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

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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

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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% (O2 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

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consciousness level decreased due to CO2 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; PO2, 101.0 mmHg; PCO2, 47.9 mmHg; and HCO3, 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
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 (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 |
| 15) | 44         | Gradually progressive respiratory failure | Mild weakness, high arch | Proximal dominant weakness and atrophy in limbs and trunk | Normal                                   | NPPV                | Not evaluated |
| 16) | 40         | Gradually progressive respiratory failure | None                  | Proximal dominant weakness and atrophy in limbs and trunk | Normal                                   | NPPV                | Not evaluated |
| 9)  | 35         | Gradually progressive respiratory failure | Right leg atrophy    | Only respiratory muscle weakness                          | Right ventricle enlargement                             | NPPV                | Not evaluated |
| 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).

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