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Case Report

Treatment Related Fluctuations in Guillain-Barre Syndrome Overlapping Cyoglobulinaemic Polyneuropathy: A Case Report

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Abstract

Guillain-Barre Syndrome (GBS) is an acute polyradiculoneuropathy leading to flaccid paresis. A Treatment-Related Fluctuation (TRF) in a patient with Guillain-Barré Syndrome (GBS) is defined as clinical deterioration within two months of symptom onset following previous stabilization or improvements with treatment. A 67 years old woman presented with rapidly progressing muscular weakness in all four limbs. Her nerve conduction study revealed demyelinating polyneuropathy in all four limbs, and her test of the cerebrospinal fluid showed an albumin-cytologic dissociation. She improved after intravenous immunoglobulins but she had two relapses within two months. Later on mixed cryoglobulins were detected and nerve conduction studies revealed mixed demyelinating and axonal polyneuropathy. We assume that cryoglobulins could be a factor precipitating fluctuations in Guillain-Barrè after suspending therapy and that, in particular conditions they should be tested in order to start a specific therapy and to prevent clinical relapses.

Keywords: Coronavirus infection • COVID-19• Nervous system

Case Presentation

A 67 years old woman was admitted to our clinic because of progressive paresthesias in the feet, paraparesis, low back pain and constipation since two days. Twenty days before the symptoms onset she presented with a flu like syndrome with fever and cough, thus she was taking an antibiotic. Twelve years prior she had suffered from a non-Hodking's marginal zone lymphoma with orbital location, treated with R-CHOP (6 cycles) with a thymic relapse two years before her admission to our department, treated with Rituximab-bendamustin. She had had a previous HBV infection. On physical examination, the patient was afebrile with blood pressure 120/80 mmHg, she had tachycardia with heart rate of 110 beats/minute, oxygen saturation of 95% on room air. The patient was conscious and had no dyspnea. The muscle strength examination showed weakness in four limbs with a Medical Research Council (MRC) scale of 4/5 in proximal and in distal of the upper extremities, with a fine postural tremor on the right arm, and 2/5 on the right and 3/5 on the left in proximal, 3/5 on the right and 4/5 on the left in distal of the lower extremities. There was a reduction in Deep Tendon Reflex (DTR) responses in all limbs with absent knee reflexes [1-2]. Vibration touch sensation was absent in lower limbs, fine sensation was present. On admission she underwent a lumbosacral spine MRI which was normal. Electroneuromyography was highly suggestive of demyelinating polyradiculoneuropathy (Table 1, 1st ENMG): tibial nerve and peroneal nerve distal latencies were prolonged on both sides, with a moderate slowdown in motor conduction velocity and a decrease of Compound Muscle Action Potential (CMAP) amplitude; F wave latency was significantly prolonged [3]. Sural and ulnar nerve sensory conductions were unremarkable. Cerebrospinal Fluid (CSF) study showed markedly elevated protein levels (400 mg/dl, normal value=40 mg/ 40dl) with a normal cell count. CSF septic screen was negative, viral PCRs and Lyme test were negative. Biochemical analysis detected ANA with a granular pattern positive at a 1:320 dilution, whose profile showed positive AMA-M2, histones, PM-Scl 100, Ku, p-ANCA, complement proteins slightly consumed with C3=78 mg/dl, C4=8 mg/dl. Antiganglioside antibodies were not found. These findings are consistent with acute motor demyelinating neuropathy. Our patient received 0.4 g/kg/day intravenous immunoglobulin for a duration of five days resulting in clinical improvement and recovery of walking ability. Twenty-two days after her hospital discharge she accessed the emergency department again, reporting progressive strength worsening since ten days, which made her unable to walk [4]. Neurological examination was identical to the one on the first hospital admission, except for muscle strength of the legs, showing worse involvement on the left side (3/5 on the right and 2/5 on the left in proximal, 4/5 on the right and 3/5 on the left in distal of the lower extremities). EMG (Table 1) showed severe reduction of CMAP amplitude of all examined nerves and a slight worsening of the demyelinating aspects; needle electromechanical tips in all examined muscles showed a nerve predominant potential, suggesting fiber axon damage [5,6]. Our patient attended ten sessions of therapeutic plasmapheresis, leading to significant improvement of the motor deficit. The patient was discharged 3 weeks later on maintenance kinetotherapy. Ten days after her discharge she was readmitted to our clinic for a new clinical worsening. The muscle strength examination showed weakness in four limbs with a Medical Research Council (MRC) scale of 4/5 in proximal and in distal of the upper extremities and 3/5 in proximal and distal lower extremities. Deep tendon reflexes were absent everywhere. Serum cryoglobulins analysis revealed mixed cryoglobulinemia, quantifiable as 40% [7-9]. Glycated hemoglobin was normal. As for oncomarkers CEA was slightly increased (4.30 ng/4.30 ml, n.v<4.00), CA125 was 42.8U/ml (n.v.<35.0). Serum onconeural antibodies were negative. Anti-MAG antibodies were negative. A whole body TC was performed but was negative for any cancer. Our patient received 0.40 g/kg/day intravenous Immunoglobulin for a duration of five days with slight clinical improvement and then prednisone 50 mg/50die with marked improvement and walking ability recovery, though needing double support. She was then discharged on a maintenance dose of oral steroids.

She was diagnosed with treatment-related fluctuation in Guillain-Barrè syndrome overlapping cryoglobulinemic polyneuropathy. After hospital discharge she underwent a reumathologic evaluation confirming the diagnosis of mixed cryoglobulinemia type II and starting an immunosuppressive treatment with cyclophosphamide 50mg/die and sparing steroid therapy (prednisone 10 mg/die), under which patient presented clinical stability, not experiencing further relapses. EMG performed one month after her discharge showed improvement of demyelinating features but persisting axonal damage (Table 1, 3rd ENMG).

As for clinical examination she was able to walk unassisted and had no deep tendon reflexes in lower limbs [10-13].

Table 1. Examination of first second and third ENMG and showed severe reduction of CMAP amplitude of all examined nerves of the aspects.

	Peroneal nerve	Tibial nerve	Ulnar nerve (motor)	Ulnar nerve (sensory)	Sural nerve
1st	DML (ms) MNCV (m/s) MAP amp (mV) Right Left Right Left Right Left	DML (ms) MNCV (m/s) MAP amp (mV) Right Left Right Left Right Left	DML (ms) MNCV (m/s) MAP amp (mV) Left Left Left	SNCV (m/s) SAP amp (mV)	SNCV (m/s) SAP amp (mV) Ri
ENMG				Left Left	ght Left Right Left
	5,1 6,8 32,7 45,2 2,8 2,8	6,5 12,8 35,6 44,9 2,8 1,5	3,2 58,1 4,3		
				49 9,8	44,4 54,5 9,4 7,7
2nd ENMG	12,2 14,5 34,4 31,6 0,9 0,9	17,3 18,9 30,4 30,2 0,5 0,3	4,2 47,7 2,6	33,9 2,8	44,8 45,2 9,2 15
3 rd ENMG	3,6 7,9 26,6 40,7 2,2 1,0	5,6 5,8 28,1 30,2 2,4 2,6	3,0 45,1 4,0	43,8 4,6	37,5 37,9 2,8 4,3

Abbreviation: DML = Distal Motor Latency; MNCV = Motor Nerve Conduction Velocity; MAP amp= Motor Action Potential Amplitude; SNCV= Sensory Nerve Conduction Velocity; SAP= Sensory Action Potential.

Discussion

All initial findings, clinical disturbances, nerve conduction studies, CSF examination were consistent with a Guillain-Barrè syndrome with treatment related fluctuations, because clinical deterioration occurred twice after intravenous immunoglobulins and plasmapheresis within the first two months after the onset of symptoms, showing an improvement in GBS disability scale of more than one grade and in the MRC score of more than five points after therapy and a decline in GBS disability scale of more than one grade and in the MRC score of more than five points after discontinuing them [14-17]. The hypothesis of paraneoplastic polyneuropathy was taken into account, given previous medical history of lymphoma and the clinical suspect of colon carcinoma, supposing onconeural antibodies could possibly justify clinical relapses but neither evidence of lymphoma relapse was found nor evidence of colon cancer as initially suspected nor onconeural antibodies were detected. Moreover paraneoplastic neuropathies are mostly axonal but our patient showed a mostly demyelinating neuropathy. A pure cryoglobulinemic polyneuropathy was also considered but NCS and CSF were more consist-tence with Guillain-Barrè syndrome. The main symptoms of CNP are sensitive such as painful or burning paresthesias in the lower limbs and in most patients, a distal symmetric sensory or sensory-motor PN is observed suggesting axonal damage possibly due to epineural vasculitis caused by immune complex deposition, with subsequent ischaemic pathology due to alterations in the blood flow. Sensory symptoms however can be accompanied by gradual progression of muscle weakness but in a distal, symmetrical distribution. The weakness is usually mild and limited to the foot extensors. PN is mostly axonal and demyelinating. PN is rarely described and poorly characterized. Our patient showed a prominent weakness with predominant involvement of proximal muscles in lower limbs, with minimal sensory complaint and NCS confirmed major motor compromise, with evidence of main demyelination. Guillain-Barrè syndrome has been previously described in association with autoimmune diseases, such as systemic lupus erythematosus and Crohn disease but, as far as we known, association with cryoglobulinaemia has not been reported yet [18,19]. We assume that cryoglobulins could be a potential trigger of relapses, conditioning their severity by provoking a concomitant axonal damage. In fact repeated ENMG of patient showed, next to demyelinating features, an increasingly important axonal involvement, particularly in lower limbs. This suspect was confirmed by prompt response to steroid and immunosuppressive treatment, guaranteeing long-term clinical stability.

Conclusion

Guillain-Barre is usually a monophasic illness but it can sometimes present a relapsing or recurrent course. Factors that could increase the risk of relapse of GBS in patients with and without TRFs are not well defined. In a study GBS group with TRFs was more frequently preceded by infectious mononucleosis secondary to CMV and EBV but other virus infections were less associated to TRFs. Myxed cryoglobuninemia could be a potential trigger of clinical relapse. This case suggested the utility of dosing cryoglobulins in specific clinical contexts, such as history of previous viral hepatitis and hematologic disease, in order to start an immunosuppressive treatment as soon as possible, preventing possible relapses.

Conflict of Interest

The authors declare there is no conflict of interest.

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