

Severe Acute Motor Axonal Neuropathy Associated with Influenza-A (H1N1) Infection and Prolonged Respiratory Failure - A Case Report

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ABSTRACT

Acute Motor Axonal Neuropathy (AMAN) is an immune-mediated disorder of the peripheral nervous system, part of the spectrum of the Guillain-Barre syndrome (GBS). An infectious event most often triggers it reported a few weeks before the onset. The reported case is of a 56 years-old woman who developed acute motor axonal neuropathy three weeks after respiratory infection with influenza A virus subtype H1N1. Despite early treatment with plasmapheresis and intravenous immunoglobulins, the patient remained tetraplegic, mechanically ventilated for five months, with repetitive unsuccessful weaning trails. The probable cause was considered to be phrenic nerve palsy in the context of acute motor axonal neuropathy. This case highlights that acute motor axonal neuropathy is a severe and life-threatening form of Guillain-Barre syndrome associated with significant mortality and morbidity. Neurological and physical recovery strongly depend on the inter-professional effort in an intensive care unit and neurology professionals.

Keywords: Guillain-Barre syndrome, acute motor axonal neuropathy, nodopathy, influenza virus A H1N1, tetraplegia, prolonged respiratory failure

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INTRODUCTION

Guillain Barre syndrome (GBS) is a most common and severe acute neuropathy with an estimated incidence rate in Europe of 0.8-1.9/100000/year [1,2]. Acute Motor Axonal Neuropathy (AMAN), a subtype of Guillain-Barre syndrome, is an immune-mediated disorder that frequently occurs after an acute infection. The pathophysiology points to the destruction of the peripheral nerves and spinal roots secondary to molecular mimicry due to the spread of cross-reactive epitopes [3,4]. Prior events are common; two-thirds of Guillain-Barre syndrome patients usually describe various gastrointestinal or respiratory infections within two to four weeks before the onset of the neurological

signs. There is a recent history of vaccination in a reduced but significant number of cases [5].

Acute motor axonal neuropathy is thus triggered by an immune response against the epitopes from the axonal membrane [6]. However, different epidemiological studies debate the role of the influenza virus as the trigger factor of autoimmune responses that lead to diffuse impairment of the nervous system [7].

The typical clinical manifestation of Guillain-Barre syndrome is rapidly progressive symmetrical bilateral lower limb weakness, swiftly spreading to the upper body and arms, accompanied by paraesthesia, with or without the involvement of cranial nerves [8]. These clinical signs can progress for hours to several days. In

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addition to the motor weakness, patients with Guillain-Barre syndrome may have a sensory impairment and autonomic system dysfunction, leading to life-threatening complications such as cardiac arrhythmias and uncontrollable blood pressure [9].

■ CASE REPORT

A 56-years-old woman presented upon waking up with a “pins and needles” sensation and distal pain in both hands, four weeks after an influenza virus A type H1N1 (A H1N1) infection.

Three hours after the onset, the symptoms rapidly progressed with bilateral distal limb weakness and severe gait impairment. The patient was referred to the local emergency services (ER) in the County Emergency Hospital, Sfantu Gheorghe, Covasna County, where the on-call neurologist attended her.

The muscle weakness progressed rapidly, from distal to proximal limbs and for a few hours, she developed complete generalised flaccid quadriplegia.

The neurological examination at that point revealed flaccid tetraplegia - grade 0/5 on the Medical Research Council (MRC) scale in distal and proximal muscles in all limbs, with absent deep tendon reflexes (DTR). Ocular motility and pupillary reflexes were intact, but the patient had severe dysphagia due to glossopharyngeal and vagus nerve palsy. There was a symmetrical distal reduction in the vibration and fine touch sensation in the ankle joints, but without any sensory complaints.

There was no spine sensory level, no pyramidal signs, no urinary incontinence or positive meningeal signs. However, the patient was fully alert and conscious, registering a Glasgow Coma Scale of 15 points. She was hemodynamically stable with a blood pressure of 150/85 mmHg, heart rate of 80 beats/minute, a temperature of 35.6 °C.

Routine blood tests revealed a slightly elevated level of white blood cells with neutrophilia (15.360/mm³ and 92% neutrophilia), a mild elevation of fibrinogen serum levels (560 mg/dl), and a high level of gamma-glutamyl transferase (204 U/L). Routine biochemistry, coagulation, metabolites (potassium, sodium) and renal functions (*creatinine, urea*) tests were within normal ranges. ELISA testing for *antiganglioside antibodies* (GM1, GM2, GM3), anti-myelin-associated glycoprotein (MAG), anti-GD1b, anti-GQ1b IgM and IgG were negative.

The serological tests for human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, syphilis and *Borrelia Burgdorferi* IgG and IgM antibodies were all negative. In addition, urine porphobilinogen, delta-aminolevulinic acid, antinuclear antibodies and rheumatoid factor were negative.

Cerebrospinal fluid analysis showed a normal cell count and raised protein levels (820 mg/dl) and normal glucose levels, suggestive of albumin-cytological dissociation. Bacterial and fungal cultures from the cerebrospinal fluid were sterile. The brain and cervical spine CT scans were unremarkable. The chest radiography was within normal limits.

Based on the clinical picture with the rapid onset ascending motor deficit, superficial and deep sensory involvement and the highly specific albumin-cytological dissociation found in the cerebrospinal fluid examination, an acute polyradiculoneuropathy was suspected, and the patient was admitted to the regional university hospital, Neurology 1 Clinic, Emergency Clinical County Hospital Mures.

Three hours after the admission, the patient suddenly developed mild tachypnea (28/min), progressive dyspnoea. The peripheral oxygen saturation was measured with a pulse oximeter at 88% with oxygen 6L/min delivered via an oxygen mask. At the same time, a urinary catheter was placed.

The patient was transferred to the intensive care unit at this stage, where mechanical ventilatory support was required.

Before orotracheal intubation, with the patient breathing oxygen 6L/min delivered via an oxygen mask, the arterial blood gas analysis revealed an arterial partial pressure of oxygen of 61.2 mmHg and arterial partial pressure of carbon dioxide 81.3 mmHg, and a pH of 7.25.

A nerve conduction study was performed on day five following admission in the Neurology 1 Clinic of the Emergency County Clinical Hospital Mures.

At this time, severe decrease in the amplitude of compound muscle action potential bilateral in the median, ulnar, peroneal and tibial nerve, with normal sensory responses and absent F wave responses. In addition, the electromyography demonstrated an acute neurogenic pathway with vigorous spontaneous activity, with fibrillation potentials and positive sharp waves (signalling active denervation) in the proximal muscles of the upper and lower limbs (deltoid and vastus lat-

eralis). These electrophysiological findings were highly suggestive for acute motor axonal neuropathy.

The clinical signs progressed rapidly with suggestive changes in cerebrospinal fluid and nerve conduction study findings; therefore, the patient was diagnosed with acute motor axonal neuropathy.

Plasmapheresis was rapidly instituted, but after four sessions, no significant clinical improvement was noted.

Five days after the plasmapheresis, the patient received 0.4g/kg/day intravenous immunoglobulin (Kedrigamma 50g/l, Human Immunoglobulin, Kedrion S.p. A, Barga, Italy) and methylprednisolone 500mg a day (Lemold Solu, Methylprednisolone 500mg, Hemo-farm, Timisoara, Romania) but with no signs of clinical improvement.

The disease's course was complicated with hyponatremia and cardiac dysautonomia, resulting in sinus tachycardia, up to 140-150 beats per minute) and labile arterial hypertension. Cardiac function as assessed by echocardiography was within normal ranges. On the third day of hospitalisation, post-admission, the sodium levels decreased, and the urinary output massively increased; diuresis over twenty hours reached approximately nine litres, 6.25 ml/kg/min. The sodium values reached a critical low of 120 mmol/L on the seventh day from the onset of hyponatraemia.

Serum cortisol and thyroid function tests were within normal ranges. The urine sodium was 58 mmol/l, and urine osmolality was 568 mOsm/kg of water.

A diagnosis of insipid diabetes was ruled out, and inappropriate secretion of antidiuretic hormone syndrome was suspected. Hyponatremia was managed with fluid restriction and sodium repletion according to daily sodium values, with natrium chloride 58.5% (Natrii Chloridum, Braun, 58.5 mg/ml, Melsungena, Germany). Unfortunately, Tolvaptan administration was not possible since the product was not available in Romania. The serum electrolytes were monitored daily, and hyponatremia gradually resolved.

The patient remained on mechanical ventilation due to repetitive failures of weaning attempts, and two weeks after the admission to the County Emergency Hospital, a tracheostomy was performed. Two months post-admission, swallowing difficulties persisted, and a percutaneous endoscopic gastrostomy replaced the nasogastric feeding tube was mounted.

During treatment in the intensive care unit, the patient acquired ventilator-associated pneumonia with

different agents. The first pathological culture from her tracheal aspirate identified described a positive culture with multi-drug resistant *Acinetobacter baumannii*, multi-drug resistant *Pseudomonas aeruginosa*, and *Candida Albicans*.

For this reason, her antibiotic therapy was adjusted according to her antibiogram overall profile and renal function tests.

A subsequent tracheal aspirate culture was done 12 days after the admission to the intensive care unit; this was positive for multi-drug resistant *A. Baumannii*, methicillin-resistant *Staphylococcus aureus*, and *Candida Albicans*.

For this reason, her antibiotic therapy was re-adjusted to Colistin, three times 3.000.000 Units per day intravenously (Antibiotice SA, Iasi, Romania), on days 30 to 44, post-admission to the intensive care unit and Linezolid (Infomed Fluids SRL) two times 600mg a day intravenously, from day 42 to 54, post-admission to the intensive care unit.

After another two weeks, her tracheal aspirate showed a positive culture for *Acinetobacter Baumannii* and *Staphylococcus aureus* but with fewer colonies. The patient also had a positive culture from her lingual scraping showing *Candida albicans* and *Candida glabrata* uti. A positive culture from her urine sample taken from the urinary catheter showed growth with *Providencia stuartii* CPE.

The patient was in a critical state for the next four months with prolonged but gradual improvement. A psychiatric assessment, undertaken early in the intensive care unit, arrived at a sleep deprivation diagnosis without additional psychological concerns.

During her stay in the intensive care unit, the undertaken psychological assessments described a state of depression manifested by insomnia, sadness, crying and feelings of uselessness and frustration and prescribed dedicated medication. The emotional stress caused by total dependence on a machine for breathing might have also negatively affected ventilator weaning. She was weaned from mechanical ventilation at day 140 post-admission.

Gradually the antibiotic therapy was stopped, her white cell blood count was normal, and no new signs of infection developed in her last days in the intensive care unit.

She maintained normal respiratory function after being weaned from mechanical ventilation, and after

150 days post-admission, the patient was transferred from the intensive care unit to the neurology department. She presented with severe general atrophies, flaccid quadriparesis (grade 0/5 MRC in all muscles, except grade 3/5 MRC on the plantar flexor and 1/5 on the plantar extensor muscles), with a Guillain Barre syndrome disability Hughes scale of 4. Nerve conduction studies were repeated before her discharge which demonstrated the persistence of severe motor axonal damage with normal sensory parameters, conclusive for acute motor axonal neuropathy.

The patient was transferred to the hospital's rehabilitation unit.

Following physical exercise and specialised kinetic therapy, she was able to walk again without aid after twelve months. However, although the patient recovered most of her lower limb motor function, she remained with a deficit in the distal muscles of the upper limbs. This impairs her from being able to feed herself autonomously.

■ DISCUSSION

The acute immune-mediated neuropathies, known under the eponym Guillain-Barre syndrome, are a heterogeneous group of peripheral nerve disorders with several variant forms. Acute motor axonal neuropathy, part of the Guillain-Barre syndrome spectrum, although a rare form, is characterised by severe motor nerve fibres degeneration, frequently debilitating and life-threatening. An antibody causes acute motor axonal neuropathy and complement-mediated attack on the axolemma of the nerve roots and motor nerve fibres, as Hafer-Macko et al. (1996) demonstrated in an immunocytochemistry pathological study [10]. The re-myelination of damaged nerve fibres should occur in several weeks, but in some cases, there is significant axonal degeneration with severe motor weakness and incomplete recovery [11].

Guillain-Barre syndrome is a rare but potentially life-threatening polyneuropathy with known negative prognostic factors that influence the mortality rate [12]. The Guillain-Barre syndrome-associated mortality has been decreased by modern intensive care unit management [13,14, 15]. Van den Berg et al. (2013) demonstrated that the mortality risk factors in these patients were age, the severity of motor weakness at hospital admission, the need for mechanical ventilation and time to peak disability [16]. The current patient survived

and recovered from a severe form of acute motor axonal neuropathy, despite all the associated risk factors.

The studies showed that the central target regions in the Guillain-Barre syndrome are the Ranvier nodes [17]. The term 'nodopathy' describes an immune-induced neuropathy with a different aetiology in which the nodal region is affected by conduction block or axonal degeneration [18,19]. The nodal region is characterised by increased mitochondria density with high metabolic demand to sustain nerve activity, and energy depletion can explain the neurological clinical signs [20]. The pathophysiological mechanism of dysfunction in the excitable axolemma at the nodal/paranodal region, caused by a dysimmune aetiology, is characterised by conduction block and axonal degeneration [21]. The electrodiagnosis hallmark of axonal degeneration is reduced distal compound muscle action potential amplitude and the absence of any demyelinating features, such as conduction block [22,23]. Our reported case's severe and extensive axonal involvement explains the need for prolonged mechanical ventilation and intensive care unit stay, with a prolonged and incomplete recovery.

After being admitted to the intensive care unit, the patient developed autonomic dysfunction related to Guillain-Barre syndrome, including labile blood pressure, tachycardia and the secretion of antidiuretic hormone syndrome. The pathogenesis of antidiuretic hormone syndrome in patients with Guillain-Barre syndrome is poorly understood but seems related to interleukin 6 (IL-6), a pro-inflammatory cytokine that can increase vasopressin secretion. It has been observed that the number of mononuclear cells from blood that secrete IL-6 are increased in the early phase of Guillain-Barre syndrome [24,25]. The current patient improved after fluid restriction and daily monitoring and adjustment of serum sodium.

Complications in patients admitted to an intensive care unit with Guillain-Barre syndrome can be related to prolonged immobilisation, mechanical ventilation or in association with specific treatments. Netto et al. (2017) demonstrated in a ten-year retrospective study of Guillain-Barre syndrome patients admitted to an intensive care unit that infectious pulmonary complications were the most common and were correlated with higher mortality rates [26]. Therefore, active surveillance of this complication and early intervention can reduce the mortality rate and improve the prognosis and quality of life in these patients.

Acute motor axonal neuropathy developed four weeks after an influenza virus A H1N1 infection [27]. Previous studies showed that the influenza virus could trigger Guillain-Barre syndrome and demonstrated a strong association between Guillain-Barre syndrome and an influenza virus infection. This was seen to occur more frequently in the first 2-3 weeks, but the risk was significantly increased after sixty days following the infection [28,29]. Other studies from the AH1N1 pandemic described an increased risk of influenza virus infection-associated Guillain-Barre syndrome in paediatric populations [30]. Most of the time, an infectious event is noted in the weeks before the onset; in the current reported case, A H1N1 infection was documented one month before the onset of symptoms.

Guillain-Barre syndrome is an immune-mediated disorder of the nerve roots and peripheral nerves; therefore, the immune-modulating treatments are usually administered to stop the immune-mediated attack of peripheral nerves, improve outcomes, and prevent disability progression [31, 32]. Unfortunately, even though the patient in the current case was treated with immune globulin intravenously and plasma exchange, she had an inadequate response to immunotherapy treatment, needing prolonged intensive care support.

On the other hand, after four months of intensive physical rehabilitation, significant neurological improvement was noted. Previous studies have demonstrated no significant difference between plasma exchange and immune globulin intravenously for improvement on the Hughes Guillain-Barre syndrome disability grade scale. Despite immunotherapy, almost 20% of patients with Guillain-Barre syndrome cases are fatal or have a persistent disability [33].

■ CONCLUSION

This case highlights that acute motor axonal neuropathy is a severe and life-threatening form of the Guillain-Barre syndrome associated with significant mortality and morbidity. Therefore, the broad spectrum of the Guillain-Barre syndrome should be carefully assessed to manage the diagnostic and treatment protocol accordingly. Despite the critical state of the patient and prolonged stay in the intensive care unit, careful monitoring and early therapeutical interventions prevented infectious and immobilisation complications. The neurological and physical recovery is strongly dependent on the inter-professional effort in an intensive care unit.

■ CONFLICT OF INTEREST

None to declare.

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