Acute neuromuscular failure acquired in the community: A state-of-the-art review

Daniel Rebolledo-García1*, Jarumi C. Diestel-Bautista1, R. Óscar Gonzalez-Vargas2, and Guillermo S. García-Ramos1

1Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City; 2Department of Neuroperinatology, Hospital Materno Perinatal Mónica Pretelini Saenz, Toluca de Lerdo, State of Mexico, Mexico

Abstract

Acute neuromuscular failure (ANF) has become a common issue in emergency rooms worldwide. A systematic research was done in multiple data sources. A total of 350 articles were found, exclusion criteria were: not-neurological acute respiratory failure, case reports, duplication, and written in languages other than English or Spanish. One hundred and six abstracts of articles that included definition, epidemiology, etiology, physiopathology, and ANF diagnosis were considered, 70 were reviewed. Finally, 32 articles focused on decision-making by non-neurological medical staff were taken. Guillain-Barré syndrome seems to be the most common etiology for ANF in Mexico. Myasthenia gravis, autoimmune and oncologic diseases are also common causes for ANF. The clinical signs for an imminent neuromuscular failure are drop head, faltering speech, nasal voice, and sialorrhea. Early diagnosis of ANF leads to better ANF outcomes; it is necessary to establish an approach for the diagnosis in Mexico.

Keywords: Neuromuscular. Weakness. Approach. Emergency.

Falla neuromuscular aguda adquirida en la comunidad: Revisión del estado del arte

Resumen

La insuficiencia neuromuscular aguda (FNA) se ha convertido en un problema común en las salas de emergencia de todo el mundo. Se realizó una investigación sistemática en múltiples fuentes de datos. Se encontraron un total de 350 artículos, los criterios de exclusión fueron: insuficiencia respiratoria aguda no neurológica, informes de casos, duplicación y escritos en idiomas diferentes al inglés o al español. Se consideraron 106 resúmenes de artículos que incluían definición, epidemiología, etiología, fisiopatología y diagnóstico de FNA, 70 fueron revisados. Finalmente, se tomaron 32 artículos enfocados en la toma de decisiones por parte del personal médico no neurológico. El síndrome de Guillain-Barré parece ser la etiología más común de FNA en México. La miastenia gravis, las enfermedades autoinmunes y oncológicas también son causas comunes de ANF. Los signos clínicos de una insuficiencia neuromuscular inminente son cabeza caída, dificultad para hablar, voz nasal y sialorrea. El diagnóstico temprano de ANF conduce a mejores resultados de ANF. Es necesario establecer un abordaje para el diagnóstico en México.

Introduction

Acute neuromuscular failure (ANF) is a neurological emergency. Is defined as a clinical syndrome characterized by muscular weakness, which reaches its maximum severity in days or weeks (< 4 weeks). It could be the onset of a muscular, nerve, neuromuscular junction, or anterior horn of the spinal cord disease; or the progression of a previously known disease.

One of the most important clinical keys to consider is the time of progression of ANF, (defined as the time from weakness-symptoms onset to hospital admission). One of the prototypes of ANF is the Guillain Barré syndrome (GBS) which progression is significantly faster (< 7 days) but could a development in 4 weeks to reach nadir in the weakness that its possible require assisted mechanical ventilation (AMV). Due to the relevance of the timing to use AMV in these patients, ANF was included in predictive GBS models criteria developed by Sharshar et al. in 2003 and Walgaard et al. in 2010.

ANF is considered worse than failure secondary to primary lung disease, because could be more insidious, leading to life-threatening hypercapnia. The typical development of respiratory failure in ANF is mixed (hypoxia/CO2 retention), with almost an absolute hypoventilation.

The arterial blood gas is abnormal in advanced stages of ANF, so, is not accurate for detecting mechanical respiratory failure from motor weakness. Because ANF is a life-threatening emergency, its necessary discriminate neurological-origin ANF cases from those caused by respiratory failure associated with lung failure or systemic diseases (sepsis and multiple organ failure). In figure 1, we illustrate anatomical etiologies of ANF. In some cases, ANF can affect one or more sites.

Methods

A review of databases as PubMed, Mendeley, SciELO, and Google Academics were searched for English and Spanish language studies of ANF of adults from January 1, 2003, to August 1, 2020. We include one article with a previous date due to its clinical relevance. Three hundred abstracts were founded and excluded duplicated, non-English-Spanish language, case reports, and respiratory failure. Guidelines about epidemiology, diagnosis, and approach in ANF were not founded. The studies cited were focused on certain and well-known diseases as GBS or myasthenia gravis (MG). The strength of recommendation in level (quality) of evidence was selected with the GRADE system (High, moderate, low, and very low quality) (Fig. 2).

Findings

Epidemiology

Between 5 and 10% of patients hospitalized in the Intensive Care Unit (ICU) in the United States developed ANF. The most frequent causes of invasive mechanical ventilation (IVM) reported in ANF patients are MG (15-28%) and GBS (20-30%).

A Mayo Clinic cohort published in 2010 evaluated 85 patients admitted to ICU over 4 years and found that the most frequent diagnoses were MG, GBS, myopathies, and amyotrophic lateral sclerosis. The results showed that 45 patients (55%) had no diagnosis before admission, 36 (42%) had poor results in resolving ANF, and ten patients had no definitive diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>27 (32)</td>
</tr>
<tr>
<td>GBS</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Myopathies</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>2</td>
</tr>
<tr>
<td>o-sarcoglycanopathies</td>
<td>1</td>
</tr>
<tr>
<td>Toxic necrotizing myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Hypernatremic myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>1</td>
</tr>
<tr>
<td>Myopathy with anti-PRS antibodies (+)</td>
<td>1</td>
</tr>
<tr>
<td>Undetermined</td>
<td>5</td>
</tr>
<tr>
<td>ELA</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Post-polio syndrome</td>
<td>3 (4)</td>
</tr>
<tr>
<td>CIDP</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Polyradiculopathy secondary to East Nile virus infection</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Polyradiculopathy secondary to Amyloidosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Kennedy Syndrome</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Congenital myasthenic syndrome</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pseudocholinesterase deficiency</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>10 (12)</td>
</tr>
</tbody>
</table>

Adapted from Sharshar et al., 2003. CIDP: chronic demyelinating inflammatory polyradiculopathy, SRP: recognition signal protein.
Advanced age was a factor in increased mortality during hospitalization in this cohort. Patients with ANF and a known etiological diagnosis had a worse prognosis, and patients with an inconclusive diagnosis had

Table 2. Final diagnoses in patients with ANF-onset without neuromuscular disease on admission

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGB</td>
<td>12</td>
</tr>
<tr>
<td>ELA</td>
<td>8</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>4</td>
</tr>
<tr>
<td>Myopathies</td>
<td></td>
</tr>
<tr>
<td>Hypernatremic Myopathy</td>
<td>4</td>
</tr>
<tr>
<td>Toxic Necrotizing Myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Myopathy with anti-RS antibodies +</td>
<td>1</td>
</tr>
<tr>
<td>Indeterminate myopathy</td>
<td>1</td>
</tr>
<tr>
<td>CIDP</td>
<td>2</td>
</tr>
<tr>
<td>Polyradiculopathy secondary to West Nile virus</td>
<td>1</td>
</tr>
<tr>
<td>Post-polio syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Kennedy’s Disease</td>
<td>2</td>
</tr>
<tr>
<td>Pseudocholinesterase deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Probable botulism</td>
<td>1</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>1</td>
</tr>
<tr>
<td>Undetermined diagnosis</td>
<td>10</td>
</tr>
</tbody>
</table>

Adapted from Sharshar et al., 2003.
CIDP: chronic demyelinating inflammatory polyradiculopathy, SRP: recognition signal protein.
higher rates of disability. Tables 1 and 2 present this cohort’s final diagnosis as a guide in cases where there is an inconclusive etiology. Table 3 summarizes the etiologies of ANF in one of the biggest series in the literature.

The prevalence of ANF in Mexico is unknown. The most etiology reported of respiratory insufficiency is from secondary origin due to systemic disease who develop secondary muscle fatigue and deserve mechanical ventilatory support, associated or not with critical illness poly-myo-neuropathy. A study by Carrillo-Perez et al. describes 26 patients where the variant of acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN) of GBS were the variants with a presentation of ANF.

MG is a common neuromuscular disorder in Mexico. The study by Echeverría Galindo et al. showed a low prevalence of ANF presentations due to a myasthenic crisis. During the 60-month follow-up in this series (n = 43), the post-surgical thymectomy period in only three patients developed ANF. No more recent studies were founded that describe the behavior of MG in the ICUs in the country.

Pathophysiology in ANF

About 2/3 of the respiratory effort is performed at rest, therefore the diaphragm constitutes the main inspiratory muscle. This muscle has a parachute shape that sustain the basal lung region. Lung ultrasound studies in healthy subjects have reported measurements of its thickness from 1.5 to 3.2 mm. Features such as age, body phenotype and smoking did not affect diaphragm’s contractility, thus, there aren’t minimal differences between population groups.

Phrenic nerve innervated the diaphragm muscle (C3, C4, and C5 roots from cervical plexus). Muscle composition is 1:1 in long and fast muscle fibers for situations that require ventilatory frequency and rich vascular perfusion that makes the muscle resistant to fatigue.

The muscles that increased ventilatory work include external intercostals, scalene, and sternocleidomastoid. Exhalation occurs passively through an elastic recoil of the thorax and does not require an expenditure of energy. Forced expiration is performed in certain situations such as coughing and requires intercostal muscles and the abdominal wall muscles.

The respiratory effort might be influenced by conditions that affect the alveolar acinus and the larger airways. The remodeling and structural changes occur in lung diseases such as chronic obstructive pulmonary disease. Physiopathology in these cases consists in significant air entrapment, a structurally abnormal diaphragm, decreased inspiratory reserve, and they have a partially compensated respiratory load, which easily predisposes them to acute states of hyperventilation.

In the ANF state, the diaphragm strength decreases by 30% or less the normal function, that produce microatelectasis, tachypnea, and respiratory alkalosis with normal or reduced PaO2. Decrease in ventilation tends to increase physiological dead space and results in increased PaCO2 (hypercapnia), respiratory acidosis, and severe hypoxemia. If the patient develops bulbar dysfunction (dysphagia and oropharyngeal weakness by affection to IX and X cranial nerves) rise in respiratory failure and predicts early IVM.

Diagnosis

Key points to focus on are the breathing pattern and diaphragmatic failure signs (nasal flaring, intercostal retraction, accessory muscles use, thoracoabdominal paradox, and weak cough reflex). In the case of specific
diseases its necessary look facial symmetry, trapezius and sternocleidomastoid muscles, palatal velum, and the presence of drop head\textsuperscript{13} (Fig. 4).

Clinical neuromuscular weakness features are ortho-pnea, hypophonia (nasal voice), slurred speech (staccato speech), and abrupt interruption in the counting maneuver from 1 to 20. Jaw weakness can be observed by asking the patient to open his/her mouth, finding the sign of a depressed smile due to deficiency of the orbicular muscle of the mouth (the myasthenic “grunt”)\textsuperscript{14}. Other findings are the nasal voice, regurgitation, choking sensation, and sialorrhea, translating into a severe bulbar dysfunction to manage secretions and increased a high risk of bronchial aspiration. Frontal baldness and delicate facial features could suggest myotonic dystrophy.

Ptosis and ophthalmoparesis suggest MG or mitochondrial disorder. Fasciculations and stretching muscular reflexes increased suggest motor neuron disease; if the clinical exam finds paraspinal muscles weakness may suggest acid maltase deficiency, and a winged scapula leads to dystrophy diagnosis. A rash of sub-acute evolution can lead to dermatomyositis diagnosis. If the heart, liver, or kidney failure are affected, the possibility of metabolic myopathy or dystrophinopathy increases\textsuperscript{15}.

**Figure 3.** Role of atelectasis in acute neuromuscular failure. Created with BioRender.com.

**Figure 4.** The clinical phenotype of the patient with acute neuromuscular failure.
If the clinical status are being safe, the sensory system should be examined. Complete motor examination must be obeyed. Some causes of ANF are accompanied by neck muscles’ weakness, resulting in a drop head syndrome, which may be a criterion for deciding on early orotracheal intubation.

We should consider the time of evolution (chronic, acute, subacute), the continuity (episodic, fluctuating, linear), the accompanying fatigue (at rest, activities of daily living, exercise), the distribution pattern (proximal, distal, generalized). The physician should have asked if the patient had bulbar or ocular involvement (i.e., diplopia, ptosis), autonomic dysfunction (i.e., blood pressure, heart rate, gastrointestinal and skin involvement); rest, stress or intermittent dyspnea, decreased in ventilation with a circadian pattern, use of medications (i.e., chemotherapy, anti-tuberculosis agents, antibiotics, statins, ethanol, cocaine), recent immunizations and positive family history in first-degree parents.

Pre-existing comorbidities in the patient may lead the interview: if there is a history of malignancy, nerve or root infiltration may occur in lymphoma or metastatic carcinoma, and paraneoplastic syndromes, such as Lambert-Eaton syndrome, MG, or paraneoplastic motor neuronopathy, should be considered. Bone marrow transplantation may predispose to autoimmune conditions to consider. Other diseases are the spectrum of monoclonal gammopathy, a chronic demyelinating inflammatory polyneuropathy (CIDP), polynuropathy, endocrinopathy, organomegaly, monoclonal M-peak, skin changes syndrome, whose presentation is rarely acute, but rather chronic and progressive might have precipitated.

In the SARS CoV 2 pandemic course, multiple cases of GBS and Miller-Fisher variants have been documented. Reports published by Galassi et al. and Toscano et al. reported that the appearance of acute weakness was 7-10 days after respiratory symptoms; the most common variant of GBS was ascending palsy and bilateral facial weakness; a respiratory failure in the nadir of the weakness (days 4-6). Electrophysiological nerve conduction test findings are acute demyelinating polyneuropathy and less, an axonal pattern. There are several cases with sensitive involvement (axonal motor-sensitive acute neuropathy or AMSAN) that axonal motor acute neuropathy (AMAN). The diagnostic approach and treatment in these cases were similar to patients with non-COVID 19-associated GBS.

**Approach to ANF**

All patients with ANF should be admitted to the ICU or intermediate care units to monitorization; we keep in mind a low threshold early ventilatory support. Clinicians should keep in mind that a complete clinical evaluation can predict ANF with a sensitivity and specificity even higher than oximetry or arterial blood gas test.

In the case of GBS, the Erasmus GBS Insufficiency Score scale presents a sensitivity of 100% and specificity of 83% and area under the curve of 0.82, respectively for predicting ANF. Pulse oximetry is a simple and fast tool that monitors tissue oxygenation. By physiology, a SatO₂ > 90% is equivalent to 60 mm Hg PaO₂, which is essential for supplemental oxygen titration nasal prongs, mask, reservoir mask, or whatever is available at the time. However, an arterial blood gas test is necessary for the measurement of PaCO₂ due to low ventilation and the formation ofatelectasis (alveolar-arterial gradient in normal limits) and respiratory acidosis, hyperlactatemia, and worsened muscle function thus arterial blood gas test in these patients has a prognostic significance.

A retrospective study by Rabinstein et al. showed that early changes in arterial blood gas analysis (pH diminished, elevated carbon dioxide, bicarbonate increased) were associated with high mortality and worse functionality outcomes, especially in etiologies that are progressive and untreatable.

A chest X-ray should be requested to look for all primary pulmonary causes (or precipitants) of respiratory failure of pulmonary origin. The lung volumes evaluated are vital capacity (VC) and maximum inspiratory pressure in a spirometer test if the clinical status is adequate. Negative inspiratory force and maximum expiratory pressure are measures in patients with neuromuscular diseases in mechanical ventilation status.

In the hospital setting, the VC and the peak expiratory flow (PEFR) are the most widely used. VC is the maximum volume exhaled after an ultimate inspiration and reflects the expiratory muscle strength; it is dependent on age, gender, and height; when it is < 30 ml/kg of ideal weight, it is suggestive of muscle weakness in patients with neuromuscular disease.

Previously, we mentioned the use of a spirometer, which takes the maximum respiratory effort; if the patient presents facial weakness, using a mask may be necessary to avoid false negatives. Regular VC is 60-70 ml/
kg. When the VC decreases to < 30 ml/kg, the patient develops a weak cough reflex, accumulation of secretions, atelectasis, and hypoxemia. Extreme low ventilation occurs with CV < 10 ml/kg; onset of high CO₂ is developed with CV < 5-10 ml/kg. If the VC decreases by 20% standing up, diaphragmatic weakness is presented. There is broad experience with them in the GBS for surveillance and decision making for orotracheal
intubation in specialized centers in developed countries; in MG, their use is very variable, and no cut-off points have been validated for these patients.

As a summary, figure 5 lists the indications for orotracheal intubation to be considered for rapid decision making. Some special tests to be requested should be correlated with each particular case that can be performed.

A simple diagnostic approach includes CPK levels, LDH, aldolase, AST, and lumbar puncture. Some antibodies (i.e., anti-AChR, anti-MuSK, and anti-gangliosides), polymerase chain reaction (cytomegalovirus and other herpes virus family), serology (Lyme disease and brucellosis), or rapid test for HIV. In selected cases, peripheral nerve, muscle, neuroimaging, and biopsy may be requested.

**Conclusion**

New-onset ANF found in the emergency department must be focused on the patient’s context. Recognition of the main clinical symptoms can help initiate multi-organ support and the prompt reversal of the causes. Etiologies are variable in the different regions; however, the GBS is the leading cause of ANF in Mexico. Initial exams are available in all second-level hospitals (serum tests, lumbar puncture, serology, endocrinological tests) and diagnosis could be established in thirteen percent of cases. Finally, we propose an approach for the cases with ANF applicable in Mexican population (Fig. 6).

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**Conflicts of interest**

The authors declare that they have no conflict of interest.

**Ethical disclosures**

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References