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Case Report

Successful Weaning from Long-Term Noninvasive Ventilation Without Tracheostomy in an Infant with Suspected Neonatal-Onset Myopathy: A Case Report

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Highlights

What are the main findings?

- Long-term noninvasive ventilation initiated in the neonatal period bridged an infant with suspected neonatal-onset myopathy to complete ventilator independence without tracheostomy.
- A severe pneumonia at 7 months of age was managed by re-escalation to continuous NIV, without reintubation or tracheostomy.

What are the implications of the main findings?

- In hypotonic infants whose carbon dioxide rises during oxygen therapy, earlier transition to noninvasive ventilation deserves consideration.
- In infants, both tolerance of noninvasive ventilation and readiness for its discontinuation may need to be established by a monitored trial.

Abstract

Background/Objectives: Long-term noninvasive ventilation, and weaning from it as the underlying condition improves, is well established in children with neuromuscular disease, but detailed accounts in neonatal-onset myopathy outside the spinal muscular atrophy spectrum are few. Case Description: We report a term male neonate with profound congenital hypotonia and hypercapnic respiratory failure attributed to a suspected neonatal-onset myopathy, in whom targeted genetic testing did not establish a molecular diagnosis. After 7 days of invasive ventilation, he was managed exclusively with noninvasive ventilation and discharged on a home ventilator; by 4 months of age, only nocturnal support was required, with daytime autonomy expanding as tolerated under CO_2 monitoring. A severe pneumonia at 7 months of age was managed by re-escalation to continuous noninvasive ventilation without intubation. At 17 months of age, nocturnal support was discontinued in a single supervised trial under overnight transcutaneous CO_2 monitoring. Complete ventilator independence was achieved despite markedly delayed gross motor milestones, coinciding with recovery of antigravity strength in the upper limbs, and was maintained at 28 months of age without tracheostomy. Conclusions: Long-term noninvasive ventilation can be feasible from the neonatal period in selected infants with neuromuscular ventilatory failure, and respiratory recovery with growth may precede recovery of gross motor function; readiness for discontinuation in infants may need to be established by a monitored trial.

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1. Introduction

Neonatal-onset myopathies frequently present with profound hypotonia and ventilatory failure requiring respiratory support from the first days of life. Consensus statements on congenital neuromuscular disorders favor noninvasive ventilation for long-term ventilatory support, with tracheostomy reserved for selected situations [1,2]. In neonatal-onset cases, however, tracheostomy with long-term home ventilation may still be chosen when extubation fails [3], and some infants remain dependent on invasive ventilation until withdrawal of care [4]. Tracheostomy in infancy is associated with substantial morbidity, including airway complications [5], impaired vocalization during a critical period of language development [6], and a considerable burden of care on families [7].

Noninvasive ventilation (NIV), defined here as mask-delivered inspiratory pressure assistance rather than continuous positive airway pressure alone, is an established long-term alternative to tracheostomy in older children and adults with neuromuscular disease (NMD), for whom structured protocols for ventilatory support and weaning are well developed [8,9]. Long-term NIV is also used in infancy [10,11], and nocturnal NIV has been described in congenital myopathy in later childhood [12]. Weaning from long-term NIV as the underlying condition improves is a recognized outcome in pediatric cohorts [13,14], although it occurs mainly in upper-airway disease and is less likely in neuromuscular disorders [14], and the infant neuromuscular literature consists almost entirely of spinal muscular atrophy type 1, in which NIV is used to prolong survival rather than as a bridge to weaning [10]. Accounts of long-term NIV initiated in the neonatal period for myopathic ventilatory failure outside the spinal muscular atrophy spectrum and continued through to weaning are few, and decisions regarding tracheostomy are often made early, before the course of the underlying myopathy has become clear.

Here, we report a term neonate with a suspected neonatal-onset myopathy of unresolved molecular etiology who, supported exclusively with noninvasive ventilation after the first week of life, achieved complete ventilator independence at 17 months of age without tracheostomy.

2. Case Presentation

A male infant was born at 38 weeks of gestation by cesarean section (birth weight of 2.97 kg, 15th–25th percentile; Apgar scores of 8 and 9 at 1 and 5 min). The pregnancy was notable for persistent polyhydramnios. The mother had preeclampsia and hypothyroidism managed with levothyroxine; family history was unremarkable. Cyanosis and desaturation developed within minutes of birth, and he was transferred to our neonatal intensive care unit on the day of birth.

On admission, the infant was profoundly hypotonic, with markedly decreased spontaneous activity, diminished deep tendon reflexes, an absent Moro reflex, and weak sucking. Capillary blood gas showed severe hypercapnic respiratory acidosis (pH 7.06, partial pressure of CO_2 [PCO_2] 92.0 mmHg) with normal plasma lactate (1.4 mmol/L; normal again at 7 months of age), and he was intubated on the day of admission, with PCO_2 normalizing within hours of mechanical ventilation. Creatine kinase was mildly elevated (200–256 U/L) during the first weeks and normalized thereafter, and urine organic acids showed mildly elevated 3-hydroxyisovaleric and ethylmalonic acids; other initial investigations were unre-

markable. Brain MRI on day 6 revealed an acute focal infarction with hemorrhage in the left temporal lobe, small bilateral occipital subdural hemorrhages, and diffuse excessive high signal intensity in the white matter, with normal myelination; electroencephalography showed mild diffuse slowing without seizures.

He was extubated on day 7 of life to high-flow nasal cannula, but hypercapnia persisted (capillary PCO_2 60–79 mmHg) despite flow escalation, prompting bilevel positive airway pressure; he did not require reintubation for respiratory causes thereafter. Chest computed tomography showed only linear atelectasis, indicating ventilatory insufficiency rather than parenchymal lung disease. At 1 month of age, a home-type ventilator was introduced with graded daily application under continuous end-tidal CO_2 ($EtCO_2$) monitoring. On a spontaneous/timed bilevel mode with a short inspiratory time, PCO_2 rose to 60–68 mmHg within hours of application; following consultation with the pulmonary rehabilitation service, which specializes in the respiratory management of patients with neuromuscular disease and had been involved in co-management from the third week of life, the mode was changed to controlled pressure ventilation with a longer inspiratory time, lowering PCO_2 to the high 40 s–50 s mmHg, and conversion to an oronasal mask at 7 weeks of age, for excessive oral air leak, brought PCO_2 into the 30 s to low 40 s mmHg range (settings in Table 1).

Table 1. Timeline of respiratory support, muscle strength, and key events.

Age	Respiratory Support/Settings	Motor Findings	Key Events/Gases
Birth–day 7	Invasive MV (admission gas: pH 7.06, PCO_2 92.0)	Profound flaccid hypotonia; absent Moro	NICU admission; brain MRI (day 6)
Day 7–1 mo	HFNC → bilevel PAP (PCO_2 60–79)	Severely decreased activity	Genetic workup (panel sent day 6)
1–2 mo	Home ventilator: S/T 15/6, RR 40, Ti 0.3 s → PCV 14–18/4, RR 40, Ti 0.5 s; nasal → oronasal mask (7 wk); PCO_2 68 → high 40 s–50 s → 30 s–low 40 s	—	PEG at 8 wk (3 d perioperative IMV)
2.5 mo	Discharge on home NIV (PCV 18/4)	Partial neck control	Caregiver training
4 mo	Nocturnal-only NIV (22:00–06:00)	—	1st rehabilitation admission; overnight $TcCO_2$ on NIV mean 38.2 (max 44.5); daytime $TcCO_2$ off vent (7 h) mean 31.8
7 mo	Re-escalation to continuous NIV with O2; mode → PC-AVAPS (pressure range 8–22, PEEP 5–7, Vt 100, RR 40)	—	Pneumonia (influenza A/RSV A/Klebsiella); 11-d admission
10 mo	Nocturnal PC-AVAPS (pressure range 8–20, PEEP 5, Vt 80, RR 40)	—	—
12 mo	Nocturnal NIV (22:00–06:00)	Bayley-III: language 103, social–emotional 105, cognitive 70, motor 61 (gross motor age-equivalent 3 mo); GMFCS level V equivalent	Developmental assessment

Table 1. *Cont.*

Age	Respiratory Support/Settings	Motor Findings	Key Events/Gases
13 mo	Nocturnal NIV	MMT: MRC 3 UE flexors, ankle DF; MRC 1–2 proximal LE; GMFCS level V equivalent	—
17 mo	Weaning admission: nocturnal PC-AVAPS (pressure range 3–15, PEEP 5, Vt 70, RR 40) → ventilator-free	—	1st night off vent: mean $TcCO_2$ 32.6 (max 47.2), SpO2 95%; observed off vent 7 d before discharge
18 mo	Ventilator-free	—	Overnight SpO2 97%, no desaturation < 88%; daytime mean $TcCO_2$ 37
20 mo	Ventilator-free	—	Follow-up MRI: lesions resolved; $EtCO_2$ 42
25 mo	Ventilator-free	Bayley-III: cognitive 55, language 58, motor 49 (gross motor age-equivalent 3 mo)	Developmental reassessment
26 mo	Ventilator-free	No respiratory symptoms	Outpatient $EtCO_2$ 38 (RR 22/min)
28 mo	Ventilator-free	No respiratory symptoms	No ICU admission since weaning; gastrostomy feeding

MV, mechanical ventilation; Mo, month; Wk, week; HFNC, high-flow nasal cannula; PAP, positive airway pressure; S/T, spontaneous/timed; PCV, pressure-controlled ventilation; Ti, inspiratory time; NIV, noninvasive ventilation; →, change in the ventilator setting; PEG, percutaneous endoscopic gastrostomy; IMV, invasive mechanical ventilation; ICU, Intensive Care Unit; MRI, magnetic resonance imaging; SpO2, saturation pulse oxygen; PC-AVAPS, pressure-controlled average volume-assured pressure support; GMFCS, Gross Motor Function Classification System (levels given as descriptive equivalents, as the system was developed for cerebral palsy); PCO_2, partial pressure of CO_2 (capillary blood gas); $TcCO_2$, transcutaneous CO_2; $EtCO_2$, end-tidal CO_2; RSV A, respiratory syncytial virus type A; Influenza A, Influenza virus type A; RR, respiratory rate; PEEP, positive end-expiratory pressure; Vt, target tidal volume. Pressures in cmH_2O; Vt in mL; PCO_2/$TcCO_2$ in mmHg.

A stepwise workup excluded spinal muscular atrophy (SMN1 MLPA), myotonic dystrophy (DMPK), Prader–Willi syndrome, chromosomal abnormalities (microarray), and lysosomal storage disease. A phenotype-driven targeted next-generation sequencing panel (1183 genes analyzed from a 4899-gene panel, covering nuclear genes for congenital myopathies, congenital myasthenic syndromes, and mitochondrial disease, together with seven mitochondrial genes: MT-ATP6, MT-ND1, MT-ND4, MT-ND6, MT-TK, MT-TL1, and MT-TG) identified two findings. First, a heterozygous in-frame deletion in RYR1 (c.14578_14580del, p.(Phe4860del); ClinVar Variation ID 133079), located in the C-terminal channel-forming region and previously reported as a de novo variant in a patient with central core disease [15], was classified as likely pathogenic by the testing laboratory; however, it was also carried by an asymptomatic parent, and the clinical genetics service judged it insufficient to explain the phenotype. Second, m.10001T>C, a previously unreported heteroplasmic variant in MT-TG (mitochondrially encoded tRNA-glycine), was classified as of uncertain significance; the laboratory reported it qualitatively as a low mutant burden in blood, and the heteroplasmy level was not quantified. Muscle biopsy was not pursued by the treating team, and exome or genome sequencing was not performed. The working diagnosis was therefore clinical: neonatal-onset myopathy of unresolved molecular etiology, based on polyhydramnios, profound generalized flaccid hypotonia with diminished tendon reflexes,

and primary hypercapnic ventilatory failure. The patient has subsequently been followed by the pediatric neurology service under a clinical diagnosis of mitochondrial disease and enrolled in a national mitochondrial disease research program through which further genomic analysis may be undertaken.

Bolus gavage feeding caused recurrent regurgitation with desaturation, and a percutaneous endoscopic gastrostomy was placed at 8 weeks of age, requiring 3 days of perioperative invasive ventilation. He was discharged at 2.5 months of age on home NIV with gastrostomy feeding after structured caregiver training.

Home NIV was managed longitudinally by the pulmonary rehabilitation service according to our center's tailored weaning protocol for neuromuscular ventilatory failure [16,17], adapted for age: nocturnal ventilation during sleep was preserved as the core support, while daytime ventilator-free time was allowed to expand as tolerated under CO_2 monitoring. Airway clearance during the period of ventilator dependence consisted of mechanical insufflation–exsufflation, delivered by caregivers as needed when secretions accumulated (insufflation/exsufflation pressures of 40 cmH_2O as taught at our center, lowered to about 30 cmH_2O according to the patient's condition), together with oropharyngeal suctioning. At the first rehabilitation admission at 4 months of age, overnight transcutaneous CO_2 ($TcCO_2$) monitoring on nocturnal NIV showed a mean of 38.2 mmHg (maximum 44.5 mmHg), and daytime $TcCO_2$ during a 7-h ventilator-free period without supplemental oxygen was 31.8 mmHg (maximum 37 mmHg); support was nocturnal-only (22:00–06:00) from this admission (Table 1 and Figure 1). Ventilatory adequacy was assessed by overnight $TcCO_2$ monitoring at rehabilitation admissions (4 and 17 months of age) and by venous blood gas at outpatient visits between admissions (Figure 1). Videofluoroscopy at 6 months of age confirmed severe dysphagia with aspiration (penetration–aspiration scale 8). At 7 months, a severe pneumonia (influenza A, respiratory syncytial virus A, and Klebsiella pneumoniae) required an 11-day admission with re-escalation to continuous NIV with supplemental oxygen; intubation was considered for transient left lower-lobe atelectasis but averted as imaging improved. During this admission the mode was changed to pressure-controlled average volume-assured pressure support (settings in Table 1). After stepwise rebuilding of daytime ventilator-free time, after discussion with the pediatric pulmonology service, he returned to the nocturnal-based strategy. Empirical mitochondrial cofactor supplementation was started by the pediatric neurology service at 10 months. By 13 months of age, although proximal lower-limb strength remained MRC grade 1–2, strength in the shoulder, elbow, and wrist flexors and ankle dorsiflexors had recovered from profound neonatal flaccidity to antigravity level (MRC grade 3). During a planned admission at 17 months of age, nocturnal ventilation was discontinued as a single supervised trial under continuous $TcCO_2$ and SpO2 monitoring during sleep. A nocturnal $TcCO_2$ of 49 mmHg (6.5 kPa), the value used to define nocturnal hypoventilation when initiating NIV in progressive neuromuscular disease [18,19], served as a reference point rather than as an absolute criterion; because the patient's condition was improving rather than progressing, the decision to remain off the ventilator rested on clinical judgment, taking into account the overnight $TcCO_2$ trend, SpO2, and clinical status. The first night off the ventilator showed a mean $TcCO_2$ of 32.6 mmHg (maximum 47.2 mmHg) with a mean SpO2 of 95%, and subsequent nights showed mean $TcCO_2$ of 28.4–41.4 mmHg with maxima of 41.4–46.5 mmHg (values recorded during in vivo sensor calibration excluded) and mean SpO2 of 96%; NIV was not reinstituted. He was observed off ventilation for 7 days and discharged ventilator-free at 17 months of age, with oropharyngeal suctioning continued as needed.

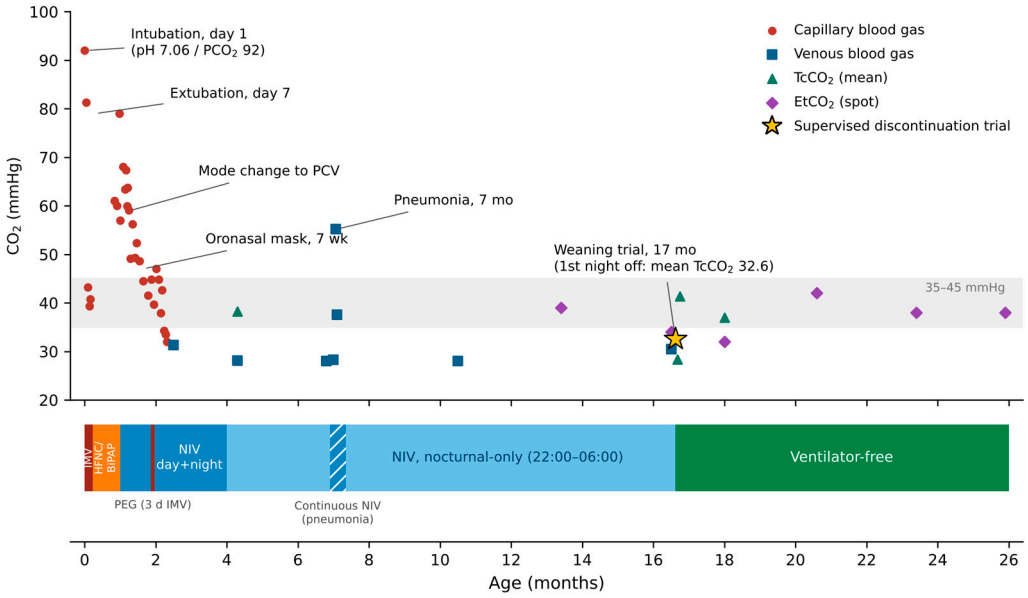


Figure 1. Integrated timeline of CO_2 trajectory and respiratory support. Top: capillary blood gas (red circles), venous blood gas (blue squares), mean transcutaneous CO_2 ($TcCO_2$, green triangles; overnight during sleep, except the daytime value at 18 months), and daytime spot end-tidal CO_2 at outpatient visits ($EtCO_2$, purple diamonds); because the measurement modalities differ, points are not connected and are shown for trajectory, not direct comparison. The shaded band indicates 35–45 mmHg; the star marks the single supervised discontinuation trial (first night off the ventilator, mean $TcCO_2$ 32.6 mmHg). Bottom: respiratory support phases. IMV, invasive mechanical ventilation; HFNC, high-flow nasal cannula; BiPAP, bilevel positive airway pressure; NIV, noninvasive ventilation; PEG, percutaneous endoscopic gastrostomy; PCV, pressure-controlled ventilation; Mo, month; wk, week.

Formal developmental assessment at 12 months of age (before weaning) showed a dissociation between domains: the Bayley-III language (103) and social–emotional (105) composites were average and the cognitive composite was 70, whereas the motor composite was 61, with a gross motor age-equivalent of 3 months (functional level corresponding to Gross Motor Function Classification System [GMFCS] level V) (Table 1). Follow-up brain MRI at 20 months of age showed resolution of the neonatal lesions. At a planned admission at 18 months of age, 6 weeks after weaning, overnight oximetry was normal (mean SpO2 97%, no desaturation below 88%) with a daytime mean $TcCO_2$ of 37 mmHg, and there were no symptoms of nocturnal hypoventilation. Serial daytime spot $EtCO_2$ measurements at outpatient visits thereafter remained normal (32–42 mmHg between 18 and 26 months of age). Developmental reassessment with the Bayley-III at 25 months of age, 8 months after weaning, showed delays across domains: cognitive composite 55 (age-equivalent 12 months), language composite 58 (receptive and expressive age-equivalents 16 and 15 months), and motor composite 49 (fine motor age-equivalent 12 months; gross motor age-equivalent 3 months). Raw scores had increased in every subtest since the 12-month assessment (cognitive 30 to 39, receptive language 13 to 19, expressive language 16 to 18, fine motor 23 to 28, and gross motor 13 to 14); the lower composite scores therefore reflected slower developmental gain relative to age, not loss of previously acquired skills. At the most recent follow-up at 28 months of age, 11 months after weaning, he remained ventilator-free, without intensive care admission or respiratory symptoms; dysphagia with aspiration persisted and gastrostomy feeding remained the principal route of nutrition. He has never undergone tracheostomy.

3. Discussion

We have described a term neonate with profound congenital hypotonia and chronic hypercapnic respiratory failure due to a suspected neonatal-onset myopathy of unresolved molecular etiology, who was supported exclusively with NIV beyond the first week of life and achieved complete ventilator independence at 17 months of age without tracheostomy, remaining ventilator-free at 28 months. This case illustrates three points: that transition to long-term NIV can be feasible even in the neonatal period in selected infants; that management principles established in older patients with NMD can be adapted to infancy; and that ventilatory autonomy may be regained with growth and partial recovery of muscle strength, even while gross motor milestones remain markedly delayed. A recently reported neonate with nemaline myopathy who recovered without tracheostomy after transient noninvasive support [20] suggests that such trajectories may be under-reported.

In adults and older children with NMD, long-term NIV rests on CO_2-guided nocturnal ventilation, extension into daytime use as required, and adjunctive airway clearance [8,9]. Our experience suggests that this framework can be applied from the neonatal period, with age-appropriate adaptations including caregiver-delivered airway clearance and the involvement of a pulmonary rehabilitation team specialized in neuromuscular respiratory care. One practical observation concerned the choice of first-line support: high-flow nasal cannula with supplemental oxygen is commonly used in such infants, but in hypercapnic (type 2) respiratory failure oxygen may improve saturation while CO_2 retention worsens, as in our patient, whose PCO_2 rose to 60–79 mmHg despite flow escalation. When CO_2 retention develops during oxygen therapy in an infant with hypotonia, earlier transition to NIV should be considered. However, acclimatization to NIV can require patient cooperation, which remains the principal barrier in this age group. Our patient tolerated NIV well, yet effective ventilation was not achieved at first: because infants, unlike older patients, cannot cooperate with mouth closure, oral air leak undermined ventilation through a nasal interface, and PCO_2 normalized into the 30 s to low 40 s mmHg range only after conversion to an oronasal mask at 7 weeks of age. NIV is therefore not suitable for every infant, and whether to try it before tracheostomy should be decided case by case. A further consideration was enteral feeding access: our patient had dysphagia with aspiration that had not fully resolved even at the most recent follow-up, so tube feeding remained the principal route of nutrition. When a nasogastric tube is used, air delivered through the mask can leak around the tube, reducing the effectiveness of NIV; in our patient, early gastrostomy avoided this interaction.

In NMD, weaning from long-term ventilation arises chiefly in conditions with a recovering course, such as Guillain–Barré syndrome, and even there conventional spontaneous breathing trials are poorly suited: brief daytime trials may be tolerated while nocturnal hypoventilation and cumulative respiratory muscle fatigue persist [21]. We therefore applied our center's tailored weaning protocol for patients with NMD [16,17]: nocturnal ventilation, which covers sleep, the period of greatest vulnerability to hypoventilation, was preserved as the core support while daytime autonomy was allowed to emerge with growth, and discontinuation was accomplished as a single supervised trial once clinical status indicated readiness. In infants, neither tolerance of NIV nor readiness for its discontinuation can be judged by the means available in older patients: explanation and coaching are not possible, and objective criteria such as a peak cough flow above 160 L/min predicting successful decannulation [22] are difficult to obtain; both could only be established by a monitored trial. Decisions rested on overnight $TcCO_2$ monitoring during admissions: in NMD, hypoventilation appears first during sleep and can be missed by daytime blood-gas sampling [23], and $TcCO_2$ reflects arterial PCO_2 adequately for this purpose [19]; after weaning, daytime spot $EtCO_2$ at outpatient visits served for surveillance. Polysomnography was not performed.

The concern in this infant was hypoventilation from respiratory muscle weakness, and nocturnal ventilation was assessed with overnight $TcCO_2$ and oximetry.

The same approach was used during intercurrent illness. During a severe viral–bacterial pneumonia at 7 months of age, support was re-escalated to continuous NIV; intubation was considered but was not required, and support was then de-escalated to the nocturnal baseline as the infant recovered. A severe lower respiratory tract infection was thus managed without invasive airway access.

Ventilatory support requirements declined progressively as the patient grew. In infancy, somatic growth enlarges the thoracic cage and increases respiratory muscle bulk, and many congenital myopathies follow a static or only slowly progressive course in which functional abilities improve during early childhood as growth outpaces weakness [2]; recovery of ventilatory autonomy after neonatal-onset respiratory failure has likewise been described in non-myopathic neuromuscular conditions [24]. In our patient, limb strength improved gradually from profound flaccidity to antigravity level in the upper limbs and ankle dorsiflexors by 13 months, and respiratory muscle function appears to have improved in parallel, allowing nocturnal ventilation to be discontinued at 17 months. This occurred while gross motor milestones remained severely delayed: at 12 months, 5 months before weaning, the Bayley-III gross motor age-equivalent was 3 months (functional level corresponding to GMFCS level V). Respiratory recovery may therefore precede the achievement of motor milestones. At reassessment at 25 months of age, 8 months after weaning, delays were present across cognitive, language, and motor domains, reflecting slower developmental gain relative to age and not regression; the dissociation we describe is therefore between respiratory recovery and motor function specifically, not a sparing of development overall. This is physiologically plausible. Ventilation has a large functional reserve, and in NMD daytime hypercapnia typically emerges only when respiratory muscle strength falls below roughly 30% of predicted [25], so a modest recovery of strength, insufficient for gross motor milestones, may be enough to cross back above the ventilatory threshold. Where NIV can be continued safely, the possibility of recovery should be weighed before an irreversible airway intervention; in this child, an early tracheostomy would have been in place during the period in which he recovered.

The molecular findings require cautious interpretation. m.10001T>C in MT-TG has not, to our knowledge, been reported previously and is classified as a variant of uncertain significance; as of 2022, only eleven MT-TG variants had been catalogued in MITOMAP, of which one was considered definitely pathogenic [26]. Pathogenic variants at adjacent positions, however, have recently been characterized (m.10000G>A [26] and m.10038G>A [27]), supporting the functional importance of this region. In our patient, the variant was identified only in blood, where it was reported qualitatively as a low mutant burden without quantification of the heteroplasmy level; because the proportion of mutant mtDNA can differ between blood and muscle [27,28], this finding neither confirms nor excludes a causal role. Reversible infantile respiratory chain deficiency, a mitochondrial myopathy of infancy that resolves spontaneously between 4 and 20 months of age [29], is unlikely on clinical grounds, as our patient lacked its hallmark lactic acidosis; however, MT-TE was not included in the panel, so its causative variant (m.14674T>C) was not tested, and this diagnosis cannot be formally excluded. Conversely, the C-terminal RYR1 deletion, classified as likely pathogenic, cannot be dismissed either. The same deletion was originally reported as a de novo variant in a patient with central core disease who presented with hypotonia at birth [15]; in our patient, by contrast, it was inherited from an asymptomatic parent, which weakens but does not exclude a causal role: RYR1-related myopathy can present with neonatal hypotonia and respiratory failure and may improve with age, and its expression is variable even within families [30]. Congenital myasthenic syndrome, a treatable condition

that can present with neonatal hypotonia and respiratory insufficiency and improve over time, was also considered. Our patient had no ptosis or ophthalmoparesis, his weakness was constant rather than fluctuating or fatigable, and there were no episodic apneic crises; the sequencing panel covered most, though not all, genes associated with congenital myasthenic syndromes without a reportable variant; and severe dysphagia, profound proximal weakness, and global developmental delay have persisted despite ventilator independence. Because repetitive nerve stimulation was not performed and the panel did not cover all genes associated with the syndrome, however, this diagnosis cannot be fully excluded. The molecular etiology therefore remains unresolved, and the treating pediatric neurology service has adopted a working diagnosis of mitochondrial disease. Our management did not depend on the molecular diagnosis: the respiratory strategy was guided throughout by the clinical phenotype and physiological monitoring.

The neonatal brain MRI findings of a focal left temporal infarction with hemorrhage and small subdural hemorrhages raise the question of whether a cerebral insult, not a myopathy, accounted for the presentation and its improvement. Several features argue against this: the hypotonia was flaccid and generalized, with diminished tendon reflexes, a pattern consistent with a primary muscle disorder; persistent polyhydramnios indicated impaired fetal swallowing antedating any perinatal event; Apgar scores of 8 and 9 were incompatible with severe perinatal asphyxia, and the profound acidosis on admission (pH 7.06) was purely respiratory (PCO_2 92.0 mmHg with normal lactate), reflecting ventilatory failure; the focal temporal lesion could not account for symmetric generalized weakness; and weakness persisted long after the lesions had resolved on follow-up imaging. On this evidence we regarded the imaging findings as perinatal lesions superimposed on the neuromuscular presentation, although the two cannot be fully separated without electrophysiological studies.

This report has limitations inherent to a single case. The molecular diagnosis remains unresolved, as it does in more than half of ventilated neonates with peripheral hypotonia even after panel sequencing [31]. With an uninformative panel and a working diagnosis of mitochondrial disease, the usual next steps would be muscle biopsy (histology, respiratory chain enzymology, and muscle heteroplasmy) or exome or genome sequencing; neither has been performed to date, although further genomic analysis may be undertaken through the research program in which the patient is enrolled. Because electrophysiological studies were also not performed, other causes, including congenital myasthenic syndrome, cannot be fully excluded. Empirical mitochondrial cofactor supplementation, started at 10 months of age, overlapped with the period of improvement, so contribution to the recovery cannot be excluded; the decline in ventilatory requirement, however, had begun well before, with daytime autonomy established from 4 months of age. Overnight CO_2 monitoring was not repeated after the weaning admission. Surveillance since then has relied on overnight oximetry at 18 months and daytime spot $EtCO_2$, which were normal but can miss hypoventilation confined to sleep. Follow-up after weaning is limited to 11 months; longer follow-up is needed. Finally, a single case cannot establish that the outcome is reproducible, particularly given the heterogeneity of diagnoses and weaning outcomes among previously reported cases (Table 2).

Table 2. Reported infants and children with myopathic or neonatal-onset neuromuscular ventilatory failure: ventilation strategy and outcome. Diagnoses differ across rows and are labeled as molecularly confirmed, clinically diagnosed, or unresolved; the table compares ventilation strategies and weaning outcomes, not etiologies.

Author, Year [ref]	Diagnosis	Ventilation	Tracheostomy	Weaned	Outcome
Cook, 2005 [3]	Nemaline myopathy, neonatal onset (genetic basis NR)	Invasive MV → tracheostomy	Yes	NR	Long-term ventilation via tracheostomy
Gentin, 2015 [12]	Congenital myopathy (childhood) (genetic basis NR)	Nocturnal NIV (AVAPS)	No	NR (chronic support)	Nocturnal gas exchange improved
Liao, 2026 [4]	XLMTM (MTM1) (molecularly confirmed)	Invasive from birth	—	No	Died after withdrawal of life-sustaining therapy
Ferreira, 2025 [24]	Diaphragmatic paralysis (OBPI) (clinical diagnosis)	NIV from birth (nCPAP → bilevel)	No	Yes, by 2 y (after plication)	Mild residual limb/thoracic findings at 4 y
Liu, 2026 [20]	Nemaline myopathy (NEB), neonatal onset (molecular diagnosis not definitive)	Invasive MV → transient NIV → HFNC → oxygen, all within the neonatal period; no home ventilation	Not reported	Yes, in the neonatal period	No clinically evident motor impairment at 3 y
Present case	Suspected neonatal-onset myopathy (RYR1 LP; MT-TG m.10001T>C VUS; unresolved)	NIV only (after day 7)	No	Yes, 17 mo	Ventilator-free at 28 mo

XLMTM, X-linked myotubular myopathy; OBPI, obstetric brachial plexus injury; NEB, nebulin gene (implicated in nemaline myopathy); RYR1, ryanodine receptor 1 gene; MT-TG, mitochondrial tRNA glycine gene; MV, mechanical ventilation; →, change in the ventilator setting; NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; AVAPS, average volume-assured pressure support; LP, likely pathogenic; VUS, variant of uncertain significance; NR, not reported.

4. Conclusions

In a term neonate with profound congenital hypotonia and chronic ventilatory failure due to a suspected neonatal-onset myopathy, long-term NIV initiated in the neonatal period bridged the infant to complete ventilator independence. This experience, consistent with established practice in neuromuscular disease, suggests that NIV can be applied from the neonatal period in selected infants and that respiratory recovery with growth may precede recovery of gross motor function. These observations derive from a single case and warrant further investigation in larger series.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (protocol code 3-2026-0302, 9 September 2026).

Informed Consent Statement: The requirement for informed consent for the retrospective review of medical records was waived by the Institutional Review Board. Written informed consent for publication of this case report was obtained from the patient's parents.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to patient privacy restrictions.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

NIV	noninvasive ventilation
NMD	neuromuscular disease
IMV	invasive mechanical ventilation
HFNC	high-flow nasal cannula
PCV	pressure-controlled ventilation
PC-AVAPS	pressure-controlled average volume-assured pressure support
PCO_2	partial pressure of carbon dioxide
$TcCO_2$	transcutaneous carbon dioxide
$EtCO_2$	end-tidal carbon dioxide
PEG	percutaneous endoscopic gastrostomy
MRC	Medical Research Council
GMFCS	Gross Motor Function Classification System
XLMTM	X-linked myotubular myopathy
OBPI	obstetric brachial plexus injury
VUS	variant of uncertain significance
MRI	magnetic resonance imaging

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