Revista Médica de Trujillo

Publicación oficial de la Facultad de Medicina de la Universidad Nacional de Trujillo - Perú

Artículo Original

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

A. Martínez-Piñeiro[1], A. Ramos Fransi[1] M.Almendrote Muñoz[1], G. Lucente[1], E. Martinez Caceres[2], I Ojanguren Saban[3], H. Perez Molto[4], Vitoria Rubio S, [4], J. Coll-Canti[1]

1Department of Neurology, Hospital Universitari Germans Trias i Pujol, Badalona, (Barcelona), Spain
2Inmunology Laboratory for Researching and Diagnosis Aplications (LIRAD) Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona (Barcelona), Spain 3Department of Pathology, Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain
4Critical Care Unit, Department of Intensive Care Medicine, Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain
Universitat Autonoma of Barcelona

Correspondencia. Alicia Martínez Piñeiro, MD

Hospital Universitari Germans Trias i Pujol

Phone: 34.934978911/34.934978916

Fax: 34.934978742

amartinezp.germanstrias@gencat.cat

Recibido: 05/01/20

Aceptado: 20/01/20

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 reactive 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 polineuropathy, difficult weaning, channelopathy, muscle fiber inexcitability, anti-ganglioside antibodies

DOI: http://dx.doi.org/10.17268/rmt.2020.v15i01.04

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 unkown 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 (≥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 inhibite muscle voltage-gated Na (Nav1.4) channels by patch-clamp analysis[37].

Previous data suggest that acute immune-mediated neurophaties (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 counsciousness 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 uranil 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

 DOI: http://dx.doi.org/10.17268/rmt.2020.v15i01.04

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

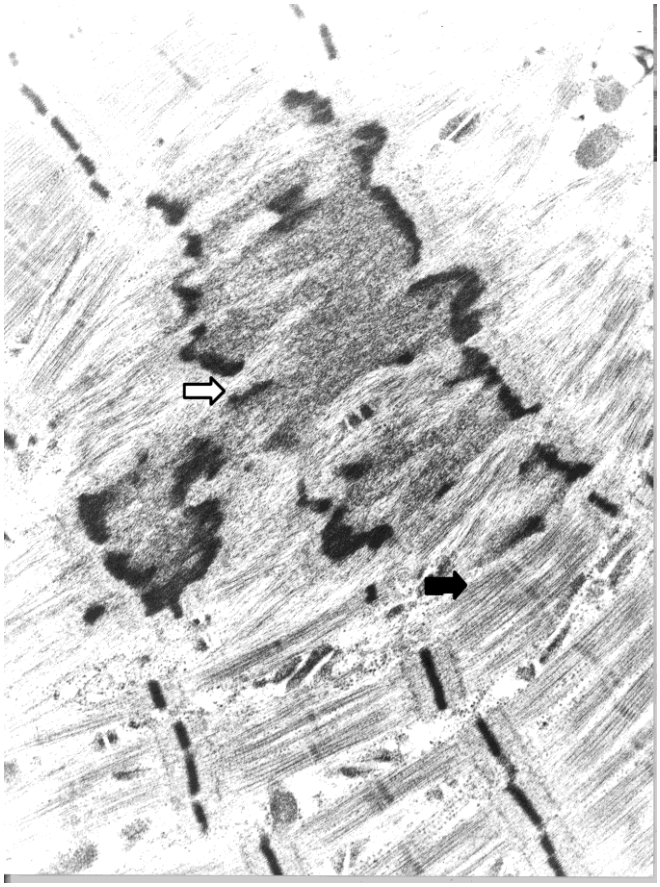

Figure 1: Uranil acetate stain electron microscopy showing selective loss of thick myosin filaments

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 (-80ºC).

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., Autoinmunity 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)	MechanicalVentilation Time (d)	Exitus
51	45/M	Hepathic 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

 DOI: http://dx.doi.org/10.17268/rmt.2020.v15i01.04

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 germen isolated in blood, urine or spute. G+: Gram possitive, G-: Gram negative, G+/G-: both types of germen, 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.

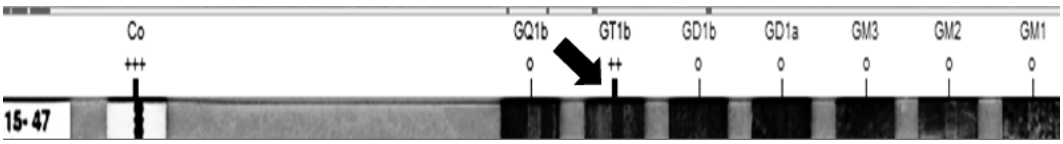

Figure 2. Immunostaining showing GT1b anti-ganglioside reactivity

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(α2-3)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 wheter 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

DOI: http://dx.doi.org/10.17268/rmt.2020.v15i01.04

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.

References

(1) Mac Farlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. Lancet 1977; 2:615
(2) Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry 1984; 47:1223-1231
(3) Lacomis D, Giulani MJ, Van Cott A, Kramer DJ. Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects. Ann Neurol 1996; 40:645-654
(4) Lacomis D. Zochodne DW, Bird SJ. Critical illness myopathy. Muscle Nerve 2000; 23:1785-1788
(5) Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Provonost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Medicine 2007; 33:1876-1891
(6) Bercker S, Weber-Carstens S, Deja M, Grimm C, Wolf S, Behse F, Busch T, Falke KJ, Kaisers U. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med 2005; 33:711-715
(7) Hough CL, Steinberg KP, Taylor Thompson B, Rubenfeld GD, Hudson LD. Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. Intensive Care Med 2009; 35:63-68
(8) Tennilä A, Salmi T, Pettilä V, Roine RO, Varpula T, Takkunen O. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med 2000; 26:1360-63
(9) de Letter MA, Schmitz PI, Visser LH, Verheul FA, Schellens RL, Op de Coul DA, van der Meché FG. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. Crit Care Med 2001; 29:2281-2286
(10) De Jonghe B, Sharsar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphaël JC, Outin H, Bastuji-Garin S; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002; 288: 2859-2867
(11) Bednarik J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polyneuromyopathy. J Neurol 2005; 252: 343-351
(12) Witt NJ, Zochodone DW. Bolton CF, Grand'Maison F, Wells G, Young GB, Sibbald WJ. Peripheral nerve function in sepsis and multiple organ failure. Chest 1991; 99:176-184
(13) Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005; 64: 1348-1353
(14) Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodóvar A, Garnacho-Montero MC, Moyano-Del-Estad MR. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med 2001; 27:1288-1296
(15) Latronico N, Shehu I, Seghelini E. Neuromuscular sequelae of critical illness. Curr Opin Crit Care 2005; 11:381-390
(16) Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D, Slutsky AS; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003; 348:683-693.
(17) Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatry 2008; 79:838-841
(18) Novak KR, Nardelli P, Cope TC, Filatov G, Glass JD, Khan J, Rich MM. Inactivation of sodium channels underlies reversible neuropathy during critical illness in rats. J Clin Invest 2009; 119:1150-1158
(19) Z'Graggen WJ, Lin CS, Howard RS, Beale RJ, Bostock H. Nerve excitability changes in critical illness polyneuropathy. Brain 2006; 129:2461-2470
(20) Rich MM, Pinter MJ, Kraner SD, Barchi RL. Loss of electrical excitability in an animal model of acute quadriplegic myopathy. Ann Neurol 1998; 43:171-179
(21) Allen DC, Ramamurthy A, Mills KR. Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy
(22) Z'Graggen WJ, Brander L, Tuchscherer D, Scheidegger O, Takala J, Bostock H. Muscle membrane dysfunction in critical illness myopathy assessed by velocity recovery cycles. Clin Neurophysiol. 2011; 122:834-41
(23) Rich MM, Pinter MJ. Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. J Physiol 2003; 547: 555-566
(24) Filatov GN, Rich MM. Hyperpolarized shifts in the voltage dependence of fast inactivation of Nav1.4 and Nav1.5 in a rat model of critical illness myopathy. J Physiol 2004; 559:813-820
(25) Teener JW, Rich M. Dysregulation of sodium channel gating in critical illness myopathy. J Muscle Res Cell Motil 2006; 27:291-296
(26) Kraner SD, Novak KR, Wang Q, Peng J, Rich M. Altered sodium channgel-protein associations in critical illness myopathy. Skelet Muscle. 2012; 2:17
(27) Button B, Baker RD, Vertrees RA, Allen SE, Brodwick MS, Kramer GC. Quantitative assessment of a circulating depolarizing factor in shock. Shock 2001; 15:239-244
(28) Haeseler G, Foadi N, Wiegand E, Ahrens J, Krampfl K, Dengler R, Leuwer M. Endotoxin reduces availability of voltage-gated human skeletal muscle sodium channgels at depolarized membrane potentials. Crit Care Med 2008; 36:1239-1247
(29) Ilyas AA, Willison HJ, Quarles RH, Jungalwala FB, Cornblath DR, Trapp BD, Griffin DE, Griffin JW, McKhann GM. Serum antibodies to gangliosides in Guillain-Barré syndrome. Ann Neurol 1988b; 23:440-447
(30) Sheikh KA et al. The distribution of ganglioside-like moieties in peripheral nerve. Brain 1999; 122:449-460

(31) Hafer-Macko C, Hsieh S-T, Li CY, Ho TW, Sheikh K, Cornblath DR, McKhan GM, Asbury AK, Griffin JW. Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. Ann Neurol 1996; 40: 635-44
(32) Takigawa T, Yasuda H, Kikkawa R, Shigeta Y, Saida T, Kitasato H. Antibodies against GM1 ganglioside affect K+ and Na+ currents in isolated rat myelinated nerve fibers. Ann Neurol 1995; 37: 436-42
(33) Weber F, Reinhardt R, Aulkemeyer P, Brinkmeier H. Anti-GM1 antibodies can block neuronal voltage-gated sodium channels. Muscle Nerve 2000; 23:1414-1420
(34) Kuwabara S, Ogawara K, Sung JY, Mori M, Kanai K, Hattori T, Yuki N, Lin CS, Burke D, Bostock H. Differences in membrane properties of axonal and demyelinating Guillain-Barré Syndromes. Ann Neurol 2002; 52:180-187
(35) Yuki N, Susuki K, Koga M, Nishimoto Y, Odaka M, Hirata K, Taguchi K, Miyatake T, Furukawa K, Kobata T, Yamada M. Carbohydrate mimicry between human ganglioside GM1 and Campylobacter jejuni lipooligosaccharide causes Guillain-Barré syndrome. Proc Natl Acad Scie U S A 2004; 101:11404-11409
(36) Horstman AL, Bauman SJ, Kuehn MJ. Lipopolysaccharide 3-deoxy-D.manno-octusolonic acid (Kdo) core determines bacterial association of secreted toxins. J Biol Chem 2004; 279:8070-8075
(37) Usuki S, Nakatani Y, Taguchi K, Fujita T, Tanabe S, Ustunomiya I, Gu Y, Cawthraw SA, Newell DG, Pajaniappan M, Thompson SA, Ariga T, Yu RK. Topology and patch-clamp analysis of the sodium channel in relationship to the anti-lipid a antibody in campylobacteriosis. J Neurosci Res 2008; 86:3359-3374
(38) Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707-710
(39) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13:818-29(40) Helliwell TR, Wilkinson A, Griffiths RD, Mc Clelland P, Palmer TE, Bone JM. Muscle fibre atrophy in critically ill patients is associated with the loss of myosin filaments and the presence of lysosomal enzymes and ubiquitin. Neuropathol Appl Neurobiol 1998; 24:507-517
(41) Ohsawa T, Miyatake T, Yuki N. Anti-B-series ganglioside-recognizing autoantibodies in an acute sensory neuropathy patient cause cell death of rat dorsal root ganglion neurons. Neurosci Lett 1993; 157:167-170
(42) Willison HJ,O'Leary CP, Veitch J, Blumhardt LD, Busby M, Donaghy M, Fuhr P, Ford H, Hahn A, Renaud S, Katifi HA, Ponsford S, Reuber M, Steck A, Sutton I, Schady W, Thomas PK, Thompson AJ, Vallat JM, Winer J. The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. Brain 2001; 124:1968-1977
(43) Rojas-Garcia R, Gallardo E, De Luna N, Juarez C, Martinez-Hernandez E, Carvajal A, Casasnovas C, Fages E, Davila-González P, Illa . Bulbar involvement in patients with antiganglioside antibodies against NeuNAc(alpha2-3)Gal. J Neurol Neurosurg Psychiatry 2010; 81:623-628
(44) Perez Ca, Ravindranath MH, Soh D, Gonzales A, Ye W, Morton DL. Serum anti-ganglioside IgM antibodies in soft tissue sarcoma: clinical prognostic implications. Cancer J. 2002; 8:384-394
(45) Willison HJ, Veitch J, Swan AV, Baumann N, Comi G, Gregson NA, IllaI, Zielased J, Hughes RA. Inter-laboratory validation of an ELISA for the determination of serum anti-ganglioside antibodies. Eur J Neurol 1999; 6:71-77
(46) Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Clinical review: Critical illness polyneuropathy and myopathy. Crit Care 2008; 12:238
(47) Turgeon AF, Hutton B, Fergusson DA, McIntyre L, Tinmouth AA, Cameron DW, Hébert PC. Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. Ann Intern Med 2007; 146:193-203
(48) Mohr M, Englisch L, Roth A, Burchardi H, Zielmann S. Effecs of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. Intensive Care Med 1997; 23:1144-1149

Citar como:. Martínez-Piñeiro A, . Ramos Fransi A, Almendrote Muñoz A, Lucente G, Martinez Caceres E, Ojanguren Saban I, Perez Molto H, Rubio SV, Coll-Canti J. Are anti-ganglioside antibodies detectable in serum from patients with critical illness myopathy and polyneuropathy? Rev méd Trujillo 2020;15(1):26-34

 DOI: http://dx.doi.org/10.17268/rmt.2020.v15i01.04