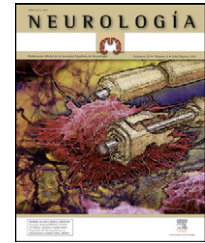




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LETTERS TO THE EDITOR

Guillain-Barré syndrome as first presentation of non-Hodgkin lymphoma[☆]

Síndrome de Guillain-Barré como forma de presentación de un linfoma no Hodgkin

Dear Editor:

Guillain-Barré syndrome (GBS) is an autoimmune polyradiculopathy described by Guillain, Barré, and Strohl in 1916 as an acute areflexic motor paralysis with varying degrees of sensory impairment. In Western countries it is the most common cause of acute flaccid tetraparesis.¹ In a great many cases, GBS is aetiologically related to a previous infection, which is frequently respiratory or gastrointestinal.² Researchers have also described GBS cases linked to recent vaccinations,³ haematological malignancies,⁴ and connective tissue diseases.⁵ Peripheral nervous system impairment caused by either Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL) has been thoroughly described⁶; however, GBS does not commonly appear as an initial manifestation of NHL.^{7,8} We present the case of a patient with NHL whose first clinical manifestation was the appearance of GBS.

The patient, a 74-year-old woman with a history of autoimmune hypothyroidism and chronic polyarthralgia with dorsal and lumbar spondylosis, was being treated with levothyroxine and occasional non-steroidal anti-inflammatory drugs. The patient visited our clinic several months ago due to nonspecific asthenia with increased acute-phase reactants (ESR, ferritin, and C-reactive protein). Doctors found no other associated symptoms based on the medical history and examination of organs and organ systems. An exhaustive study including complete blood count, biochemical markers, thyroid function, immunoglobulins, protein electrophoresis, tumour markers, autoimmune study, and antibody serology did not return a diagnosis. A thoracic–abdominal CT scan revealed no changes apart from degenerative signs with no axial skeleton fractures or compressions. She visited the doctor due to symptoms of paraesthesia, weakness in the lower limbs (LL) extending proximally, and lumbar pain that had progressed over

48 h. She was afebrile and had no other associated symptoms. The patient initially presented distal weakness of the lower extremities (grade 3–4/5) with plantar reflex suppression, hypaesthesia of the feet, and no other relevant findings from the neurological examination. Symptoms exacerbated over the next 24 h, and the patient experienced ascending progressive bilateral paralysis that extended to the sites of attachment of both thigh muscles, with tendon reflex suppression in the lower limbs and loss of control over the bladder sphincter. We could not detect a sensory level or any cranial pair involvement. Doctors found no loss of strength or sensitivity in the upper extremities and observed only slight bilateral hyporeflexia of the biceps that could not be confirmed subsequently. In the days that followed, the patient reported paraesthesia in the hands and loss of agility, which could not be detected by the daily physical examination. Cerebellar exam found normal results for the upper extremities, extrinsic eye movements, and photomotor reflex. The patient did not present nystagmus or diplopia. There were no signs of meningeal irritation. The blood test revealed leucocytosis of 22 600/ μ L, ESR 52 mm/h, GOT 42 U/L, GGT 51 U/L, LDH 990 U/L, ferritin 551 ng/mL and TSH 9.69 μ U/mL. All other parameters were normal. Thoracic radiography showed no significant findings. Lumbosacral MRI with intravenous contrast did not show significant alterations in the lumbosacral spinal cord or the spinal segments that were viewed (up to D9). A Tc-99m-based bone scan was also performed, revealing uptake at D10, the left sacroiliac joint, shoulders, hips, and knees. These lesions were found to be osteoporotic in origin. A lumbar puncture delivered clear liquid with 20 leucocytes (60% mononuclear and 40% polymorphonuclear), glucose 55 mg/dL (plasma glucose 78 mg/dL) and proteins 76 mg/dL. No oligoclonal bands were observed in the liquid. Both the culture and the anti-Hu antibody titre were negative. The cytological study of the CSF found no malignant cells. A nerve conduction study completed 24 h after the patient's clinical condition had deteriorated showed decreased conduction velocity in the motor nerves examined in the lower limbs. Their morphology and amplitude remained normal. In sensory nerves of the lower limbs, amplitude of action potentials was preserved with a slightly increased duration; nerve conduction speed was slow. Stimulation of the nerves in the lower limbs did not produce any identifiable F-responses. Examination of the median nerve revealed normal sensory and motor parameters and normal F-responses. The study concluded that the patient had a sensory and motor

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axonal-demyelinating polyneuropathy specifically affecting the lower limbs and compatible with GBS. In view of the diagnosis, the patient was treated with intravenous gammaglobulin (400 mg/kg/day during 5 days), but neurological symptoms did not improve. The patient's lack of response to treatment and the fact that there was no clear cause of the neurological symptoms led doctors to believe that she might be suffering from an underlying disease that had not been diagnosed. She later suffered a relapse with the same nonspecific asthenia and increase in acute phase reactants. Doctors detected persistent leucocytosis with no fever and no focal infectious in blood tests. They therefore requested a peripheral blood smear, which revealed pathological alterations. NHL diagnosis was confirmed by bone marrow aspiration and biopsy which showed diffuse infiltration by a B-cell lymphoproliferative process. The haematology department then began administering chemotherapy with CHOP-rituximab. After 6 cycles of treatment (approximately 6 months after diagnosis), the patient's routine bone marrow biopsy showed complete remission. However, a cranial and cervical–thoracic–abdominal–pelvic CT scan showed abnormalities in the cranial vault, left tenth rib, D10 vertebral body, and left iliac blade with soft tissue masses caused by a neoplastic process. At that moment, she had only experienced minimal recovery of strength in the lower limbs (strength grade 1/5). All other neurological alterations remained the same. She was prescribed intrathecal cytarabine and received 6 more cycles of systematic chemotherapy according to the same protocol. A PET-CT scan was performed upon completion of treatment and showed refractory haematological disease, with persistence of lymphomas in the left pleura, both hips, thoracic spine, mediastinum, and retroperitoneal space. In light of these findings, active treatment was cancelled and the patient began receiving palliative care only. She died of septic shock 2 months after chemotherapy was suspended.

Peripheral nervous system impairment caused by lymphoma varies depending on the type of lymphoma and comprises several different kinds of peripheral neuropathies.^{6,8} This being the case, GBS has been described in association with a number of different haematological neoplasms, but especially with HL.⁶ However, GBS appearing in association with NHL is very rare and few cases have been described in the literature.^{7–10} There are only 2 recorded cases in which neurological symptoms appeared prior to the diagnosis of NHL,^{7,8} as in the case of our patient. The diagnosis of GBS is mainly based on typical clinical data which are then confirmed by results from the CSF analysis and the nerve conduction study.^{11,12} The clinical data in our case are consistent with a diagnosis of GBS. The most remarkable finding is the appearance of bladder impairment which might be explained by an autonomic dysfunction of that organ.¹³ Another rarity of this case was the presence of mononuclear pleocytosis in the CSF. This fact should alert doctors to the possibility of an infection or another alternative diagnosis, especially when counts exceed 50 cells/ μ L.⁵ Nevertheless, this fact has been questioned by other authors^{14,15} whose research has shown that GBS can appear with pleocytosis, and that once infectious disease has been ruled out, it may even be a typical finding in severe or devastating GBS.¹⁵ Studies on the pathogenesis of GBS suggest that antibodies may be directed against

different components of the peripheral nervous system.^{1,2} There is a link between the presence of certain antibodies and the different ways GBS may present and progress. However, the pathogenic significance of these antibodies has not yet been clarified.¹² Demyelinating forms of GBS are the most studied by researchers, who have found them to be linked to autoimmune responses to cell membrane gangliosides because of molecular mimicry. However, less than 20% of all cases are positive for anti-ganglioside antibodies.^{1,16} This inflammatory response mainly occurs in patients who have previously suffered infection with *Campylobacter jejuni*.¹ Many different pathogenic mechanisms are involved in the association between polyneuropathy and lymphoma, but the most accepted ones are direct infiltration of the nerve trunks by lymphoma cells through adjacent ganglia; vascular impairment with nerve infarction; and an immune-mediated inflammatory response of the type occurring in GBS,⁶ which would therefore constitute a type of paraneoplastic syndrome. On the other hand, peripheral nervous system impairment caused by lymphoma may be due to toxicity caused directly by haematological treatment, especially when high doses of vincristine are used; most published cases of this impairment are caused by vincristine.^{4,9} GBS is not counted among the classic paraneoplastic neurological syndromes. In this specific case, researchers did not find characteristic onconeural antibodies that would link this neurological syndrome to a concrete type of neoplasia.⁵ We believe that the most plausible pathophysiological mechanism explaining GBS in this patient would be the development of an immune-mediated paraneoplastic syndrome, since symptoms coincide with the type of GBS typically triggered by a previous infection. We can rule out lymphomatous meningeal infiltration, as in these cases impairment is usually focal or asymmetric.¹⁷ We cannot offer a clear explanation for the fact that our patient did not improve after treatment with immunoglobulins or after apparent remission of NHL, but negative outcomes despite conventional treatment are well-documented and the mechanisms explaining treatment failure remain unknown.¹² Nevertheless, certain hypotheses may shed light on this subject. First of all, the patient was treated with 12 cycles of chemotherapy (CHOP-rituximab), and it is a known fact that peripheral nervous system impairment can occur with use of any of a number of antineoplastic drugs, including vincristine and rituximab.^{17,18} These drugs may have contributed to the patient's persistent neurological deterioration. On the other hand, we do not believe that the apparent remission of the lymphoma actually took place, given that staging studies during treatment showed evidence of organ damage. This indicates that the stimulus causing the formation of antibodies was still present¹⁹ and explains why neurological symptoms did not abate. There are studies describing cases in which remission of the haematological process caused neurological manifestations to resolve.¹⁷ However, in other cases, improvement of the haematological condition was not followed by a good neurological outcome or a favourable response to conventional treatment for GBS.¹⁹ To summarise, although the appearance of GBS associated with lymphoma has been described in the literature, it is very rare, especially if it is associated with NHL.^{7–10} It is rarer still for neurological symptoms to present before the haematological condition has been diagnosed.^{7,8} We

therefore believe it is important to highlight the following: even though it would be quite rare, a case of GBS that cannot be clearly linked to any of the processes or entities with which it is usually associated, which appears with abnormal laboratory results that are not typically seen in classic GBS, or which evolves at an alarming rate and responds poorly to conventional treatment should lead the doctor to consider the possibility of an underlying case of lymphoma.

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Emotional memory: Synthesis of a study proposal[☆]

La memoria emocional: síntesis de una propuesta de estudio

Dear Editor:

Affective responses are evolutionarily prior to or more primitive than cognitive ones. For example, basic responses (pleasure, aversion) may be experienced before the individual is aware of the object provoking the reaction, that is, before classifying and recognising that object.¹ This means

that emotion plays an unmistakable role in the adaptation process by allowing us to attach importance to stimuli or events that could either jeopardise or favour survival.² We attach importance to such stimuli based on the way that emotion evokes memory.

The amygdala and the hippocampus are the brain structures responsible for facilitating memory. Both structures are located in the medial temporal lobe, and they are related to independent memory systems that interact with each other in emotionally charged situations. In this sense, the amygdala is able to modify the way memories dependent on the hippocampus are encoded and stored. Likewise, the hippocampus can influence the amygdala's response by creating episodic representations of the emotional meaning and interpretation of events.³ Different neuroimaging studies have found correlations between the activity registered in the amygdala and the hippocampus while emotional information is being encoded.^{4–6} At the same time, patients with atrophy of the amygdala exhibit an inverse correlation

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