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 spondylitis, 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, hynæsthesia 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 hypeflexia 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/μL, ESR 52 mm/h, GOT 42 U/L, GGT 51 U/L, LDH 990 U/L, ferritin 551 ng/mL and TSH 9.69 μU/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 gam-
maglobulin (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 mar-
row aspiration and biopsy which showed diffuse infiltration
by a B-cell lymphoproliferative process. The haematol-
ogy department then began administering chemotherapy
with CHOP-rituximab. After 6 cycles of treatment (approx-
imately 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 intrathe-
cal 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 lym-
phoma varies depending on the type of lymphoma and com-
prises several different kinds of peripheral neuropathies.4,8
This being the case, GBS has been described in associa-
tion with a number of different haematological neoplasms,
but especially with HL.6 However, GBS appearing in asso-
ciation 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 dys-
function of that organ.12 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/μL.1 Nevertheless, this fact has been ques-
tioned by other authors4,15 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.16 Studies on the pathogene-
sis 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 antibod-
ies and the different ways GBS may present and progress.
However, the pathogenic significance of these antibod-
ies 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 mem-
brane 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 Campy-
lbacter jejuni.1 Many different pathogenic mechanisms are
involved in the association between polyneuropathy and
lymphoma, but the most accepted ones are direct infiltra-
tion of the nerve trunks by lymphoma cells through adjacent
ganglia; vascular impairment with nerve infarction; and an
immune-mediated inflammatory response of the type occur-
ing 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 treat-
ment, 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 para-
neoplastic neurological syndromes. In this specific case,
researchers did not find characteristic onconean antibod-
ies 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 parane-
oplastic 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 can-
not 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 mecha-
nisms 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, includ-
ing vincristine and rituximab.17,18 These drugs may have
contributed to the patient’s persistent neurological dete-
rioration. 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 haematologi-
cal process caused neurological manifestations to resolve.17
However, in other cases, improvement of the haematologi-
cal condition was not followed by a good neurological out-
come 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.

References


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 unmistakeable 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.\(^4,5\) At the same time, patients with atrophy of the amygdala exhibit an inverse correlation

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