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Are anti-ganglioside antibodies detectable in serum from patients with critical illness myopathy and polyneuropathy?

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SUMMARY

Introduction: Critical illness myopathy (CIM) and polyneuropathy (CIP) are the most common cause of acquired weakness in intensive care units (ICU). However, its exact pathogenesis remains unclear. Abnormal excitability of muscle due to a sodium channelopathy is one of the mechanisms proposed. The aim of this study is to test for the presence of anti-ganglioside antibodies in serum from patients with CIM or both combined CIM/CIP, since there is evidence that they can cause reversible dysfunction of voltage-gated sodium channels.

Methods: In a prospective way, we studied 35 patients admitted in ICU by weekly EMG. When positive spontaneous activity (PSA) was detected, a muscle biopsy was performed. Twenty patients met criteria of CIM; five of them also developed overlapping CIP. We did not detect any kind of abnormality in 10 patients during the follow up period. Sera were analyzed for the presence of anti-ganglioside antibodies (Ganglioside-profile 2 Euroline, Euroimmun).

Results: Overall, positive reactivity against anti-GT1b was found in one patient with CIM, representing 2.8% (1/35) of the total sample.

Conclusion: Reduced percentage of patients affected of CIM or CIM/CIP exhibits positive reactivity against anti-ganglioside antibodies. Thus, it could be suggested they do not play a primary role in their pathogenesis.

Key words: Critical illness myopathy, critical illness polyneuropathy, difficult weaning, channelopathy, muscle fiber inexcitability, anti-ganglioside antibodies

INTRODUCTION

Critical illness myopathy (CIM) and polyneuropathy (CIP) was first described in patients treated intensively for status asthmaticus with intravenous corticosteroids and neuromuscular junction-blocking agents⁽¹⁾ as well as in patients with sepsis and multiorgan failure who received assisted ventilation^(2,3) Since then, they have been recognized as the most common cause of acquired weakness in critically ill patients⁽⁴⁾ Its incidence is unknown so that it depends on different factors: specific intensive care unit subpopulation, diagnostic criteria used and time of diagnosis during the acute illness⁽⁵⁾. There has been reported an incidence of 34-60% in patients with acute respiratory distress syndrome^(6,7), 56-80% in those with multiorgan failure with or without sepsis or systemic inflammatory response syndrome (SIRS) and up to 100% in patients with septic shock⁽⁸⁾. According to the previous data, severity of illness⁽⁹⁾ and duration of multiple (\geq two) organ dysfunction with or without SIRS^(10,11) have been identified as independent risk factors in prospective studies. Duration of ICU stay, low serum albumin⁽¹²⁾ and hyperglycaemia⁽¹³⁾ have also been described as independent risk factors.

CIM and CIP usually share the same clinical features. They present with limb and respiratory muscle weakness, frequently leading to a failure to wean from mechanical ventilation. Overall, both cause severe disability after critical illness, involving short and long term implications on the outcome of patients affected. CIP has been associated with increased duration of mechanical ventilation, length of ICU and hospital stay⁽¹⁴⁾ Nearly a third of patients with CIP, CIM or both do not recover independent walking or spontaneous ventilation⁽¹⁵⁾; furthermore, they are thought to be the leading cause of disability in patients who survive from acute respiratory distress syndrome⁽¹⁶⁾ According to the findings from the 1-year follow-up in the CRIMYNE study, CIP might be the main contributor to persistent disability, while CIM should be associated with a faster recovery⁽¹⁷⁾ Despite this striking impact on the

outcome of critically ill patients, the exact pathogenesis of CIM and CIP is unknown. Data published until nowadays suggest that multiple pathophysiological mechanisms are involved. In the theater of a critically ill patient with a probable concomitant sepsis and under steroids and neuromuscular blocking agents, metabolic and hormonal (hyperglycemia and insulin resistance) disturbances developed leading to energetic failure. On the other hand, several studies provide experimental and clinical evidence of a dysfunction (hypoexcitability or inexcitability) of nerves^(18,19) as well as muscle membrane^(20,21,22) due to an acquired channelopathy with sodium channel inactivation^(18,23,24,25,26) Circulating depolarization factor (CDF)⁽²⁷⁾ and an endotoxin that reduces muscle sodium channel availability at depolarized membrane potentials⁽²⁸⁾ have been proposed as etiopathogenic agents^(27,28)

The relationship between anti-glycolipid antibodies and acute neuropathy has been studied since late nineties⁽²⁹⁾. It has been demonstrated that ganglioside GM1 is enriched in nodal and paranodal structures, where it has regional co-localization with sodium and potassium channels⁽³⁰⁾. Furthermore, autopsy studies of AMAN cases have shown immunoglobulin and complement deposits localized at the node of Ranvier where sodium channels are clustered, and at the internodal axolemma⁽³¹⁾ Electrophysiological studies on anti-GM1 antibody-mediated nerve injury have shown variable and divergent results; nonetheless, *Takigawa et al.* found that rabbit anti-GM1 antibodies increased potassium current elicited by step depolarization, and in the presence of active complement blocked sodium channels irreversibly⁽³²⁾. More recently, *Weber et al.* reported that IgG anti-GM1 antibodies, raised in rabbits, could reversibly block the voltage-gated Na⁺ current, specially, in the presence of complement⁽³³⁾ From a clinical point of view, *Kuwabara et al.* measured indices of axonal excitability in patients with AMAN and AIDP; they found an increase of refractoriness in AMAN but not in AIDP

patients, which was reversible during four weeks period from onset⁽³⁴⁾.

Taking into account that sepsis is one the main risk factor for CIM and CIP, relevant evidence concerning the carbohydrate mimicry between both human ganglioside GM1 and sodium channel and *Campylobacter jejuni* lipo-oligosaccharide has been reported. *Yuki et al.* suggested that the carbohydrate mimicry between human ganglioside GM1 and *Campylobacter jejuni* lipo-oligosaccharide might be the cause of Guillain-Barré syndrome in certain patients⁽³⁵⁾. On the other hand, molecular mimicry between alfa subunit of Nav channel and Kdo2-Lipid A present in *Campylobacter jejuni* and other gram negative bacteria such *E. Coli* has been demonstrated⁽³⁶⁾. *Usuki et al.* found that sera from immunized chicken with anti-ganglioside antibodies and anti-Kdo2-Lipid A could inhibit muscle voltage-gated Na (Nav1.4) channels by patch-clamp analysis⁽³⁷⁾.

Previous data suggest that acute immune-mediated neuropathies (mostly AMAN) share critical pathogenic features with CIP/CIM, and set the rationale base for this study, whose main goal is to test for the presence of anti-ganglioside antibodies in sera of patients diagnosed of CIM/CIP, as a first step to determine if they should play a role in their pathogenesis.

PATIENTS AND METHODS

The candidates for this prospective study were identified in daily screening log in the Department of Intensive Care Medicine, University Hospital Germans Trias i Pujol, Barcelona. Patients were eligible if they were at least 18 years old, presented a score ≥ 6 in the Sepsis-related Organ Failure Assessment (SOFA) index⁽³⁸⁾ while they were under mechanical ventilation and a stay in ICU longer than 2 weeks. Exclusion criteria were documented history of prolonged immobility or neuromuscular disease and peripheral neurological (neuropathy, neuromuscular junction pathology or myopathy) or spinal cord disorders as reason of admission in the ICU.

We obtained written informed consent from the surrogate decision maker within the four days after admission. Ethics approval was provided by the Ethics Committee of Hospital Universitari Germans Trias i Pujol.

Apache II score was calculated in all patients at the moment of their admission in ICU⁽³⁹⁾

All patients included underwent an electrophysiological evaluation (5 channels Medelec Synergy equipment, Vyasis Healthcare, UK) at the moment of their inclusion and weekly during their stay in the ICU until they were extubated or died.

Nerve conduction studies were performed from motor (median, peroneal and posterior tibial) and sensory (radial and sural) nerves using conventional procedures. Repetitive stimulation at 3 Hz (median nerve with recording from the abductor pollicis brevis or accessorius nerve with recording from the trapezius muscle) was done in all patients to screen for neuromuscular transmission defects. Coaxial needle electromyography of tibialis anterior, quadriceps and deltoids muscles was performed at multiple insertion points in order to detect pathological spontaneous activity (PSA) and to analyze motor unit potentials features, if the consciousness level and degree of muscle weakness of the patient allowed their recording.

When pathological spontaneous activity (PSA) was detected in the needle electromyographic study, a biopsy of the quadriceps muscle (*Bergström needle*) was performed within the next 24-48 hours, whenever coagulation study and platelet count were normal. For electron microscopy evaluation, muscle biopsy specimens were fixed in glutaraldehyde, postfixed in osmium tetroxide and embedded in Epon. Thin sections were stained with uranyl acetate and lead citrate and examined with transmission electron microscope (JEOL 1010). Although early fiber IIa atrophy and varying degrees of fiber necrosis have been described as signs of primary myopathy in CIM, selective loss of thick (myosin) filaments has been considered

as the main CIM diagnosis criteria from the histological point of view⁽⁴⁰⁾ (Figure 1)

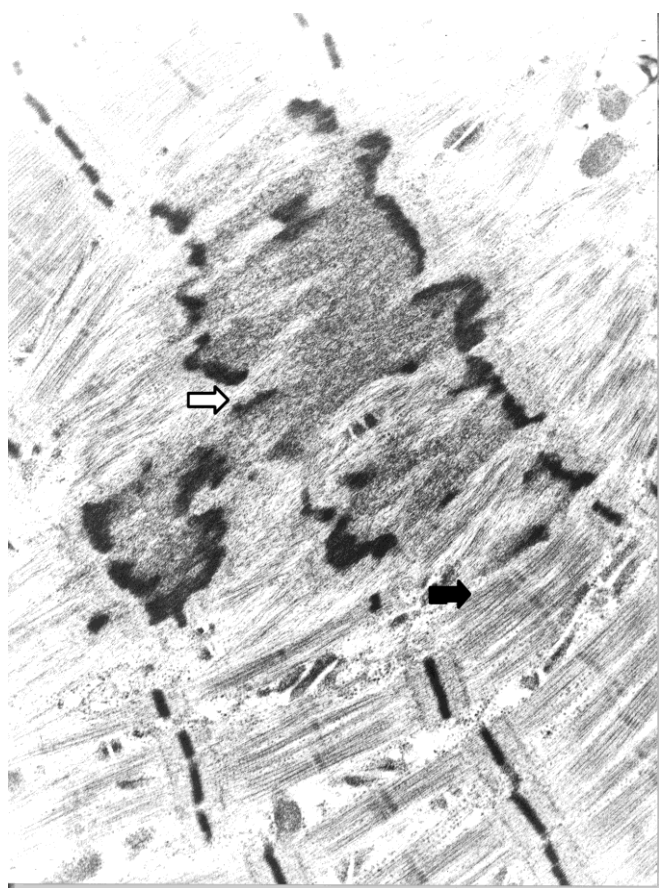


Figure 1: Uranil acetate stain electron microscopy showing selective loss of thick myosin filaments

CIP was diagnosed by electrophysiological criteria, when a complete loss of both SNAPs and CMAPs was detected. Muscular strength, according MRC scale, was measured one day immediately after cessation of mechanical ventilation and every month until normal muscular strength was achieved.

Those patients without any kind of abnormality in electrophysiological studies performed during the follow-up period acted as a control group. Venous blood samples were extracted simultaneously with each EMG performed and the serum obtained was cryopreserved (-80°C).

Sera from both patients diagnosed of CIM, combined CIM and CIP and controls were tested for the presence of antibodies against gangliosides. We selected the serum sample obtained during the first EMG study where PSA was detected in CIM patients. In the control

group, we chose the serum extracted two weeks after their admission, which represents the period with highest likelihood of CIM/CIP development (unpublished observations).

All samples were analyzed by a qualitative method, *Profile 2 Euroline, Euroimmun*, (Lubeck, Germany). Most of antigen substrates used were from bovine brain, except the GM3 antigen that was from dog erythrocytes. This test specifically detects IgG and IgM class antibodies to GM1, GM2, GM3, GD1a, GD1b, GT1b and GQ1b. No cross reactions with other autoantibodies have been found. Interferences have not been demonstrated with haemolytic, lipaemic and icteric sera. The blot strips were incubated in a first reaction step with diluted patient serum (1:51). In the case of positive samples, specific antibodies of the class IgG and IgM will bind to the antigens. To detect the bound antibodies, a second incubation was carried out using an enzyme-labelled anti-human IgG/IgM (alkaline phosphatase-labelled anti-human IgG/IgM, goat, 10x concentrate), which is capable of promoting a colour reaction. Finally, a third incubation with substrate solution was done before placing the test strip on the evaluation protocol. This is a qualitative method: based on signal intensity, the results can be divided into negative, borderline and positive (mild, moderate and strong) results. Sera from clinically characterized patients with Guillain-Barré syndrome (GBS) (n=71), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (n=13), multifocal motor neuropathy (MMN) (n=18) and Miller-Fisher syndrome (MFS) (n=5), as well as sera from 60 healthy blood donors were investigated for IgG and IgM class antibodies against gangliosides GM1, GM2, GM3, GD1a, GD1b, GT1b and GQ1b. Antibodies against gangliosides were detected in 16 of the GBS sera (23%), 5 of the CIDP sera (38%), 8 of the MMN sera (44%) and 4 of the MFS sera (80%; exclusively autoantibodies of class IgG against GQ1b). Eleven blood donors (18%) were positive for IgM antibodies against GM1 (3%) or against GM2 (15%). Autoantibodies against the other

gangliosides did not occur in healthy persons (Table 1)

Table 1. Prevalences of autoantibodies against gangliosides (%). Meyer W. et al., Autoimmunity reviews 1: 71 (2002)

Patient group	Ig-class	GM1	GM2	GM3	GD1a	GD1b	GT1b	GQ1b
GBS(n=71)	IgG	6	1	0	0	1	0	1
	IgM	13	10	1	1	3	3	1
CIDP(n=13)	IgG	0	0	8	0	0	0	0
	IgM	0	8	15	23	8	0	0
MMN(n=18)	IgG	0	6	6	0	0	0	0
	IgM	28	22	17	11	11	6	0

GBS: Guillain-Barré Syndrome; CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; MMN: Multifocal motor neuropathy

RESULTS

A total of 35 patients were included (24 males, 11 females; mean 61 years). The most frequent reason of ICU admission was sepsis (17/35, 48.5%), followed by pancreatitis (7/35, 20%) (Table 2).

Table 2. Clinical characteristics of patients

ID	Age(yrs) /Sex(M/F)	Reason of admittance	Day Fib	Neuromuscular Diagnosis	Infection	ICU Stay (d)	Mechanical Ventilation Time (d)	Exitus
51	45/M	Hepatic encephalopathy	1	CIM+CIP	Unknown	12	12	YES
20	49/M	Respiratory insuficiency	2	CIM+CIP	G+/G-	38	23	YES
27	59/M	Haemorrhagic shock		CIM+CIP	Unknown	32	9	YES
35	49/M	Sepsis	7	CIM+CIP	Fungal	41	11	YES
42	73/M	Traumatic	29	CIM+CIP	None	34	34	YES
34	71/M	Pancreatitis	10	CIM	G-	75	76	YES
48	78/F	Sepsis	1	CIM	Unknown	13	13	YES
46	60/M	Pancreatitis	9	CIM	G-	21	17	YES
22	65/M	Pancreatitis	13	CIM	Virus(CMV)	32	21	YES
23	64/F	Pancreatitis	14	CIM	G-(2)	52	52	YES
37	67/F	Sepsis	7	CIM	G+	14	11	NO
44	64/M	Pancreatitis		CIM	G+/G-	22	13	NO
32	24/M	Traumatic	32	CIM	G+/G-	52	52	NO
18	61/F	Sepsis	13	CIM	G+(2)/G-	66	68	NO
16	50/F	Sepsis	21	CIM	G-(3)	73	66	NO
8	72/M	Sepsis	2	CIM	G+	10	9	YES

15	78/F	Sepsis	12	CIM	G+	36	34	NO
58	54/M	Sepsis	1	CIM	Unknown	29	13	YES
59	66/F	Respiratory insufficiency	1	CIM	G+/G-	29	22	NO
33	70/M	Respiratory insufficiency	12	CIM	G-	90	85	NO
45	71/M	Sepsis	14	CIM	G- / Fungal	54	41	NO
53	76/M	Sepsis	9	CIM	G-(2)	42	28	NO
12	25/F	Traumatic	12	CIM	G-	21	21	NO
57	55/M	Sepsis	11	CIM	Unknown	18	19	YES
55	78/F	Sepsis	5	CIM	G+	22	13	NO
38	48/F	Pancreatitis	---	Normal	G+	40	7	NO
49	46/F	Graft vs host	---	Normal	G+	13	9	NO
31	59/M	Sepsis	---	Normal	G-	14	9	NO
40	23/M	Pancreatitis	---	Normal	Unknown	19	17	NO
39	77/M	Sepsis	---	Normal	Unknown	13	8	NO
21	71/M	Sepsis	---	Normal	G-(3)	14	11	NO
24	74/M	Respiratory insufficiency	---	Normal	G+	15	16	YES
25	84/M	Sepsis	---	Normal	G-	9	5	NO
39	77/M	Sepsis	---	Normal	Unknown	13	8	NO
52	71/M	Meningitis	---	Normal	G+	14	7	NO

Yrs: years, M: male, F: female, "Day Fib": Days from admission until fibrillation potentials were detected in EMG study. "Infection": Type of germs isolated in blood, urine or sputum. G+: Gram positive, G-: Gram negative, G+/G-: both types of germs, Virus, Fungal, Unknown or None. "Neuromuscular diagnosis": CIM: Critical Illness Myopathy, CIP: Critical Illness Polyneuropathy. ICU: Intensive Care Unit

In 23 patients, the first EMG abnormality encountered was the presence of fibrillation potentials. Muscle biopsy could be performed in 20 of them, showing typical pathological changes of critical illness myopathy in the electron microscopy examination (Figure 1). Two patients also exhibited histological features suggestive of CIM, despite fibrillation potentials were not detected during EMG studies performed during the follow-up period. Conversely, none of the patients with normal muscle biopsy presented PSA. Five patients were diagnosed of overlapping CIP/CIM according to the criteria previously stated.

In 10 patients we did not detect any abnormality during the electrophysiological evaluation, acting as a control group. Muscle biopsy only was performed in two of them, without any type of pathological abnormality.

Overall, mortality was 40% (14/35). Control group patients who survived (9/10) reached normal muscular strength before from those survivors from CIM/CIM+CIP patients group (13/25) (Z-score 3,8021; $p < 0,01$) (Table 2)

Moderate IgM reactivity against GT1b ganglioside was found in one patient diagnosed of CIM without CIP (2.8%) (Figure 2). She was a 78 years old woman (patient number 17) who was admitted in ICU because of sepsis by staphylococcus aureus after infection of her knee prosthesis. CIM diagnosis was made on the 12th day after her admission. She required of mechanic ventilation for 34 days. She reached normal muscle strength 101 days after she was discharged of ICU.

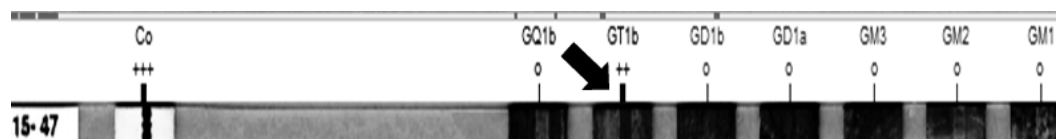


Figure 2. Immunostaining showing GT1b anti-ganglioside reactivity

DISCUSSION

Antibodies against gangliosides GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b are detectable in a reduced percentage of patients affected of CIM or CIM/CIP in our series. Despite all patients selected had a SOFA index score ≥ 6 , because severity of illness has been identified as an independent risk factor for CIM/CIP⁽⁹⁾, we only found moderate reactivity IgM against GT1b ganglioside in one patient diagnosed of CIM without CIP. GT1b is prominent in cultured dorsal root ganglion neurons⁽⁴¹⁾ Reactivity against disialylated gangliosides, included GT1b, as well as GD1a and GM3, has been associated with chronic sensory ataxic neuropathy with relative preserved motor function in the limbs⁽⁴²⁾ and bulbar involvement, which seems to be related to reactivity against NeuNAc(α 2-3)Gal, terminal epitope shared by GT1b, GM3 and GD1a gangliosides⁽⁴³⁾. Thus, the absence of sensory neuropathy assessed by EMG criteria in the patient with moderate reactivity against IgM class GT1b ganglioside antibody makes this finding unreliable from the pathogenic point of view. Furthermore, *Rojas-Garcia et al.* reported that reactivity against gangliosides containing disialosyl groups, in addition to antibodies against GM3, GD1a and GT1b, is more commonly found than isolated reactivity⁽⁴⁴⁾

Antibodies against ganglioside GT1b were detected in 3% of patients with GBS (n=71) and 6% of patients with MMN (n=18) by means of the test employed in this study. They were not detectable in Miller-Fisher syndrome patients (n=5) neither in healthy blood donors (n=60). Nonetheless, IgM antibodies to GT1b, GM3 and GD2 were found in healthy volunteers during a study designed to determine whether they might be a marker of tumor burden and predict the

clinical outcome of patients with soft tissue sarcoma⁽⁴⁴⁾

Despite it should not be expected anti-gangliosides antibodies play a primary role in the pathogenesis of CIM/CIP according to the results obtained, we have to consider two limitations of this study: sample size and method used for testing anti-ganglioside antibodies in sera. Enzyme-linked immunosorbent assay (ELISA) is the principal method for antibody detection. Moreover, standardized ELISA method between laboratories within the European Inflammatory Neuropathy Cause and Treatment (INCAT) group was established in order to avoid the wide variations between in assay performance between laboratories⁽⁴⁵⁾ However, *Caudie et al.* found anti-GT1b antibodies in 3.6% (9/249) of consecutive patients admitted with Guillain-Barré syndrome by means of ELISA, similar to the results obtained with the test employed in our study.

The involvement and failure of other organs and the strong association with sepsis and systemic inflammatory syndrome (SIRS) has raised the hypothesis as to whether critical illness polyneuropathy and myopathy is only a part of a systemic illness. It has been proposed that microcirculation disturbances and pro-inflammatory cytokines lead to a cascade of electrical, bioenergetic, inflammatory and proteolytic pathway system alterations whose final consequence is the clinical, electrophysiological and pathological setting of CIP/CIM⁽⁴⁶⁾. Thereby, as a result of this high coexistence of sepsis and multiorganic failure, the treatment with immunoglobulin (IVIg) of this pathology has been debated over the last decade. There is some evidence that IVIg have survival benefit in critical ill patients with

sepsis⁽⁴⁷⁾ but over CIM/CIP there are opposing opinions, all of them based on open studies and case series⁽⁴⁸⁾. The results obtained in our prospective study do not provide evidence to support the use of immunoglobulin as a treatment for CIM/CIP. Nonetheless, we are cautious to raise any therapeutic conclusion because of our study limitations.

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