern Med 61: 1897-1901, 2022
http://internmed.jp

【 CASE REPORT 】

Nemaline Myopathy Initially Diagnosed as Right Heart Failure with Type 2 Respiratory Failure

Mizuki Ito[1,2], Sayuri Shima[1], Ryunosuke Nagao[1], Shoko Nakano[1], Konoka Esaka[1], Akihiro Ueda[1], Shingo Maeda[3], Ryoma Moriya[3], Masashi Kondo[3], Kazuyoshi Imaizumi[3], Seiya Noda[4,5], Masahisa Katsuno[4], Ichizo Nishino[6] and Hirohisa Watanabe[1]

Abstract:
Nemaline myopathy (NM) is a rare muscle disease with various clinical types. In some cases, NM can lead to type 2 respiratory failure and right heart failure. We herein report a patient with congenital NM with nebulin gene mutation who presented with acute right heart failure and type 2 respiratory failure due to respiratory muscle paralysis after upper respiratory tract infection, needing a permanent ventilator for assistance. However, the limb and trunk muscle strengths were within normal limits. This case showed that NM should be considered as a cause of right heart failure and type 2 respiratory failure.

Key words: nemaline myopathy, right heart failure, type 2 respiratory failure, nebulin, respiratory muscle paralysis

(Intern Med 61: 1897-1901, 2022)
(DOI: 10.2169/internalmedicine.8314-21)

Introduction

Nemaline myopathy (NM) is a rare muscle disease with various clinical types. Some are congenital due to gene mutations and present as floppiness or mild muscle weakness in infants (1). Other cases are acquired via human immunodeficiency virus, monoclonal gammopathy of undetermined significance, and others; these present like myositis (2).

NM can predominantly present with respiratory muscle damage. This type of NM is characterized by respiration needing ventilator assistance but with preserved limb movements and the ability to walk unassisted.

In the present study, we encountered a case of congenital NM with a nebulin gene mutation, presenting with acute right heart failure and type 2 respiratory failure secondary to respiratory muscle paralysis after upper respiratory tract infection. The patient needed permanent ventilator assistance, although the muscle strength of her limbs and trunk were within normal limits.

Case Report

A 29-year-old woman visited a nearby doctor due to acute severe dyspnea and pedal edema 2 weeks after an upper respiratory tract infection. Heart failure was suspected because of decreased oxygen saturation and bilateral pleural effusion on X-ray. This prompted referral to our hospital.

Upon admission, the patient's blood pressure was 114/75 mmHg, her heart rate was 105/min, and her oxygen saturation was 98% (O_2 2 L nasal). She had coarse crackles in her bilateral chest and pitting edema on her legs. An electrocardiogram revealed a left anterior branch block, right ventricular hypertrophy, and left atrial enlargement. Chest X-ray and computed tomography (CT) showed an increased cardiothoracic ratio, bilateral pleural effusion, thoracic deformity, and scoliosis, but no pneumonia. Echocardiography showed no

[1]Department of Neurology, Fujita Health University School of Medicine, Japan, [2]Department of Neurology, Fujita Health University Bantane Hospital, Japan, [3]Department of Respiratory Medicine, Fujita Health University School of Medicine, Japan, [4]Department of Neurology, Nagoya University Graduate School of Medicine, Japan, [5]Department of Neurology, National Hospital Organization Suzuka Hospital, Japan and [6]Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Japan
Received: July 12, 2021; Accepted: October 3, 2021; Advance Publication by J-STAGE: November 13, 2021
Correspondence to Dr. Hirohisa Watanabe, nabe@med.nagoya-u.ac.jp

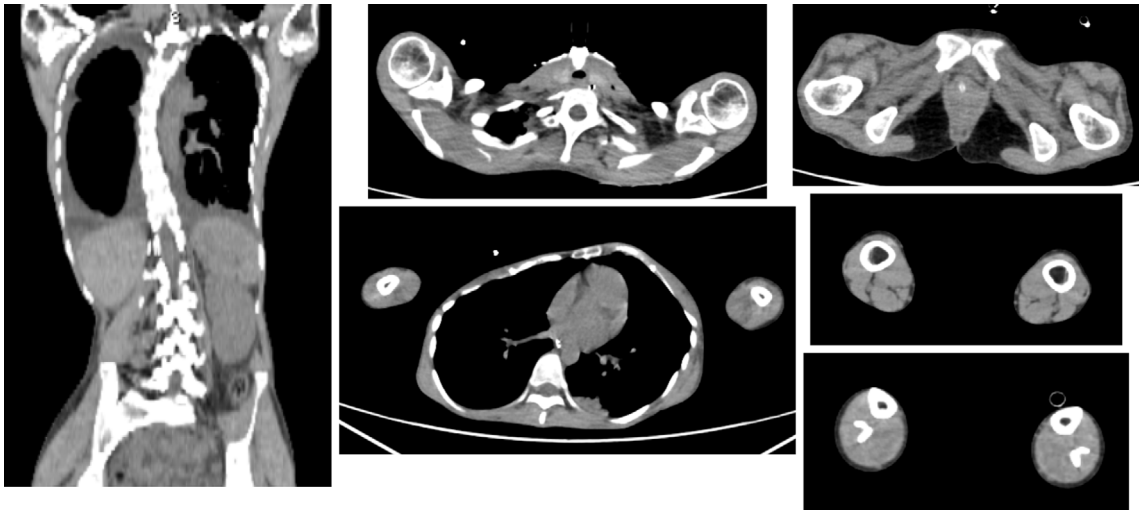


Figure 1. Chest and skeletal muscle computed tomography (CT). Chest CT showing thoracic deformity and scoliosis. Skeletal muscle CT showing muscle atrophy of the limbs and trunk.

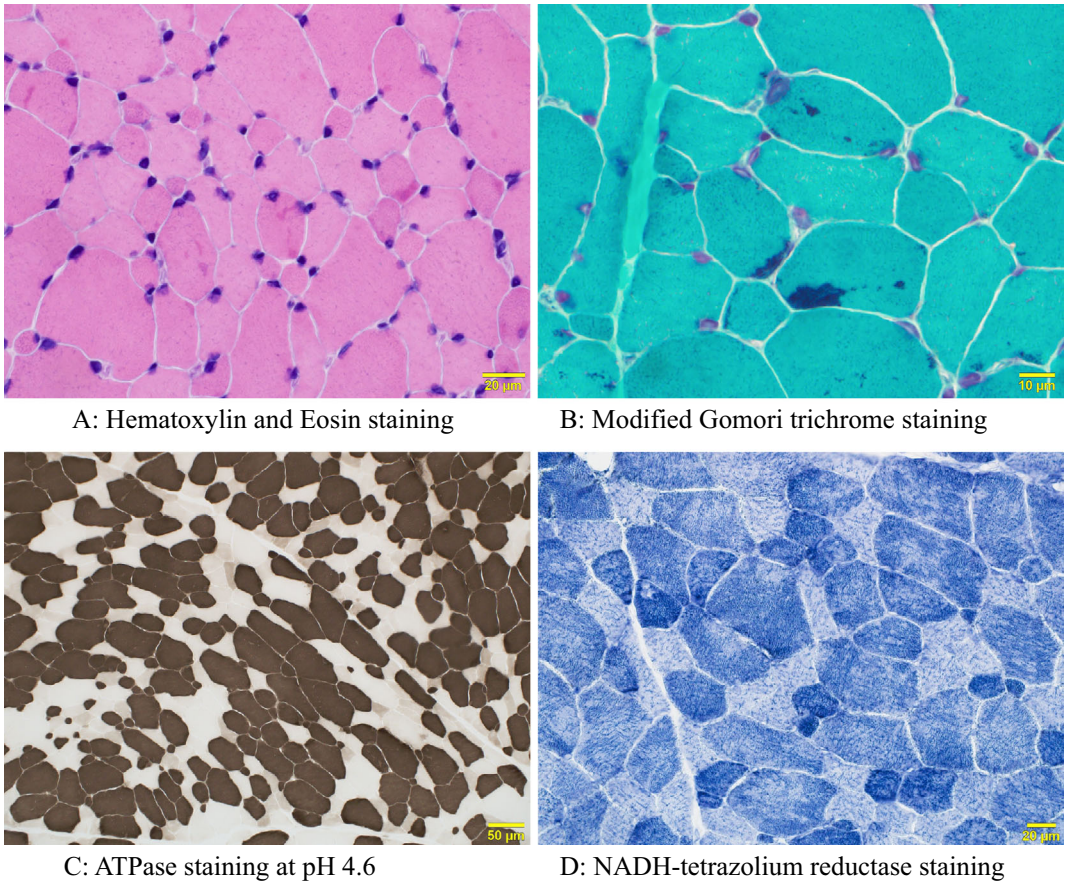
obvious myocardial hypokinesis or akinesis, and the ejection fraction was about 60%. She had moderate tricuspid regurgitation, and her estimated tricuspid regurgitation pressure gradient (TRPG) was significantly increased to 75.4 mmHg. There was right-sided heart enlargement and flattening of the interventricular septum. Her laboratory test data showed mild liver dysfunction and an increased N-terminal pro-brain natriuretic peptide (NT-proBNP) of 1,485 pg/mL. Blood gas values under O_2 2 L administration were as follows: pH, 7.245; PO_2, 50.0 mmHg; PCO_2, 96.4 mmHg; and HCO_3, 40.9 mmol/L.

The patient was diagnosed with chronic type 2 respiratory failure and acute right heart failure due to pulmonary hypertension, and she was immediately started on diuretics and dobutamine. Because of her poor respiratory condition, noninvasive positive pressure ventilation (NPPV) was also started. Although these treatments were started, her consciousness level decreased due to CO_2 narcosis at night, so the patient needed intubation and mechanical ventilation. After starting ventilator management, the right heart failure and pulmonary hypertension gradually improved. Blood gas values under room air were as follows: pH, 7.427; PO_2, 101.0 mmHg; PCO_2, 47.9 mmHg; and HCO_3, 30.9 mmol/L. NT-proBNP decreased to 96 pg/mL. Echocardiography showed improvement, with the tricuspid regurgitation becoming mild and TRPG decreasing to 23.9 mmHg. Improvements were seen in the right-sided heart enlargement and the interventricular septum flattening, but these were still present. However, despite improvements in the right-sided heart failure, the type 2 respiratory failure persisted, and the patient still needed ventilator assistance. Due to chest CT findings of thoracic deformity and scoliosis (Fig. 1), neuromuscular disease was suspected, prompting referral to the neurology department.

The patient's medical history was obtained from her mother. The patient had had no problems in her daily life thus far, but she had had scoliosis in junior high school and had not been good at exercising from an early age.

She was sedated on the Richmond agitation-sedation scale at -1, so she could open her eyes and follow our orders. Therefore, we decided to take neurological findings to the greatest extent possible. We noted based on these findings no extraocular muscle paralysis, but she had facial muscle weakness. There was respiratory muscle weakness that required mechanical ventilation. Under sedation, the specific limb and trunk muscle strengths were unknown. The deep tendon reflexes of the extremities were reduced, and muscular atrophy of the extremities and trunk was diffusely prominent without laterality. She had no apparent sensory impairment. Creatinine kinase levels were low (38 IU upon blood sampling). Skeletal muscle CT showed marked muscle atrophy of the limbs and trunk (Fig. 1). Electromyography showed myogenic changes, such as early recruitment in the right biceps and right vastus lateralis. These examinations prompted suspicion of muscle disease, so a muscle biopsy was performed. Her quadriceps femoris muscle biopsy sample showed fiber size variability and rounding of muscle fibers, but no inflammatory cell infiltration, necrotic fibers, or regenerated fibers (Fig. 2A). Furthermore, we detected many nemaline bodies (Fig. 2B), and type 1 fiber predominance and intermyofibrillar network disorganization was observed (Fig. 2C, D) in her muscle biopsy sample. Therefore, we made a diagnosis of NM. As she had no siblings and did not have a clear family history in her parents but had shown scoliosis at an early age, congenital disease was suspected. A genetic analysis revealed mutations in the nebulin gene (c.20158-6A>G: p.Leu6721Arg, c.20131C>T: p.Arg6711 Trp).

While the patient's general condition improved, her respiratory muscle paralysis persisted. Therefore, she underwent tracheostomy, and her breathing was under ventilator management. This stabilized her respiratory condition, and sedation was stopped. Surprisingly, after sedation was stopped, the limb and trunk muscle strength recovered to the normal



A: Hematoxylin and Eosin staining B: Modified Gomori trichrome staining

C: ATPase staining at pH 4.6 D: NADH-tetrazolium reductase staining

Figure 2. **A muscle biopsy of the quadriceps femoris. A: Hematoxylin and Eosin staining. There is fiber size variability and rounding of muscle fibers but no inflammatory cell infiltration, necrotic fibers, or regenerated fibers. B: Modified Gomori trichrome staining. There are many nemaline bodies. C: ATPase staining at pH 4.6. Type 1 fiber predominance was observed. D: NADH-tetrazolium reductase staining. Intermyofibrillar network disorganization was observed.**

range (grasping power: 21.9/19.0 kg), and she did not need any assistance while walking. Only the respiratory muscle paralysis remained. Therefore, the patient was discharged from our hospital with a portable ventilator, and has been able to live a normal daily life without any problems aside from the need for breathing assistance.

Discussion

We reported a case of NM that developed alongside acute right heart failure due to pulmonary hypertension triggered by upper respiratory tract infection. The patient presented with chronic type 2 respiratory failure due to severe respiratory muscle paralysis and required a ventilator despite a normal muscle strength of the extremities. When considering muscle diseases in which muscle strength of the extremities is normal and only respiratory muscle paralysis is observed, it is necessary to consider NM, Pompe disease, hereditary myopathy with early respiratory failure, rigid spine with muscular dystrophy, early-onset myopathy-areflexia-respiratory distress-dysphagia syndrome, etc. The present case was differentiated from other diseases and diagnosed with NM by a muscle biopsy and genetic analysis.

NM is classified into congenital and acquired types, and congenital types are further classified into three types: severe congenital, benign congenital, and adult-onset types (3). It should be noted that NM cannot be ruled out even if there are no myopathic symptoms in early childhood, as there are cases in which myopathic symptoms are rarely observed in early childhood (Table). The patient in our case has not been good at exercising since an early age, and she also had chest deformity and scoliosis. It may be possible that the patient had developed NM in infancy, and she had a mutation in the nebulin gene (c.20158-6A>G: p.Leu6721Arg, c.20131 C>T: p.Arg6711Trp). The analyses of the amino acid substitutions in p.Leu6721Arg and p.Arg6711Trp using a mutation prediction algorithm suggested that both were pathogenic mutations in previous reports (4-6). Therefore, we suspected that she would be classified as the benign congenital type.

Notably, most cases of NM due to nebulin gene mutation are of the benign congenital type, with only a few severe congenital type cases reported (7). A previous report showed that 85% of cases were able to walk but not run, and 25% of cases had scoliosis surgery in congenital myopathy with a mutation in the nebulin gene, if not necessarily the benign congenital type of NM. Therefore, the presence of scoliosis

Table. Clinical Features of Adult-onset Nemaline Myopathy with Characteristic Muscle Weakness Distributions.

Ref	Age requiring respiratory assistance (year)	Trigger of respiratory disturbance	Symptoms in childhoods	Muscle symptoms at the onset of type 2 respiratory failure	Echocardiographic abnormalities	Types of ventilators	Gene mutation
8)	47	Gradually progressive heart failure	Slightly delayed gait	Weakness and atrophy in limbs and trunk	Bilateral ventricular dilatation and decrease of left ventricular contraction	NPPV	Not evaluated
10)	65	Acute progressive heart failure	None	Generalized but distal dominant weakness and atrophy	Dilatation of right atrium and ventricle	NPPV	Nebulin
13)	49	Ingestion of diazepam	None	Only respiratory muscle weakness	Mild left septal ventricle hypertrophy and mild mitral and aortic regurgitation.	NPPV	Not evaluated
14)	31	Pneumonia	Not good at exercising, scoliosis, thoracic deformity	Proximal dominant weakness and atrophy in limbs and trunk	Normal	Tracheostomy + ventilator	Not evaluated
	62	Gradualy progressive respiratory failure	Mild weakness, high arch	Proximal dominant weakness and atrophy in limbs and trunk	Normal	NPPV	Not evaluated
15)	44	Gradualy progressive respiratory failure	None	Proximal dominant weakness and atrophy in limbs and trunk	Normal	NPPV	Not evaluated
16)	40	Gradualy progressive respiratory failure	None	Only respiratory muscle weakness	Right ventricle enlargement	NPPV	Not evaluated
9)	35	Gradualy progressive respiratory failure	Right leg atrophy	Distal dominant weakness and atrophy with laterality	Normal	NPPV	Nebulin
Our case	29	Upper respiratory tract infection	Not good at exercising, scoliosis	Only respiratory muscle weakness	Right-sided heart enlargement and the interventricular septum flattening	Tracheostomy + ventilator	Nebulin

NPPV: non-invasive positive pressure ventilation

and difficulty exercising from an early age might help identify patients with NM (8).

Generally, there is little myocardial damage in NM (7), and NM with a nebulin mutation may carry a risk of respiratory failure (9). However, previous reports have also shown that NM-related heart failure was due to myocardial damage (6, 10). In the present case, the administration of diuretics and dobutamine in the acute phase improved the right heart failure, and after this improvement, treatment of the cardiac function became unnecessary. Furthermore, echocardiography showed only a mild abnormality, normal ejection fraction, and no myocardial hypokinesis or akinesis. Therefore, we considered that there was at least no severe myocardial damage.

In NM, dissociation exists between the muscle strength of the respiratory muscles and other skeletal muscles, and the respiratory muscles are more vulnerable than other skeletal muscles (11, 12). In our case, the causes of right heart failure were considered to be hypoxemia, hypercapnia, and pulmonary hypertension because of hypoventilation due to her respiratory muscle weakness.

As triggers of respiratory disturbance in benign congenital-type NM, respiratory tract infections are important, but some cases are triggered by the administration of sedatives, however, others are triggered simply by an exacerbation of heart failure. The triggers for exacerbation of respiratory disturbance are varied (Table) (8-10, 13-16). Several cases have been reported in which NPPV was able to help control the patient's respiration (Table), but the present patient needed ventilator management because of the ejection and suction of sputum. If her sputum could be settled, her respiratory management might be able to be switched to NPPV.

After the patient's respiratory condition recovered with ventilator management, her limb and trunk muscle strength recovered to normal except for in the respiratory muscles. In general, NM is characterized by proximal dominant symmetric muscle weakness and atrophy, but there have been case reports in which distal dominance or laterality is observed or only respiratory muscle paralysis is observed. It is thus difficult to distinguish NM by the distribution of muscle weakness and atrophy alone (Table). However, as we mentioned before, benign congenital, adult-onset, and sporadic late-onset NM often show normal limb and trunk muscle strength, with only respiratory muscle paralysis observed (Table). Therefore, it is necessary to distinguish NM when the distribution of muscle weakness is predominant in the respiratory muscles.

This case is valuable, showing that it is necessary to consider NM in patients with type 2 respiratory failure and right heart failure, especially when the muscle strength of the limbs and trunk are normal and only respiratory muscle paralysis is observed.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This study was supported partly by an Intramural Research Grant (2-5) for Neurological and Psychiatric Disorders of NCNP.

References

1. Ryan MM, Schnell C, Strickland CD, et al. Nemaline myopathy: a clinical study of 143 cases. Ann Neurol **50**: 312-320, 2001.
2. Chahin N, Selcen D, Engel AG. Sporadic late onset nemaline myopathy. Neurology **65**: 1158-1164, 2005.
3. Shimomura C, Nonaka I. Nemaline myopathy: comparative muscle histochemistry in the severe neonatal, moderate congenital, and adult-onset forms. Pediatr Neurol **5**: 25-31, 1989.
4. Hamanaka K, Miyatake S, Koshimizu E, et al. RNA sequencing solved the most common but unrecognized *NEB* pathogenic variant in Japanese nemaline myopathy. Genet Med **21**: 1629-1638, 2019.
5. Tsunoda K, Yamashita T, Motokura E, et al. A patient with slowly progressive adult-onset nemaline myopathy and novel compound heterozygous mutations in the nebulin gene. J Neurol Sci **373**: 254-257, 2017.
6. Ohara M, Saito Y, Watanabe M, et al. An adult nemaline myopathy patient with respiratory and heart failure harboring a novel *NEB* variant. eNeurologicalSci **21**: 100268, 2020.
7. Romero NB, Sandaradura SA, Clarke NF. Recent advances in nemaline myopathy. Curr Opin Neurol **26**: 519-526, 2013.
8. Colombo I, Scoto M, Manzur AY, et al. Congenital myopathies: natural history of a large pediatric cohort. Neurology **84**: 28-35, 2015.
9. Mizuno Y, Mori-Yoshimura M, Oya Y, Nishikawa A, Nishino I, Takahashi Y. Two cases of nemaline myopathy presenting with hypertrophy of distal limbs with prominent asymmetry. Rinsho Shinkeigaku (Clin Neurol) **57**: 691-697, 2017 (Abstract in English).
10. Nagata R, Kamimura D, Suzuki Y, et al. A case of nemaline myopathy with associated dilated cardiomyopathy and respiratory failure. Int Heart J **52**: 401-405, 2011.
11. Sasaki M, Yoneyama H, Nonaka I. Respiratory muscle involvement in nemaline myopathy. Pediatr Neurol **6**: 425-427, 1990.
12. Sasaki M, Takeda M, Kobayashi K, Nonaka I. Respiratory failure in nemaline myopathy. Pediatr Neurol **16**: 344-346, 1997.
13. Falgà-Tirado C, Pérez-Pemán P, Ordi-Ros J, Bofill JM, Balcells E. Adult onset of nemaline myopathy presenting as respiratory insufficiency. Respiration **62**: 353-354, 1995.
14. Kudou M, Kobayashi Y, Yamashita K, Kita H, Yasuba H, Hamada K. Two cases of nemaline myopathy diagnosed after episodes of respiratory failure. Nihon Kokyuki Gakkai Zasshi (Ann Jpn Respir Soc) **44**: 474-478, 2006 (Abstract in English).
15. Kelly E, Farrell MA, McElvaney NG. Adult-onset nemaline myopathy presenting as respiratory failure. Respir Care **53**: 1490-1494, 2008.
16. Ishiguro T, Takayanagi N, Kanazawa M, et al. Nemaline myopathy detected with respiratory failure and right ventricular heart failure. Nihon Kokyuki Gakkai Zasshi (Ann Jpn Respi Soc) **47**: 163-167, 2009 (Abstract in English).