Association between acute motor axonal neuropathy and septic shock due to Acinetobacter baumannii

Caso clinico di neuropatia acuta motoria assonale associato a shock settico da Acinetobacter baumannii

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INTRODUCTION

Molecular mimicry is an important pathogenic factor that is often involved in autoimmune diseases. It is a valid example of the similarity criterion, applied to the conventional medicine. This phenomenon was first proposed in 1968 by George Snell, who hypothesized that germs could have one or more antigens in common with individual glycoproteins [1]. A mechanism of molecular mimicry by the lipopolysaccharide of the gastrointestinal pathogen Campylobacter jejuni is to date hypothesized to be involved in the development of the Guillain-Barré syndrome and its acute motor axonal neuropathy (AMN) variant. In particular, it is postulated that the immune response to ganglioside-like structures of the lipopolysaccharide identifiable in some Campylobacter jejuni strains can cross-react with human nerve gangliosides, leading to development of the clinical syndrome [2, 3].

In this report, we describe an unusual case of AMAN following septic shock due to Acinetobacter baumannii.

CASE REPORT

A 25 year old Italian man, employed as a humanitarian aid worker in Nepal, was transferred to our Intensive Care Unit from the Hospital of Kathmandu, where he had been hospitalized one week earlier because of rapidly developing weakness of all four limbs. His history was unremarkable, except for the onset of fever, sore throat, and dry cough 10 days before hospitalization. During the stay in the Nepalese facility, empirical antibiotic therapy with intravenous meropenem 3 g TID and oral azithromycin 500 mg OID had been started because of fever, radiological signs of bilateral lower lobe consolidation, and borderline leukocytosis (10x10^3 mL) with neutrophilia (81%). Because of progressive respiratory distress and hypotension, mechanical ventilation and dopamine infusion had been started. Cerebrospinal fluid analysis had revealed a slightly elevated protein concentration (42 mg/dL) without pleocytosis. Intravenous immunoglobulin administration had been started at a dose of 0.4 g/kg per day.

Upon admission at our Intensive Care Unit, there was marked proximal and distal muscles weakness with flaccid tetraplegia, facial diplegia, absence of tendon reflexes, and no sensory disturbances. There was no fever, and the patient was under mechanical ventilation and dopamine infusion because of respiratory failure and hypoten-
sion with oliguria. Chest X-ray confirmed evolving regions of consolidation in both lower pulmonary lobes. A bronchoalveolar lavage revealed positivity for a multidrug-resistant *A. baumannii* infection. The strain was resistant to all antibiotics tested including carbapenems. It was sensitive only to colistin, and intermittently sensitive to tobramycin and piperacillin/tazobactam.

The subsequent characterization of the genome, performed by repetitive sequence-based PCR (rep-PCR, DiversiLab, bioMérieux) showed that the strain was not similar to any *A. baumannii* previously isolated in our Department and in the whole region of Florence, supporting the hypothesis that the organism was already present at admission in our Unit.

Treatment with intravenous colistin sulphomethate sodium was started (1 MU TID). Electroneurographic examination showed lack of compound muscle action potentials from all limbs with the exception of a low-amplitude response from the right peroneal nerve, suggesting motor nerve axonal impairment. Distal motor latency, motor conduction velocity, and sensory nerve conduction parameters were all normal. Needle examination revealed sporadic fibrillation potentials. Positive titers of anti-GM1, GD1b, and GD1a IgG were found by an ELISA test. A diagnosis of AMAN with *A. baumannii* pneumonia was made. Plasmapheresis was started on day 8.

Three months after the onset of the disease, the patient showed respiratory autonomy and was haemodynamically stable without drugs. He was transferred to a rehabilitation facility, where clinical conditions gradually improved during the following weeks. After 9 months from discharge, the patient showed a complete recovery of muscular function.

**DISCUSSION**

AMAN is a variant of Guillain-Barré syndrome characterized by acute onset of flaccid, symmetrical, ascending paralysis with areflexia, and relative preservation of sensory functions [3]. Weakness may involve dysphagia, dysarthria, facial diplegia, flaccid quadriplegia, and respiratory failure. Pathologically, the disease is a non-inflammatory antibody-mediated, complement-dependent axonopathy with normal motor conduction velocity and latency, reduced amplitudes of compound muscle action potentials indicating axonal degeneration, and absence of demyelinating features with normal sensory potentials. Although the pathogenesis is still unclear, an association with antecedent infection by *Campylobacter jejuni* and IgG autoantibodies against gangliosides is to date hypothesized, as AMAN patients commonly show antibodies to *C. jejuni*, anti-GM1, and anti-GD1 [4]. The presence of specific ganglioside-like moieties in the lipopolysaccharide (LPS) of *C. jejuni* suggests that molecular mimicry between the LPS and gangliosides may play a role in the pathogenesis of AMAN by triggering the production of anti-ganglioside autoantibodies or T-cells [5]. Phenomena of molecular mimicry in AMAN subjects have been reported for several serotypes of *C. jejuni*, but also for other microorganisms (e.g., *Campylobacter coli*, *Brucella melitensis*, *Cytomegalovirus*, and *Mycoplasma pneumoniae*) [6].

*A. baumannii* is a Gram negative, non-motile, rod-shaped bacterium whose progressive spread is gaining more and more attention worldwide. To date, it causes approximately 2% to 10% of all Gram-negative bacterial infections observed in the US and Europe [7]. Major risk factors for infection by *A. baumannii* include invasive procedures, open wounds, long-term hospitalization, as well as use of antimicrobial agents [8]. Although both skin to skin contact and food colonization have been proposed as possible routes of transmission, the primary mean is hypothesized to be colonization of abiotic surfaces, e.g., plastic catheters or mechanical ventilators [9-11]. Interestingly, *A. baumannii* was the bacterium most commonly isolated from open wounds in the Vietnam war [12]. Similarly, it has been hypothesized that the subsequent infection outbreak occurred among US soldiers serving in Iraq and Afghanistan regions during the years between 2002 and 2004 was in most cases driven by infection of open wounds [13]. As other similar species, *A. baumannii* shows a multiple-layer cell envelope, including an outer membrane and an inner cytoplasmic membrane, separated by a periplasmic space [14]. Some unique characteristics explain its ability to rapidly develop antibiotic resistance, including the small amount of porins - membrane channels that mediate a number of functions, including adhesion to other bacterial cells and penetration of antibiotics across the bacterial membrane - the ability to
increase the expression of multiple efflux pumps, allowing to remove antibiotic or antimicrobial agents detrimental to the bacterium, and the ability of acquire foreign DNA from the environment, including plasmids with several antibiotic resistance genes.

From a clinical point of view, *A. baumannii* often infects the respiratory tract, leading to severe cases of pneumonia with relatively high mortality rate [15]. Other clinical presentations include wound infection, meningitis, urinary tract infections, sepsis or septic shock. Treatment of these infections may be difficult as a result of resistance to most classes of antibiotics: imipenem proved to be effective in most cases, whereas administration of colistin is a valid alternative in case of imipenem resistance [16].

Since the bacterium does not produce any known cytotoxic and possesses only a limited number of virulence factors, it has been hypothesized that this fulminant course may reflect an exaggerated host response to the endotoxin - LPS of *A. baumannii* [17]. The ability of endotoxins from other bacteria (e.g., *Escherichia coli*, *Neisseria meningitidis*, and so on) to trigger a vigorous systemic inflammation is well established, and is known to depend on the fact that endotoxins stimulate white blood cells to release pro-inflammatory cytokines. Detection of endotoxines typically occurs via specific pattern-recognition receptors, like the Toll-like receptor (TLR-4) and the MD-2 [18]. In particular, the lipid A is a lipid component of an endotoxin held responsible for toxicity of Gram-negative bacteria. It is the innermost of the three regions of the LPS, and its hydrophobic nature allows it to anchor the LPS to the outer membrane. Lipid A with six acyl groups (hexa-acylated form) has been indicated to be a strong stimulator of the TLR4/MD-2 complex. This type of lipid A is conserved among a wide variety of Gram-negative bacteria, and those bacteria are easily recognized by host cells for activation of defensive innate immune responses [19]. Though little is known about the endotoxic potential of *A. baumannii*, its LPS seems to have some characteristics in common with those of both *Campylobacter jejuni* and *Escherichia coli*, namely the presence of Lipid A with six acyl groups and so a high capacity to activate the human system TLR4/MD2 [20]. This report is the first to describe a case of AMAN syndrome in a patient with septic shock due to *A. baumannii*. Though causality cannot be demonstrated, the possibility that the infection by *A. baumannii* may have favored the development of the neurological picture via a mechanism of molecular mimicry should be taken into account.

**Keywords:** acute motor axonal neuropathy (AMAN), *Acinetobacter baumannii*, septic shock.

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**SUMMARY**

In this report, we describe a case of acute motor axonal neuropathy (AMAN) following septic shock due to *Acinetobacter baumannii*. The aetiology of AMAN is still not fully clarified. An association with a potential infection by *Campylobacter jejuni*, resulting in stimulation of autoimmune response against gangliosides mediated by a phenomenon of molecular mimicry, is believed to play a major role. Since the lipopolysaccharide of *A. baumannii* has a structure that is similar to that of *C. jejuni*, we hypothesise that the infection by *A. baumannii* in our patient may have had a pathogenic role in the development of the neurological picture via a mechanism of molecular mimicry.

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**RIASSUNTO**

In questo report, descriviamo il caso clinico di un paziente con sindrome da neuropatia acuta motoria assonale (AMAN) associata a un quadro di shock settico da *Acinetobacter baumannii*. L’etiologia dell’AMAN è tuttora non del tutto chiarificata. Si ritiene che un ruolo maggiore sia svolto dall’associazione con una potenziale infezione da *Campylobacter jejuni*. La struttura del lipopolisaccaride (LPS) della parete di *A. baumannii* presenta analogie con quella del LPS di *C. jejuni*. Pertanto avanziamo l’ipotesi che, nel nostro paziente, l’infezione da *A. baumannii* abbia potuto giocare un ruolo patogenetico nello sviluppo del quadro neurologico mediante un meccanismo di mimetismo molecolare.
REFERENCES


