Revista Chilena de Neurocirugía 43: 2017

Association between Wegener´s granulomatosis and severe lumbar pain

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Rev. Chil. Neurocirugía 43: 83-86, 2017

Resumen

Introducción: La granulomatosis de Wegener (GW) es una enfermedad autoinmune sistémica caracterizada por vasculitis granulomatosa necrotizante que afecta principalmente a las vías respiratorias superiores, pulmones y riñones. Sin embargo, con menos frecuencia puede afectar a los músculos, las articulaciones, la piel, los ojos, el sistema cardiovascular y el sistema nervioso. La presencia de dolor lumbar consiste en una manifestación clínica inusual debido a la afectación del sistema nervioso. **Objetivo:** El objetivo de este estudio es alertar a los profesionales de la salud acerca de la posibilidad de cortar el dolor lumbar estar relacionado con la granulomatosis de Wegener, su impacto en la vida diaria del paciente, así como los signos clínicos y las formas de diagnóstico. **Materiales y Métodos:** Revisión de la literatura utilizando PubMed, MEDLINE, Google Scholar, SciELO, EBSCO. Los trabajos seleccionados entre 1995 y 2013 por un total de 48 obras de las cuales se seleccionaron 21 de acuerdo con sus informes de afectación neurológica, diagnóstico y tratamiento. **Discusión:** Los síntomas neurológicos pueden ocurrir en 22-50% de los pacientes durante el curso de la GW. sistema nervioso (SNC) central es poco frecuente (sólo 2-8% de los pacientes) dolor lumbar .Severe es una manifestación clínica poco frecuente y puede estar asociada con la participación de sistema nervioso central y periférico. CNS debido a la compresión de la médula espinal a nivel lumbar. sistema nervioso periférico debido a la compresión de las raíces nerviosas. **Conclusión:** La granulomatosis de Wegener es ser una enfermedad sistémica puede presentar diferentes manifestaciones clínicas De acuerdo con el sitio involucrado. Es asociaciones con el dolor lumbar es rara y la refleja la afectación neurológica. Por lo tanto, en pacientes con dolor lumbar grave sin diagnóstico confirmado, granulomatosis de Wegener no debería ser considerado.

Palabras clave: Granulomatosis de Wegener, dolor lumbar, vasculitis granulomatosa necrotizante, compresión de la médula espinal, neuropatía periférica.

Abstract

Introduction: Wegener's granulomatosis (WG) is a systemic autoimmune disease characterized by necrotizing granulomatous vasculitis which primarily affects upper respiratory tract, lungs and kidneys. However, less frequently can affect muscles, joints, skin, eyes, cardiovascular system and nervous system. The presence of lumbar pain consists in an unusual clinical manifestation due to the involvement of the nervous system. **Objective:** The objective of this study is to alert health professionals about the possibility that severe lumbar pain be related to Wegener's granulomatosis, it's impact on the patient's daily life as well as clinical signs and diagnosis forms. **Materials and Methods:** Literature review using PubMed, MEDLINE, Google Scholar, SciELO, EBSCO. Selected works from 1995 to 2013 totaling 48 works of which 21 were selected according to their reports of neurological involvement, diagnosis and treatment. **Discussion:** Neurological symptoms may occur in 22-50% of

patients during the course of WG. Central nervous system (CNS) involvement is uncommon (only 2-8% of patients).Severe lumbar pain is a rare clinic manifestation and it can be associated with the involvement of central and peripheral nervous system. CNS due to compression of the spinal cord at the lumbar level. Peripheral nervous system due to compression of nerve roots. **Conclusion:** Wegener's granulomatosis for being a systemic disease can present different clinical manifestations according to the involved site. It's associations with lumbar pain is rare and reflects it's neurological involvement. Therefore, in patients with severe lumbar pain without confirmed diagnosis, Wegener's granulomatosis should be considered.

Key words: Wegener's granulomatosis, lumbar pain, necrotizing granulomatous vasculitis, spinal cord compression, peripheral neuropathy.

Introduction

Heinz Klinger was the first to describe Wegener's granulomatosis in 1931 during a study conducted at the University of Berlin. About 5 years later, Friedrich Wegener, a German pathologist, described a similar clinical presentation in three patients. After observing these similar clinical presentations in seven other patients years later, he established its diagnosis criteria[21]. Thus, Wegener's granulomatosis is a rare systemic autoimmune disease characterized by necrotizing granulomatous vasculitis that primarily affects the small vessels. Generally it affects the upper and lower airways, lungs, and kidneys. Less often, it can affect muscles, joints, skin, eyes, cardiovascular and nervous system[13,2,10,3].

The involvement of the central and peripheral nervous systems are not uncommon, being in approximately 22-50% of patients[13]. Peripheral neuropathy (especially mononeuritis multiplex) can be present at 10.6 - 21.2% of patients and less than 10% with involvement of the central nervous system[13,3]. Lumbar pain consists in a rare feature of neurological involvement of the patient, which can happen by central or peripheral nervous system.

Pathogenesis

Although its etiology is still unknown, there are hypothesis that its pathogenesis involves components of cellular and humoral response. The T-cell mediated immunity is responsible for the production and release of pro-inflammatory cytokines including Tumor necrosis factor α (TNF-α) and interferon γ that stimulate the expression of surface antigens in activated neutrophils. Among these antigens are proteinase 3 (PR3) and myeloperoxidase which are markers for c-ANCA (cytoplasmic) and p-ANCA (perinuclear- Neutrophil Cytoplasmic Antibody) respectively. The interaction of ANCA with their antigens result in degranulation of neutrophils and formation of toxic products, increasing the inflammatory reaction and leading to tissue damage[2,10].

Neurological manifestations and lumbar pain

Neurological manifestations may be present in 22-50% of patients during the course of the disease[13]. The literature mentions three mechanisms by which the nervous system may be affected, proposed by Drachman: 1) necrotizing vasculitis involving brain, spinal and radicular vessels; 2) contiguity extravascular granulomas in the paranasal sinuses, nasal cavities or orbits; 3) primary necrotizing granulomas in the skull, meninges, cranial nerves or brain[3,11,5].

Peripheral nerves are more commonly affected by multiple mononeuritis and sensorimotor distal symmetric polyneuropathy. The main symptoms include pain, numbness and muscle weakness in the affected sites[2,3]. Lumbar pain can also occur due to lumbar nerve root compression, an infrequent event. The formation of granulomatous mass along with necrotizing vasculitis which is a characteristic of the disease, lead to compression and consequent ischemia of the nerve root, causing pain as well as sensory and motor deficit in the area innervated by the affected root. Therefore, in the lumbar level injuries, pain may also affect the lower limbs in accordance with the nerve pathway involved. In these cases, as a diagnostic aid can be made a biopsy of nerve root would prove the presence of necrotizing granulomatous vasculitis.

The involvement of the central nervous system mainly includes cerebral ischemic events, involvement of cranial nerves, subdural hematoma, subarachnoid hemorrhage, and more rarely spinal cord compression by involvement of the dura mater, another possible cause of low back pain. Upon reaching the dura mater, vasculitis and granulomatous inflammation typical of GW promotes the formation of a tissue mass and a thickening of the dura that surrounds and compresses the spinal cord, may also affect its nerves and cause symptoms such as weakness, numbness and pain[5,1,20]. To assist in diagnosis, in addition to clinical manifestations, imaging tests such as MRI are of paramount importance to identify the granulomatous mass, dural thickening as well as its extent and affected sites.

As a result of this granulomatous inflammation, diseases such as herniated discs, lumbosacral plexopathy, lumbosacral radiculopathy, osteitis and synovitis can affect lumbar area, causing severe pain in this region.

Diagnosis

For diagnosing should be used clinical patient data, imaging tests such as chest radiography, MRI or CT scan, biopsy of the lesion and also the presence of anti-neutrophil cytoplasmic antibody (ANCA) - serum marker of Wegener's granulomatosis - demonstrated by indirect immunofluorescence or ELISA (Enzyme-Linked Immunosorbent Assay). The c-ANCA pattern is more related to GW, with a specificity of 90%, but its negativity is insufficient to rule out the diagnosis. The title of ANCA must be accompanied as it can be directly related to disease activity[13,14,18].

The American Academy of Rheumato-

Table 1. Diagnostic criteria of the American College of Rheumatology pub-lished in 1990
Nasal or oral inflammation
Nodules, fixed infiltrates or cavitation on chest radiography
Microscopic hematuria or more than 5 erythrocytes per high-power field
Granulomatous inflammation present in the biopsy
Table 1: Presence of at least two of these criteria may mean a diagnosis of Wegener's granulomatosis with 82.2% sensitivity and 92% specificity compared to other vasculitis.

logy recommends the use of the diagnostic criteria published in 1990: nasal or oral inflammation; nodules, fixed infiltrates or cavitation on chest radiography; microscopic hematuria or more than five erythrocytes per high-power field; granulomatous inflammation on biopsy. Having at least two of these criteria may mean a diagnosis of GW with 82.2% sensitivity and 92% specificity compared to other vasculitis[2,15,16].
The presence of severe back pain associated to the items listed in Table 1 or in patients previously implanted with GW may represent neurological involvement in the disease course. Thus, these signals are extremely important to differential diagnosis of low back pain due to other causes.

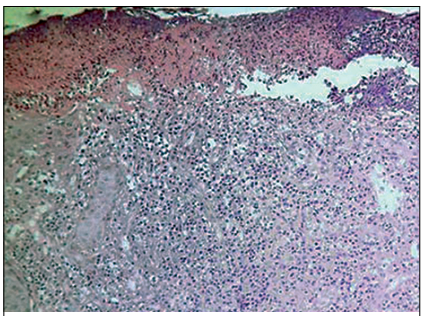

Figure 1. Histology of skin showing epidermal ulceration and dense dermal infiltrate composed of lymphocytes, neutrophils, eosinophils and some scattered giant cells.

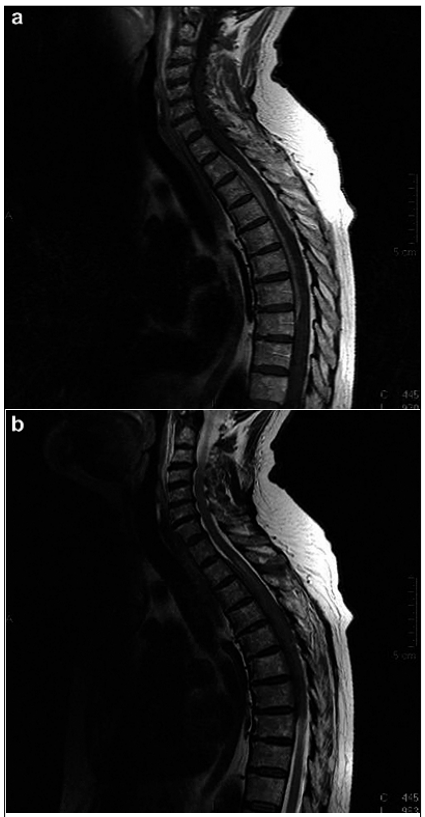

Figure 2. (a) Sagittal view showing extensive thickening of the dural space surrounding and compressing the spinal cord; (b) sagittal image showing hyperintense edema in the thoracic spinal cord extending super and inferiorly.

Histological findings

A biopsy of the lesion may be performed to confirm the diagnosis and exclude differential diagnosis. The histological manifestations include parenchymatous necrosis, small vessel vasculitis and granulomatous inflammation not vernix[2]. The inflammatory infiltrate is usually composed of lymphocytes, neutrophils, plasmocytes, eosinophils, polymorphonuclear giant cells and evidence of leukocytoclastic vasculitis. [10,19]

Image exams

MRI is the main tool used to identify neurological involvement. Previous articles shows dural involvement at the thoracic level of the spinal cord, as shown in the following Figure 1.
The Figure 2 shows the thickening and dural mass formed compressing the spinal cord and extending from Th2 to Th8, normointense on T1 with limited enhancement after gadolinium administration and hypointense on T2[20].
The mass and dural thickening characteristic of GW can reach and injure various levels of the spinal cord according to their length and must be differentiated from other diseases such as neurosarcoidosis, cancer, infectious meningitis, tuberculosis and neurosyphilis through clinical manifestations radiological exams and biopsy of the lesion[6,7].

Treatment

The conventional treatment consists of corticosteroids like prednisone 1 mg / kg / day for 4-6 weeks, gradually withdrawn completed in 6 months. It should be associated cyclophosphamide 2-3 mg / kg / day adjusted according to the number of lymphocytes - which must be kept around 1,000 / mm³ and withdrawn after 1 year of remission[13,2,4]. The main side effects of this treatment shall include predisposition to infection and nausea, may associate antiemetics, and antibiotics prophylactically.
There are also reports of cases with neurological involvement in patients with refractory Wegener's granulomatosis treated with weekly injections of rituximab 375 mg / m² for 4 weeks and were able to achieve remission of the disease associated with the decline of ANCA titles and depletion of B cells in peripheral blood[9,17,12].
Therefore, in patients with lumbar disease related to GW two directions to the treatment can be taken: conventional treatment when the lumbar disease is part of the initial manifestations of the disease or treatment of refractory shapes which consists most of the cases of neurologic involvement, with rituximab.

Conclusion

Although it is a rare disease, Wegener's granulomatosis has distinct clinical patterns, which may affect various tissues and cause varying degrees of

injuries. Its neurological involvement is not uncommon, but its association with low back pain is rare and occurs primarily as a result of spinal cord or nerve root compression arising from vascular injury on dura mater and the subsequent inflammatory process generated. In patients with severe lumbar pain without apparent cause, GW and its neurological involvement should be considered. As diagnostic tools should be associated clinical data, imaging tests, serological marker ANCA and if possible, histopathological analysis of the injury in order to seek higher emplacements for diagnostic confirmation.

Recibido: 27 de agosto de 2016
Aceptado: 25 de septiembre de 2016

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