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Case Report

Axonal Polyneuropathy in A Child with Respiratory Failure: A Case Report of Plasmapheresis-Associated Recovery

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Abstract:
In pediatric intensive care units, polyneuropathy may be masked by primary respiratory failure due to overlapping clinical presentations that are frequently attributed to pulmonary disease rather than an underlying neuromuscular disorder. Early diagnosis remains challenging, and evidence for the use of plasmapheresis in pediatric neuropathy is limited. We report the case of a previously healthy 11-year-old child who presented with acute respiratory failure requiring mechanical ventilation. During ventilatory support, no neuromuscular blocking medications were utilized, and sedation was maintained using a continuous intravenous infusion of midazolam. Despite the resolution of lung pathology, the patient remained ventilator-dependent, with multiple failed extubation attempts over 20 days. Neurological evaluation revealed generalized hypotonia, absent deep tendon reflexes, and electrophysiological findings consistent with axonal polyneuropathy. A diagnosis of polyneuropathy, critical illness polyneuropathy (CIP), was considered. The patient showed significant clinical improvement following treatment with plasmapheresis and subsequent intravenous immunoglobulin (IVIg). Neuromuscular disorders, particularly CIP, should be considered in the differential diagnosis of children presenting with unexplained respiratory failure and prolonged ventilator dependence. Early neurological evaluation, including electrophysiological studies, is essential for timely diagnosis and management, thus improving outcomes. Plasmapheresis may offer a beneficial treatment option in CIP, particularly those who remain ventilator-dependent, and are refractory to extubation.

Keywords: critical illness polyneuropathy; plasmapheresis; respiratory failure; ventilator-dependency
Abbreviations: AMAN: acute motor axonal neuropathy; CIP: critical illness polyneuropathy; CT: computed tomography; IVIg: intravenous immunoglobulin

Introduction

Polyneuropathy can lead to respiratory failure and/or difficult extubation in pediatric intensive care units (PICUs). Prolonged stay on mechanical ventilation might result in the axonal critical illness polyneuropathy (CIP) (*1*, *2*). Long-term ventilation therapy also leads to respiratory and diaphragmatic muscle weakness with failure of extubation (*3*). Children who are at risk of developing neuromuscular dysfunction as a result of critical illness are less likely to be identified, evaluated, and less likely to receive appropriate treatment (*4*). The axonal CIP needs high index of suspicion for its prompt diagnosis as it often hides behind the respiratory failure. The axonal CIP is diagnosed by nerve conduction studies (NCV) (*5*). Yet, other causes of axonal polyneuropathy should be suspected as well. It may be a complication of Guillain–Barré Syndrome (GBS) which is an acute immune-mediated peripheral polyneuropathy and the most prevalent cause of childhood flaccid paralysis. It typically manifests as an acute, non-febrile, monophasic, post-infectious disease with ascending weakness and areflexia. Autonomic, sensory, and brainstem abnormalities may also be observed (*6*). Respiratory failure is the most dangerous and potentially fatal consequence of GBS, which affects 20–30% of children who require

mechanical ventilation, but it usually follows ascending motor symptoms (*7*). CIP may be confused with drug induced neuropathy, as metronidazole, nitrofurantoin, chemotherapy drugs as cisplatin, paclitaxel, and vincristine, antiretroviral drugs, amiodarone, thalidomide, and colchicine (*8*). We describe a child with CIP who was failed several extubation attempts and responded to plasmapheresis and subsequent intravenous immunoglobulins.

Case Presentation

A previously healthy, 11-year-old boy arrived at the Emergency Department at Mataria Teaching Hospital, Cairo, Egypt, on 22 October 2023, complaining of acute-onset cyanosis, respiratory distress, and disturbed consciousness. Initial evaluation upon arrival revealed that he was drowsy, not arousable, not oriented to time, place, and person, with a Glasgow coma score of 4/15, cyanosed, and in respiratory distress, requiring rapid sequence intubation and placement on artificial ventilation. Initial vital signs were a temperature of 36.5°C, respiratory rate of 25 breaths per minute, oxygen saturation of 75% on room air, pulse 94 beats per minute, and blood pressure of 120/70 mmHg. He was immediately admitted to the pediatric intensive care unit for further assessment and monitoring. By taking history, he had received an antibiotic prescription for sinusitis two weeks previously and denied taking any other medications, such as metronidazole, nitrofurantoin, or steroids. He had been afebrile during that illness. Two days prior to hospitalization, the boy experienced respiratory distress, decreased oral intake and fatigue and no vomiting or diarrhoea. On the day of admission, he became cyanosed and collapsed suddenly. On examination, there was no facial asymmetry and both pupils were reactive to light. There were no signs of meningeal irritation or petechial rashes. The patient had diminished air entry and fine crepitation bilaterally with normal rhythmic heart sounds. Muscle tone and reflexes could not be assessed on admission because the patient was sedated and on ventilatory support.

Laboratory data upon admission to our hospital revealed normal level of hemoglobin 14.3 g/dl, white blood cells (10.2x 10^3/µL), platelets 298x 10^3/µL, elevated C-reactive protein (CRP) (24 mg/dL), blood glucose level of 250 mg/dL, normal liver and kidney functions, normal coagulation profile, hyponatremia (sodium 116 mEq/L), potassium 4 mEq/L, and ionized calcium 1.03 mmol/L. Arterial blood gas analysis demonstrated pH 7.22, $PaCO_2$ 70.2 mmHg, and bicarbonate 28.7 mEq/L. The toxicology screen was negative. No abnormalities were found on the cranial computed tomography (CT) scan. Chest CT scan showed consolidation patches in the right upper lobe and left lower lobe, suggesting pneumonia. He was initially managed as respiratory failure presumed to be secondary to extensive pneumonia; thus, the patient was started on double antibiotic therapy with correction of electrolytes. During his stay in the PICU, the patient continued on ventilator support, receiving tube feeding and physiotherapy. The sedation, by midazolam infusion was initiated at a dose of 0.1 mg/kg/h, titrated as needed, and tapered over the following three days, and the patient was conscious, alert, but noticeably weak. Concurrent respiratory assessment revealed inadequate spontaneous respiratory effort, and the patient remained ventilator-dependent to maintain adequate oxygen saturation. Over the subsequent days, the patient underwent three failed extubation attempts, despite the resolution of the initial pulmonary pathology and stable vital signs. Since attempts to wean the patient off the ventilator worsened his symptoms, further neurological evaluation was necessary to investigate possible underlying neuromuscular causes. Neurological examination revealed generalized hypotonia affecting all four limbs, with no active movement against gravity.

Muscle strength was graded as follows: upper limbs, proximal 2–3/5, distal 1–2/5, and lower limbs, 1/5 in both proximal and distal muscle groups. Deep tendon reflexes were absent in the lower limbs and diminished in the upper limbs, and the gag reflex was absent, indicating bulbar involvement. There was no sensory level on examination. Magnetic resonance imaging (MRI) of the brain and spine was performed to exclude central causes, which revealed no abnormalities suggestive of encephalitis, myelitis, or structural lesions. A bedside chest ultrasound was conducted, which showed bilateral diaphragmatic weakness, supporting the suspicion of peripheral neuromuscular involvement affecting respiratory muscles. Serum creatine phosphokinase (CPK) level was within normal limits. Subsequent neurophysiological studies were conducted. Nerve conduction study (NCS) revealed normal conduction velocities but reduced amplitudes in all motor nerves, with absent F-waves, indicated a motor axonal neuropathy. Electromyography (EMG) showed no denervation at rest; however, at minimal volition, low-amplitude, prolonged, and polyphasic motor unit action potentials were observed. At maximal effort, the interference pattern was markedly reduced. These findings were consistent with a generalized motor axonal polyneuropathy. GBS was suspected; however,

cerebrospinal fluid analysis could not be performed, as the patient's family declined lumbar puncture due to concerns about potential risks. Fundus examination was performed and showed no evidence of papilledema or other abnormalities.

Considering the patient's ventilator dependence, evidenced by five failed extubation attempts over a 20-day period, and the findings from NCS and EMG consistent with a motor axonal polyneuropathy, plasmapheresis was initiated. The child underwent a total of eight sessions of plasmapheresis, initially administered once daily for the first three sessions, followed by once every other day for 5 sessions. Following the first six sessions of plasmapheresis, the patient received intravenous immunoglobulin (IVIg) at a dose of 2 g/kg total, administered over 5 consecutive days (0.4 g/kg/day). The course was not repeated, as the patient began to show clinical improvement with improved power of the upper limbs and recovery of the gag reflex upon suction. The child was able to move his lower limbs after eight sessions of plasmapheresis. Corticosteroids were not administered during the course of illness.

Extubation was attempted six times, with attempts made approximately every 3 to 4 days, depending on the patient's respiratory and neurological status, until the patient was successfully extubated (having been on a ventilator for 3.5 months) and remained on non-invasive ventilation for the next 10 days. Four months following his admission, the patient was discharged with nasal bilevel-positive airway pressure (BiPAP) support at night, power grade 4/5 in both upper and lower limbs, and the ability to walk with aids. The child then underwent physical therapy and followed up with the pulmonology clinic, until he regained significant improvement in diaphragmatic muscle movement, to the point that the patient no longer required any respiratory support (five months after the onset of the disease). Over the next two weeks, the patient began swimming exercises to strengthen his limbs and girdle muscles.

Discussion

This report describes an 11-year-old child who developed acute respiratory failure and prolonged ventilator dependence during his PICU stay, with neurophysiological findings showing motor axonal polyneuropathy. Several conditions were considered in the differential diagnosis of this child, including drug-induced peripheral neuropathy, ventilator-associated polyneuropathy, CIP, and GBS. Accurate differentiation was challenging yet, vital because management and prognosis differs depending on the cause.

Our patient's initial hyponatremia may have contributed significantly to both his respiratory compromise and neuromuscular dysfunction. Hyponatremia is a well-documented cause of muscle weakness due to its impact on membrane potentials and neuronal excitability. In severe or acute cases, it can impair neuromuscular transmission, which may result in flaccid paralysis or even respiratory failure. In this context, hyponatremia could have worsened the patient's respiratory muscle weakness, further complicating the process of weaning from mechanical ventilation (9). However, in our patient, after correction of electrolyte disturbance, which was shortly after PICU admission, the patient was still hypotonic. We are not aware what caused this hyponatremia in our studied case.

Drug-induced peripheral neuropathy was taken into consideration in our case, since it is a prevalent and painful condition caused by a wide range of commonly given medications, such as antimicrobials, chemotherapeutic agents, psychotropics, cardiovascular drugs, and anticonvulsant drugs (*8*). It is potentially irreversible, causing sensory impairments and paresthesia, usually in a glove-and-stocking distribution; motor involvement is uncommon (*9*). However, in our patient, there was no evidence of exposure to such neurotoxic agents, and no temporal association could be established between medication administration and the onset of weakness. In addition, the lack of a cumulative drug history, a negative toxicology screen, and improvement with plasmapheresis minimized the possibility of a drug-induced etiology in our case (*10*).

Another diagnostic possibility was ventilator-associated neuropathy. Mechanical ventilation is life-saving for patients with acute respiratory failure; nevertheless, it challenges weaning from the ventilator due to a fast decline in diaphragm muscle endurance and strength, known as ventilator-induced diaphragmatic damage. Also, prolonged sedation, immobility, and systemic illness may exacerbate neuromuscular weakness (*11*). In our patient, bilateral diaphragmatic weakness on chest ultrasound and failed extubation attempts despite improved pulmonary status, support ventilator-associated neuropathy. However, the presence of generalized limb weakness, absent deep tendon reflexes, and electrophysiological evidence of motor axonal neuropathy suggest a more systemic peripheral nerve disorder beyond isolated ventilator-induced dysfunction due to ventilator dependence.

Critical illness polyneuropathy (CIP) was considered as well, since it is the most prevalent neuromuscular dysfunction in the intensive care units and is frequently associated with critical illness myopathy. Both disorders cause substantial weakness, ventilation dependence, increased length of stay, and protracted rehabilitation (*1*, *2*). Severe sepsis, systemic inflammatory response syndrome, multiorgan failure syndrome, and prolonged mechanical ventilation for more than seven days are the most prevalent risk factors for CIP (*4*). In our case, risk factors included systemic inflammatory response, mechanical ventilation dependence, hyponatremia, electrophysiological studies revealing motor axonal involvement, and diaphragmatic weakness.

However, our patient developed generalized hypotonia affecting all four limbs, with no active movement against gravity after withdrawing sedation within 3 days. He also responded well to plasmapheresis and IVIg. Indeed, the timing of motor neuropathy following acute respiratory failure raises important considerations, including post-infectious etiologies such as *Mycoplasma pneumoniae*. However, the absence of confirmatory microbiological evidence, such as a positive identification by polymerase chain reaction (PCR) or serology test, along with the lack of extrapulmonary manifestations typically associated with *Mycoplasma*-related neurologic complications, weakens support for this diagnosis.

Hence, GBS was also a suspected diagnostic possibility, given the history of infection two weeks prior, the acute onset of respiratory failure requiring mechanical ventilation (*6*), repeated weaning failures, the patient's acute flaccid paralysis, preserved sensory function, supportive chest ultrasound results, the absence of central nervous system pathology, good response with plasmapheresis, and neurophysiological findings indicative of motor axonal involvement, an immune-mediated axonal polyneuropathy becomes a strong diagnostic consideration. This presentation aligned with the acute motor axonal neuropathy (AMAN), subtype of GBS, which is particularly relevant in pediatric populations and shares significant overlap with other immune-mediated neuropathies (*12*). Unlike the classic demyelinating variant of GBS, acute inflammatory demyelinating polyradiculoneuropathy, which is characterized by ascending paralysis, areflexia, and slowed nerve conduction, axonal subtypes such as AMAN and acute motor and sensory axonal neuropathy often manifest with rapid and severe motor weakness and without the hallmark features of demyelination. These axonal forms are often associated with antecedent infections like *Campylobacter jejuni*, which trigger immune-mediated axonal injury via molecular mimicry (*13*). However, the absence of preceding ascending limb paralysis, along with the lack of cerebrospinal fluid analysis, was a significant limitation in our case and evaded a definitive confirmation of the diagnosis.

In our patient, the initial altered consciousness was attributed to respiratory acidosis and hypoxia, rather than central nervous system pathology, as supported by normal brain and spine MRI findings. Furthermore, electrophysiological studies demonstrated a motor axonal polyneuropathy, refuting the diagnosis of classic GBS, and suggesting the GBS subtype, AMAN *(14).* Yet, evidence is lacking to support the GBS or its variant, AMAN, in our case.

Our patient began to show clinical improvement after plasmapheresis was initiated, and he was able to walk with assistance after eight sessions. The prompt functional recovery observed in our case reinforces the therapeutic potential of plasmapheresis followed by IVIg and supports the immune pathogenesis or the drug induced polyneuropathies. The heterogenous group of immune axonal neuropathies that share underlying vasculitic pathogenesis are another possibility that seem to be very remote, due to the lack of associated systemic autoimmune disease (*14*).

Our study highlights the importance of maintaining a high index of suspicion for polyneuropathy diagnosis in children presenting with respiratory failure, and prolonged dependence on mechanical ventilation, in the absence of an identifiable pulmonary or structural neurological cause. Plasmapheresis followed by IVIg seemed to be the effective last resort in correcting the axonopathy in our reported child.

Conclusion

This case underscores the importance of considering neuromuscular disorders in the differential diagnosis of children with unexplained respiratory failure and prolonged ventilator dependence. Early neurological evaluation, and invasive electrophysiological studies, facilitate timely diagnosis and intervention, and improve the outcome. Professional medical team care is mandatory for prompt diagnosis and management in critical care settings. Plasmapheresis by IVIg may serve as an effective therapeutic option for mechanical ventilation associated axonal polyneuropathy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information. The General Organization of Teaching Hospitals and Institutes (GOTHI) Research Ethics Committee approved the study on September 11, 2024, (approval number: HM000183). Written informed consent from the child's parents was obtained for publication of the case report.

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