Demyelinating diaphragmatic nerve damage as a cause of respiratory failure in a child of the first year of life: a case report

V.V. Kopylov, P.A. Muratov, Yu.S. Aleksandrovich, K.V. Pshenisnov, I.V. Aleksandrovich

Abstract

INTRODUCTION: Impaired neuromuscular transmission is one of the rarest causes of acute respiratory failure in children. OBJECTIVE: Demonstration of a clinical case of acute respiratory failure in a child of the first year of life against the background of a demyelinating lesion of the diaphragmatic nerve. MATERIALS AND METHODS: A retrospective analysis of the peculiarities of the course of the disease in a child of nine months requiring long-term control mechanical ventilation. RESULTS: The article describes the stages of diagnostic search for the causes of acute cerebral and respiratory failure of unclear origin in a child of the first year of life, special attention is paid to differential diagnosis, which made it possible to identify the primary pathological process. CONCLUSIONS: A distinctive feature of this case was the severe course of acute cerebral and respiratory failure against the background of primary demyelinating damage to the diaphragmatic nerves on both sides, which is casuistic, especially in pediatric practice, but should be taken into account in the absence of other obvious causes of acute respiratory failure.

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Introduction

Respiratory failure (RF) is one of the most often causes of emergency admission to pediatric intensive care units. In most cases, it’s related to obstructive diseases of the respiratory tract or with lung tissue damage lung. These causes of disease are diagnosed and treated without difficulty, but in some cases the reason of children’s respiratory failure remains unclear, especially when there’s no apparently reasons for its development [1].

The respiratory system is complex, consisting of many hierarchically subordinate elements, among which it is hardly possible to single out the most significant ones, since when any functional structure is damaged, respiratory distress or respiratory failure of varying severity develops.

By the classification of Y.N. Shanin and A.L. Kostuchenko, there are two development options for acute and chronic respiratory failure, depending on the level of damage to the respiratory system. The first type of course is connected with ventilation and involves a violation of the biomechanics of breathing of various origins, the second (parenchymal) develops with direct damage to the lung tissue [2].

The greatest diagnostic difficulties are observed with the development of ventilation respiratory failure, the causes of which may not be clear. But if we proceed from the classification of RF proposed by B.E. Votchalom (1973), then differential diagnosis can be significantly simplified. He distinguishes such types of RF as centrogenic, neuro­muscular, thoraco­diaphragmatic (parietal) and bronchopulmonary [3].

If the causes of RF of central origin in most cases lie on the surface and do not require a deep diagnostic search, then identifying the mechanisms of development of neuro­muscular and thoraco­diaphragmatic RF are difficult. These reasons require the doctor to have deep knowledge in the field of neurology, physiology and pathological physiology of breathing. Although these causes of RF are relatively rare, they can cause irreversible problems that can be avoided with timely diagnosis. Niccolo Machiavelli in his treatise “The Prince” wrote: “...at the beginning the disease is easily curable, but difficult to detect, but over time, unrecognized or untreated, it becomes easily detectable, but difficult to cure” [4]. Thus, timely accurate diagnosis is the basis for the success of treatment and recovery of the patient.

One of the rarest causes of respiratory failure, both in adults and children, is damage to the phrenic nerve of various genuses [5, 6].

When analyzing publications in the PubMed database for the period from 2018 to 2023 using keywords “respiratory failure”, “diaphragmatic nerve”, “dysfunction”, “pediatric”, only fifteen papers were found, of which only three
were devoted to phrenic nerve dysfunction as a cause of respiratory failure in clinical practice [7–9]. The remaining twelve examined the fundamental and pathogenetic aspects of phrenic nerve injury, assessing its function, including the use of experimental models, which served as the basis for their exclusion.

In a detailed study of studies devoted to the development of respiratory failure with damage to the phrenic nerve in adults and children, we found that only one of them is a description of clinical cases of diaphragm dysfunction in young children with Zika syndrome, while the authors note a high probability of developing life-threatening complications and detailed outcomes [7].

In the article Fuller D.D. et al. (2021) describes a case of late-onset Pompe disease in a thirty-five-year-old patient, which caused phrenic nerve dysfunction and progressive respiratory failure, causing the death of a man aged fifty-four [8].

Ghani M.O.A. et al. (2021) conducted a study to examine the incidence of phrenic nerve dysfunction after cardiac surgery in neonates and young children. The authors found that the only risk factor for paresis/paralysis of the right phrenic nerve is the location of the drainage tube in the area of the upper parts of the right pleural cavity [9].

Taking this into account, it can be argued that damage to the phrenic nerve is an extremely rare cause of respiratory failure in pediatric practice (with the exception of patients after cardiac surgery), which, in the absence of vigilance among general anesthesiologists and resuscitators, can cause late diagnosis and treatment of the underlying disease. This indicates the need for appropriate differential diagnosis of respiratory failure of unknown genesis, which is especially important in young children.

**Objective**

The purpose of the study is to demonstrate a case report of respiratory failure in a one-year-old child with demyelinating lesions of the phrenic nerves.

**Case report**

A child 9 months 3 weeks old was admitted to the hospital at 10:04 p.m. with a diagnosis: acute left-sided purulent otitis media. According to his mother, he became lethargic the night before, and from 6:00 p.m. he completely refused food and water. In the morning of the day of hospitalization, he was lethargic, the child did not get up or sit, his mother noted severe muscle hypotension. At 4:00 p.m., after a walk (during which he was sleeping), the child began to cry monotonously, there was an episode of pallor and cyanosis of the skin, rolling of the eyes, and throwing back of the neck. An ambulance was called and the child was admitted to the emergency department. The mother denies any injuries to the child, but suggests that the child could have fallen while playing with older children. The child was not left unattended, he did not have a fever or experience vomiting. Preventive vaccinations were not carried out due to parental refusal.

In the intensive care unit: Glasgow score 12 accounting for drug sedation. The pupils was symmetrical, the eyeballs are in the center, the photoreaction is present. There are no acute neurological symptoms. The skin was pale pink, clean, warm, the mucous membranes are pink and moist. There were no microcirculation disturbances. Heart sounds are clear, sonorous, rhythmic, heart rate 130 per minute; blood pressure 118/62 mmHg. The heart rhythm was sinus. A computed tomography scan revealed left-sided purulent otitis media, a paracentesis was performed, and pus was obtained. When examining the cerebrospinal fluid, there was no evidence of infection of the central nervous system (clear cerebrospinal fluid, cytosis 1/3, protein 0.23 g/l, glucose 2.86 mmol/l). Pathogenetic and symptomatic treatment was started. The child’s parents categorically refused antibiotic therapy upon admission to the ICU, but subsequently consent was obtained.

On the first day of treatment, the child’s condition remained serious and unstable. Severe muscle weakness and muscle hypotonia persisted, and the child developed a palpable rash on the face and chest. Twelve hours after admission, sinus tachycardia rose to 167 beats per minute, arterial hypertension 124/74 mmHg, snoring breathing with a decrease in SpO2 to 88 % and central cyanosis. In the next 24 hours, the condition continued to progressively deteriorate; pronounced muscle hypotonia, hyporeflexia, hyper-salivation, tachycardia 165–170/minute and arterial hypertension 125/75 mmHg remained. The condition is regarded as progression of cerebral edema. To eliminate intracranial hypertension, mannitol 0.25 g/kg and furosemide 1 mg/kg were administered, without significant clinical effect, the neurological status remained the same. According to electroencephalography — without epileptiform activity. Quite pronounced changes in the bioelectrical activity of the brain were noted in the form of disorganization with processes of irritation, slowdown, and irregular polymorphic activity.

On the second day of treatment in the intensive care unit, due to the progression of respiratory failure, the patient was intubated and connected to mechanical ventilation with parameters corresponding to the age of the child [10]. Over the next two days, the condition remained stable, without significant dynamics. Respiratory support continued. When sedation was withdrawn, depression of consciousness persisted to the level of stupor, the child periodically tried to follow an object with its eyes, but quickly got tired, severe muscle hypotonia and hyporeflexia persisted. The cough reflex was significantly reduced. When attempting to wean from invasive respiratory support (transfer to non-invasive ventilation with PEEP), the child quickly became exhausted and breathing became ineffective. It has been suggested that there is damage to the central nervous system of metabolic genesis. In order to exclude hyperammonemia, a test for...
ammonia levels in the blood (30 µmol/l) and a urine test for aciduria were performed, which excluded metabolic damage to the central nervous system. Over the next few days, the child’s condition remained serious and unstable; pathological neurological symptoms persisted in the form of divergent strabismus, flaccid tetraparesis (more in the upper extremities), bulbar syndrome, and left-sided ptosis. On the ninth day, the patient was prescribed ethylmethylhydroxypyridine succinate (0.5 ml/day), thiamine chloride (0.5 ml/day), pyridoxine hydrochloride (0.5 ml/day) to improve metabolism. On the fourteenth day of treatment, the patient showed regression of cerebral symptoms, restoration of movements in the limbs, effective breathing and clear consciousness; the patient was extubated. He was transferred to oxygen therapy via high-flow nasal cannulas. However, during the day, respiratory failure increased, which is why the patient was intubated again and ventilation was continued. Within two days after being transferred to ventilation, the patient fully recovered clear consciousness and movements in the limbs. On the twenty-second day there was a second attempt at extubation, which was successful. After extubation, the patient received oxygen therapy through high-flow nasal cannulas for 24 hours and did not require further respiratory support. His condition stabilized, neurological symptoms regressed, his breathing pattern was satisfactory, and he began to show an emotional reaction. On the twenty-sixth day he was transferred to a specialized pediatric department for further therapy and observation.

The patient underwent electroneuromyography — no convincing evidence for a denervation or myogenic process was obtained, but the patient has signs of demyelinating damage to the phrenic nerve on both sides in the form of a decrease in conduction velocity: on the right — 12 m/s, on the left — 15 m/s (normal 40–60 m/s). In the ICU, the patient received infusion and drug therapy, presented in Table 1. The basis for prescribing fluconazole was the appearance of thrush on the oral mucosa. Vitamins were prescribed by the treating neurologist.

The subsidy of fluid to the patient was in the amount of 150 ml/kg/h. The duration of control mechanical ventilation was 22 days, treatment in the ICU — 26 days, in the hospital — 45 days. He was discharged home in satisfactory condition with the main diagnosis: “Acute metabolicencephalomyopathy”.

**Table 1. Characteristics of medications**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone, intravenous</td>
<td>55 mg/kg/day</td>
<td>13 days</td>
</tr>
<tr>
<td>Cefoperazone / sulbactam, intravenous</td>
<td>66 mg/kg/day</td>
<td>8 days</td>
</tr>
<tr>
<td>Ayclovir, intravenous</td>
<td>30 mg/kg/day</td>
<td>3 days</td>
</tr>
<tr>
<td>Fluconazole, intravenous</td>
<td>5 mg/kg/day</td>
<td>6 days</td>
</tr>
<tr>
<td>Thiamini chloride, intravenous</td>
<td>0.5 ml/day</td>
<td>15 days</td>
</tr>
<tr>
<td>Cyanocobalamine, intravenous</td>
<td>0.5 ml/day</td>
<td>19 days</td>
</tr>
<tr>
<td>Piracetam, intravenous (by decision of the medical council)</td>
<td>1.5 ml once daily</td>
<td>9 days</td>
</tr>
<tr>
<td>L-carnitine, per os (by decision of the medical council)</td>
<td>100 mg/kg/day</td>
<td>Before discharge from the hospital</td>
</tr>
<tr>
<td>Ubidecarenone, per os (by decision of the medical council)</td>
<td>5 mg/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

During the hospitalization of the child, attention was drawn to the symptoms of acute brain failure, which served as the basis for a comprehensive clinical and laboratorial diagnosis to determine the cause of damage to the central nervous system, but it did not lead to success, despite a large list of possible diseases that could cause this condition. During the differential diagnosis, causes such as trauma, neuroinfection, poisoning, congenital metabolic diseases, ischemic stroke, infant botulism, brain tumors, polynuromyelopathy and demyelinating diseases were excluded.

All common causes as injury, neuroinfection, metabolic syndromes, ischemic stroke, brain benign tumors and infant botulism laboratory and instrumental tests was unconsidered, but patient retained cerebral and respiratory insufficiency. It was cause for searching disease with neuromuscular etiology.

The patient did not experience pathological changes in the concentrations of C-reactive protein, procalcitonin and lactate during the entire period of treatment in the ICU. When examining the cerebrospinal fluid and blood using the polymerase chain reaction method, there were no herpes viruses; antibodies (immunoglobulins M and G) to herpes viruses were also not detected, on the basis of which the diagnosis of viral meningoencephalitis of herpetic etiology was excluded.

Traditional electroneuromyography was done, it did not reveal pathological changes in the peripheral nerves innervating the skeletal muscles, but a decrease in the conductor speed along the phrenic nerves was obtained, which made it possible to make the correct diagnosis and continue adequate treatment aimed at restoring the function of the nerves.

MRI in FLAIR-mode and antibody for myelin tissue aren’t performed. Electroencephalography did not search epileptimorphy activity. But the patient had changes in the bioelectrical activity of the brain with its disorganization, irritation processes, slowdown, and irregular polymorphic activity. With drug therapy and respiratory support, the patient managed to stabilize his condition and completely regress neurological symptoms with the restoration of satisfactory muscle tone and adequate breathing. Unfortunately, there are no descriptions of such cases in the literature avail-
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able to us, which does not allow us to compare therapy with treatment options used by other specialists.

Taking into account the symptoms of the disease, it can be argued that it was the primary damage to the phrenic nerves that was the cause of respiratory distress, severe muscle hypotension and depression of consciousness, which were most likely manifested by severe hypoxemia and hypercapnia. It is hardly possible to unambiguously identify the cause of damage to the phrenic nerves at this stage, but we can assume that it arose as a result of an autoimmune pathological process, which became the cause of demyelination.

In recent years, more and more studies have appeared indicating the presence of diseases known collectively as “nodopathies”. For example, the work of A. Uncini (2015) is widely known; in his work he gives a clear description of these diseases. In his opinion, nodopathy is a pathophysiological continuum from transitional nerve conduction block to axonal degeneration, while the conduction block can be quickly reversible without the development of excessive temporal dispersion, but axonal degeneration (depending on the specific disorder and its severity) always ultimately follows behind the conduction block, although this is more typical for adults [12]. Conduction block may be caused by paranodal myelin detachment, node elongation, sodium channel dysfunction, other persistence of intracellular water and ions, and abnormal polarization of the axolemma. There are currently no such works for children.

A number of studies exist in literature indicating that one of the links in the pathogenesis of peripheral neuropathies are autoimmune processes caused by the appearance of antibodies to cell adhesion molecules at the nodes of Ranvier [13–15]. The presence of these antibodies is associated with the appearance of specific clinical and pathomorphological signs different from classical chronic inflammatory demyelinating polyneuropathy, however, at this stage of scientific development this is only a hypothesis, so clear recommendations for treatment using corticosteroids are currently missing for such diseases [16]. In the presented case, corticosteroids were also not used due to the high risk of their side effects and infectious complications, especially considering that no convincing clinical, laboratory and instrumental data for autoimmune or paraneoplastic encephalitis were identified.

**Conclusion**

A distinctive feature of this clinical case was the severe course of acute cerebral and respiratory failure against the background of primary demyelinating lesions of the phrenic nerves on both sides, which is casuistry, especially in pediatric practice and was established only by conducting targeted electroneuromyography, since all other obvious causes of acute respiratory failure were excluded.

**Disclosure.** The authors declare that they have no competing interests.

**Author contribution.** All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

**Consent for publication.** Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

**Ethics approval.** The present study protocol was approved by the local Ethics Committee of the St. Petersburg State Pediatric Medical University (reference number: 25/01; 13.04.2023).

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