Neurosarcoidosis: la necesidad de un diagnóstico definitivo frente a un posible diagnóstico

Neurosarcoidosis – the necessity of definite vs possible diagnosis

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ABSTRACT

A 39-year-old Caucasian female presented with two months of numbness/tingling and change in temperature sensation of extremities. Examination revealed decreased strength of bilateral hip flexion/extension (4+/5), and left plantar flexion (4/5); extended reflex area of C6-C8, absent lower extremities deep tendon reflexes and slight extension of right plantar reflex; impaired pinprick and temperature sensations from D7 downwards; vibratory anesthesia from left tibiotarsal joint and reduced on the right hallux; proprioceptive defects in ≥25% of lower extremities examination. Neuroaxis MRI showed intramedullary hyperintense lesions on C2, D6 and a longitudinal extensive lesion on C7-D3. On CSF analysis: protein (100.8 mg/dL), ACE (12 U/L) and CD4+/CD8+ ratio (6.3).

Although spinal biopsy was not performed, imaging was suggestive of neurosarcoidosis and corticosteroids improved the symptoms. Our case questions the need for definite diagnosis taking into account the risk/benefit of the spinal biopsy, and displays the difficulty of distinguishing isolated vs initial picture of sarcoidosis.

Keywords: Neurosarcoidosis, sarcoidosis, transverse longitudinal myelitis, spinal cord.

RESUMEN

Mujer caucásica de 39 años de edad que presenta dos meses de entumecimiento/hormigueo y cambios en la sensación térmica de las extremidades. La exploración reveló una disminución de la fuerza de flexión/extensión bilateral de la cadera (4+/5), y de la flexión plantar izquierda (4/5); extensión del área refleja de C6-C8, ausencia de reflejos tendinosos profundos de las extremidades inferiores y ligera extensión del reflejo plantar derecho; alteración de las sensaciones de pinchazo y temperatura desde D7 hacia abajo; anestesia vibratoria de la articulación tibiotarsiana izquierda y reducida en el hallux derecho; defectos propioceptivos en ≥25% de la exploración de las extremidades inferiores. La RMN del neuroeje mostró lesiones hiperintensas intramedulares en C2, D6 y una lesión longitudinal extensa en C7-D3. En el análisis del LCR: proteínas (100,8 mg/dL), ECA (12 U/L) y ratio CD4+/CD8+ (6,3).

Aunque no se realizó biopsia espinal, el diagnóstico por imagen era sugestivo de neurosarcoidosis y los corticosteroides mejoraron los síntomas. Nuestro caso cuestiona la necesidad del diagnóstico definitivo teniendo en cuenta el riesgo/beneficio de la biopsia espinal, y muestra la dificultad de distinguir cuadro aislado vs cuadro inicial de sarcoidosis.

Palabras clave: Médula espinal, mielitis longitudinal transversa, neurosarcoidosis, sarcoidosis.

CASE PRESENTATION

An otherwise healthy female in her 30's presented to the emergency department with a two-month course of numbness, tingling and change in temperature sensation in both feet and hands. While the hands maintained symptomatic stability, ascending sensitive changes progressed from the lower limbs to the abdomen. The patient reported unbalanced gait with decreased strength of lower limb associated with falls. Examination revealed decreased strength (Medical Research Council grade) of bilateral hip flexion and extension (4+/5), and left plantar flexion (4/5). Extended reflexogenic area of C6-C8 reflexes was noted, with absent lower extremities reflexes, and right positive Babinski sign. Pinprick and temperature sensations were impaired from D7 dermatome downwards. Vibratory anesthesia was present from left tibiotarsal joint downwards and mildly reduced on the right hallux, with proprioceptive errors in hallux examination.

A spine CT scan was unremarkable, and she was forwarded to outpatient follow-up for further investigations.

Investigations and differential diagnosis

Neuroaxis magnetic resonance imaging (MRI) revealed medullary lesions in C2, D6 and an extensive intramedullary lesion with cord expansion from the level of C5 to D5 with abnormal hyperintense signal on T2-weighted and fluid attenuation inversion recovery (FLAIR) series with contrast enhancement (Figure 1). This LETM was bordered above and below by edema. On T1 axial after contrast there was a posterior cord lesion, resembling a "trident sign" (Figure 1H).

Initial blood tests (basic blood panel, sedimentation rate, glycated hemoglobin, iron tests, vitamin B12, folate, thyroid function tests, serum protein electrophoresis, syphilis and Borrelia serologies, human immunodeficiency virus, hepatitis B and C virus, angiotensin converting enzyme (ACE), coagulation) including autoimmunity (complement, anti-nuclear, anti-neutrophil cytoplasmic and anti-dsDNA antibodies), were normal. Anti-MOG and anti-AQ4 antibodies were negative. Lumbar puncture demonstrated increased cerebrospinal fluid (CSF) protein (100.8 mg/dL), ACE (12 U/L) and CD4+/CD8+ ratio (6.3). Ol-

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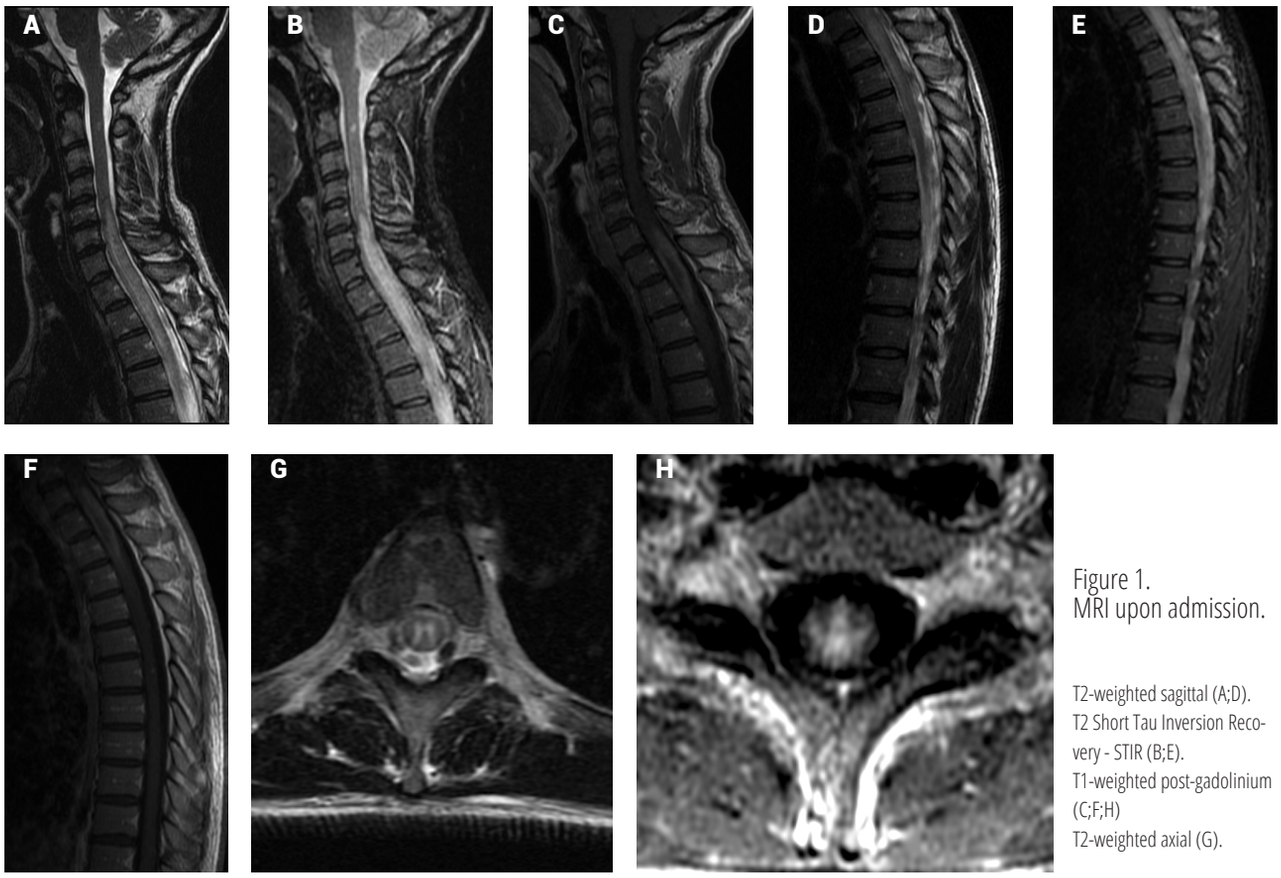


Figure 1.
MRI upon admission.

T2-weighted sagittal (A;D).
T2 Short Tau Inversion Recovery - STIR (B;E).
T1-weighted post-gadolinium (C;F;H)
T2-weighted axial (G).

Long segment cord abnormality with hyperintensity on T2 and T2-STIR and cord expansion (A, B, D, E) from C5 to D5, consistent with longitudinal extensive transverse myelitis (LETM) with an additional medullary foci of C2 hyperintensity in T2 and T2-STIR. There is heterogeneous enhancement, more evident peripherically. G) "H-sign" T2 central hyperintensities along the medullar gray matter. H) T1 Axial view post gadolinium demonstrating posterior cord lesion, with the 'trident sign' highlighted.

igoclonal band were negative both in blood and CSF. A whole-body CT did not show any systemic involvement of sarcoidosis nor signs of malignancy.

She was hospitalized after developing post-lumbar puncture headache with CSF hypotension, with progressive clinical worsening, for further investigation and to initiate systemic corticosteroids.

Although she did not exhibit any respiratory disfunction, she performed a pulmonary function test, which was unremarkable. Since she was under systemic corticosteroids, which would compromise the results of bronchoalveolar lavage, and the lack of evidence of pulmonary involvement, we did not perform a bronchofibroscopy or other related study.

TREATMENT

Considering the typical MRI abnormalities, raised CSF ACE and CD4+/CD8+ ratio and total or partial exclusion of alternative diagnoses, sarcoidosis with exclusive CNS involvement was considered and methylprednisolone (MP) at 1 g/day intravenously for 5 days was initiated, followed by maintenance oral prednisolone 60 mg daily. On day 2 of MP, she reported improvement of sensation and gait and, on day 4, she showed improvement of lower extremities' strength.

Outcome and follow-up

In the following months, she remained without new symptoms. She referred that the right leg was clumsy, sexual dysfunction and urinary urgency. Upon examination, she presented with a cushingoid appearance, full motor strength, normal deep tendon reflexes (though left Achilles reflex was weaker), a positive left Babinski sign, absent vibratory or proprioceptive defects, pinprick hypoesthesia of right leg and suspended sensitive defect on D5-D12.

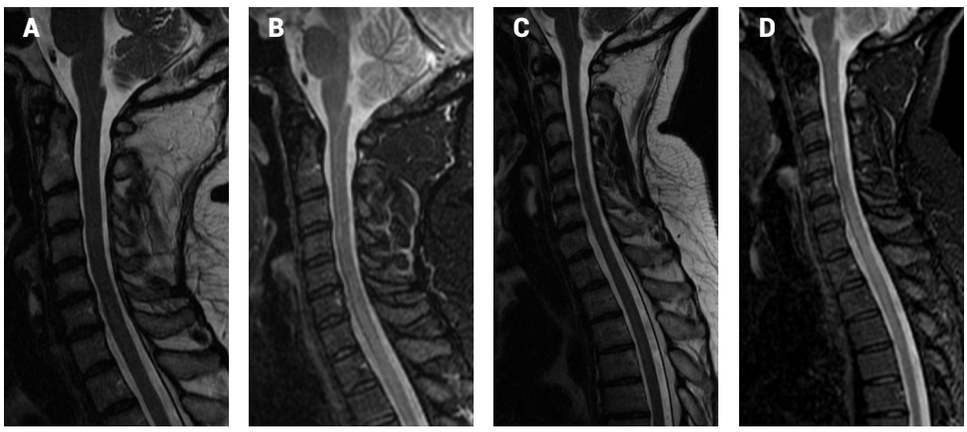
It was decided to slowly taper off prednisolone and methotrexate was initiated.

At control neuroaxis MRI, three months after initiating corticosteroids, there was pronounced reduction of the previously exhibited hyperintense signal. At almost four months after initial treatment with corticosteroids, the area of high signal intensity on C5-D5 and C2 were reduced on T2-weighted series associated with cerebral atrophy and a discrete hyperintense focus on T2 FLAIR in the left semioval center (Figure 2).

DISCUSSION

Definite diagnosis of NS requires central nervous tissue biopsy, which is associated with risk of substantial morbidity[1-9]. Unless there is a high

Figure 2. MRI after 3 (A; B) and 4 (C;D) months of corticosteroids.



T2-weighted sagittal (A;C). T2 Short Tau Inversion Recovery - STIR (B;D). There is an imagiologic improvement with pronounced reduction of medullary hyperintense signal, compatible with diminishing of the edema and there was no longer evident enhancement after contrast.

suspicion of tumor, biopsy should be avoided, and treatment should be initiated as soon as possible after all other etiologies were excluded, especially Neuromyelitis Optica and Myelin oligodendrocyte glycoprotein antibody-associated disease, and clinical picture being suggestive of NS.

A positive serology for AQ4-IgG and MOG-IgG is helpful to distinguish these patients. However, we can't forget that some are seronegative and that makes the distinction from NS more challenging. All these diagnoses have imaging similarities: LETM, cord swelling, post-gadolinium enhancement, and central axial T2 hyperintensity. The "trident sign", best seen on T1 axial post-contrast, is described as a unique imaging feature and a key diagnostic factor. It corresponds to a predilection for the subpial dorsal cord area, although not exclusive to this condition, it can be useful. It is thought to represent the pattern of perivascular spread of leptomeningeal granulomatous inflammation along small to medium-sized vessels and the dorsal location of the lymphatic system of the spinal meninges. Additionally, it is also believed that the increased blood-cord permeability of the vessels in this region to be contributary.

Our clinical case demonstrated on MRI intramedullary contrast enhancement spanning >3–4 levels[8], increased CSF protein[5], increased CSF ACE, which has high specificity[2], and increased CD4+/CD8+ ratio, pointing towards the NS. After considering malignancy, infectious and demyelinating diseases unlikely, we initiated treatment with corticosteroids with immediate neurological improvement, which supports the diagnosis of NS.

Although image on MRI could suggest lymphoma and it could not be completely ruled out even though whole-body CT did not show any signs of malignancy, treatment with corticosteroids caused the significant reduction of lesions as well as improvement of clinical picture, which guided us more towards the possible diagnosis of NS.

After five months under treatment, there were still residual deficits that prevented the patient from returning to her occupation, as it was physically demanding. Additionally, she complained about worsening eyesight which could be a corticosteroid or methotrexate side-effect or even sarcoidosis involvement. She was under physical therapy and was referred to psychology and ophthalmology follow-up. For her hypovision, eyeglasses were prescribed, which she already had used as a teenager, and no signs of ocular toxicity nor sarcoidosis involvement were found.

Though no proof of systemic sarcoidosis was found, it was not certain that she did not have any other system involved since whole-body flourodeoxyglucose positron emission tomography was not performed as a positive finding by itself is not diagnostic and such investigation is expensive and not widely available.

Moreover, this case might be an initial clinical picture of systemic sarcoidosis instead of an isolated NS case, though only time will tell.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Re- search and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors declare not having any conflict of interest related to this paper.

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