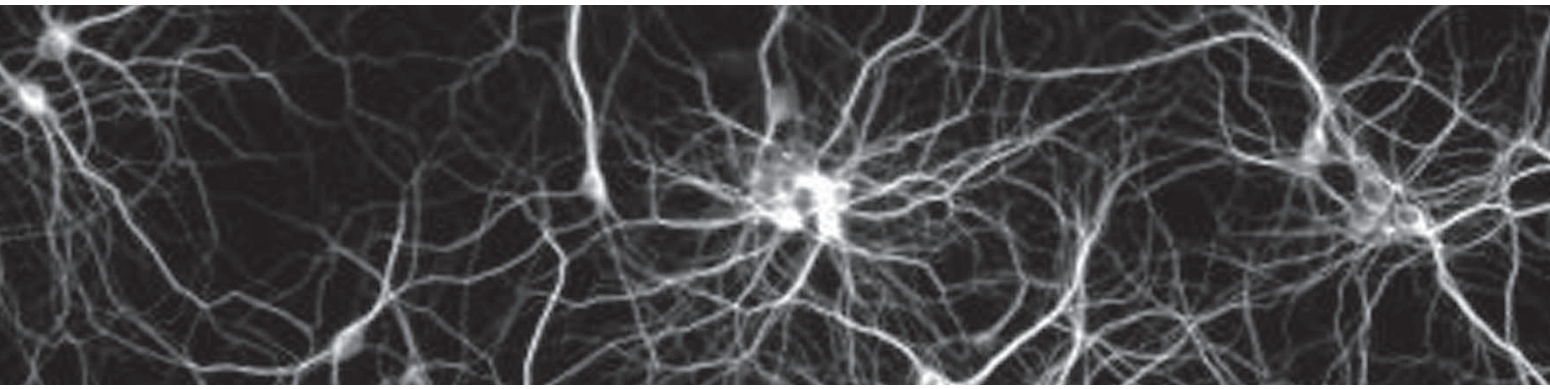

# Engorgement of deep medullary veins as a key diagnostic MRI feature of neurosarcoidosis in an adult man: an unusual presentation of neurosarcoidosis

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ABSTRACT – *Objectives:* The objective of this paper is to present our diagnostic pathway in patients with a non-specific presentation of neurosarcoidosis (NS) without other systemic manifestations specific to sarcoidosis, with an emphasis on the role of magnetic resonance imaging (MRI). *Case description:* A 39-year-old patient who has been suffering from incontinence and paresthesia of the extremities for six years was subjected to numerous tests, including ophthalmological, radiological, neurological, and cardiological, but without clarifying the etiology of the complaints. Other anamnestic complaints during admission include instability when walking, nausea, and blurred vision. *Results:* Neurological examination demonstrated intention tremor on the extremities and on a wider basis gait resembling sensory ataxia. Cerebrospinal fluid (CSF) analysis showed an increased total number of cells, a significantly increased level of total proteins, intrathecal synthesis of oligoclonal IgG bands, and a decreased glucose value. MRI of the brain revealed patchy T2/FLAIR hyperintensities subcorticaly and periventricularly, along the frontal horn and in the putamen on the left side. The enhancement of diffusely dilated medullary veins was seen on the postcontrast images. On the SWI images, numerous small and patchy areas of signal loss were seen, which ultimately led to the diagnosis of NS in addition to a negative broad differential diagnosis. *Conclusion:* Despite numerous diagnostic meth-

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ods, in many cases, MR has a key role, especially for patients with central nervous system involvement without signs of systemic sarcoidosis.

**Keywords:** magnetic resonance, cerebrospinal fluid, paresthesias, sarcoidosis

## INTRODUCTION

Sarcoidosis is defined as a multisystem inflammatory disease of autoimmune etiology predominantly affecting lymph nodes and lungs characterized by the pathognomonic formation of noncaseating granulomas, typically occurring in young adults between 20 and 40 years of age (1). Neurosarcoidosis (NS) refers to the involvement of the central or peripheral nervous system, and simultaneous affection of CNS or PNS with other systems is estimated to be 5%–10% of all cases. Isolated NS is extremely rare, with an approximated incidence of 0.2/100 000 (2). Clinical presentations of NS vary and result from the nature and volume of the affected tissue. The most common clinical presentations of NS are cranial and peripheral neuropathy, hypothalamic and pituitary involvement, pachymeningitis, leptomeningitis, psychiatric disorders, vasculitis, and affection of the spinal cord (3).

Diagnosis is established after an extensive diagnostic work-up, including neurological examination, neurophysiological studies, cerebrospinal fluid analysis (CSF), and magnetic resonance imaging (MRI) as the most important imaging modality. Brain or nerve biopsies are important methods in establishing pathohistological diagnosis. So far, there are no NS specific CSF biomarkers (4).

MRI features, with obligatory contrast administration, include meningeal, leptomeningeal, and vessel wall enhancement, along with brain and spinal cord parenchymal lesions. An MRI SWI (susceptibility-weighted imaging) examination is warranted in this case due to the potential association between deep medullary vein engorgement and neurosarcoidosis. Notably, recent studies have demonstrated that medullary vein engorgement was present in 7 out of 21 patients, with a higher prevalence observed in the male population (5, 6).

Treatment includes corticosteroids and immunosuppression, and for those with severe disease or treatment unresponsive patients, biological therapies, including TNFα antagonists, are available.

## CASE DESCRIPTION

A 39-year-old male patient has been referred for occasional episodes of right-sided limb-ascending paresthesias accompanied by nocturnal enuresis, blurred vision, and gait instability lasting for six years. Paresthesias appeared in irregular intervals and in variable parts of the affected limb, lasting never more than 30 minutes. During the patient's interview, he reported that his father has lung-affecting sarcoidosis.

There were no comorbidities present in patient's history. In 2017, an ophthalmologic assessment showed bilateral temporal and upper quadrant visual field defects due to blurred vision. The same year, a neurological examination revealed the intentional tremor with an ataxic wide-based gait. EEG, carotid Doppler ultrasound, and electromyoneurography (EMNG) findings were normal with a negative Fabry disease test. Initial brain MRI revealed an oval 11 mm lesion in the basal ganglia region corresponding primarily to a subacute vascular lesion. Following MR angiography excluded aneurysmal dilatation and stenosis. Due to the worsening of the aforementioned difficulties, the patient underwent a new diagnostic work-up in 2022. Chest x-ray findings and chest multi-slice computer tomography (MSCT), were inconclusive with doubtful left hilar lymphadenopathy. In December 2022, CSF analysis demonstrated increased total cell count (107, out of which 91 were small lymphocytes), significantly elevated levels of total proteins (1,55 g/L), intrathecal oligoclonal band synthesis, and slightly decreased levels of glucose (2,10 mmol/L). In addition, CSF analysis ruled out *Borrelia burgdorferi*, *Listeria*, *Morbillivirus*, *Rubella*, VZV, and HSV1 infection and showed elevated intrathecal chitotriosidase levels (CSF to serum chitotriosidase ratio Q 3,30). This was the only spinal tap that was performed and analysis of flow cytometry in CSF was not done. Autonomic nervous system testing was normal and EMNG did not reveal signs of polyneuropathy and serum calcium, chitotriosidase and angiotensin-converting enzyme (ACE) were normal. MRI depicted subcortical and periventricular areas of increased T2 fluid-attenuated inversion recovery (FLAIR) signal in-

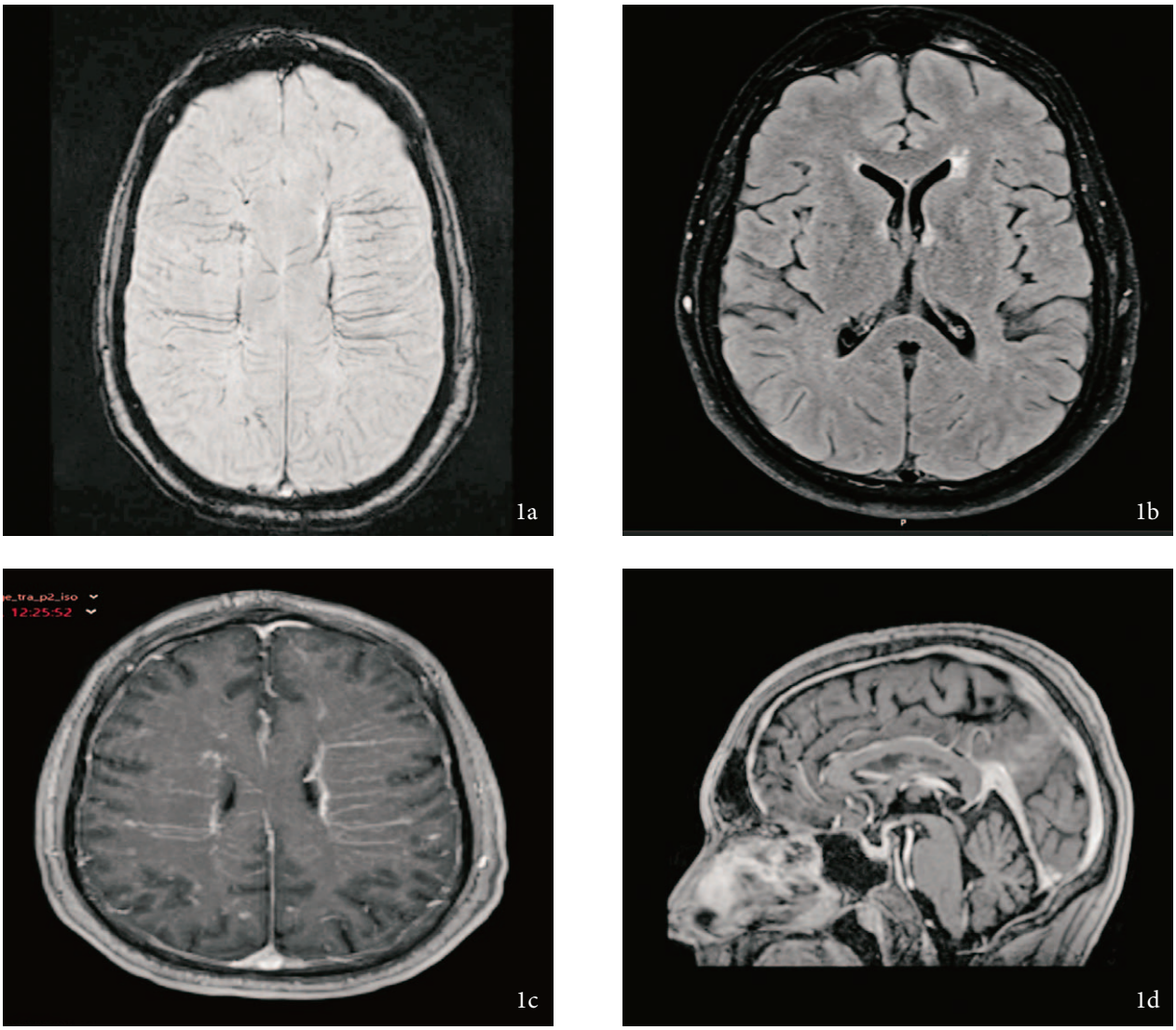


Fig. 1. *a) SWI MR shows multiple small subcortical areas of signal loss corresponding to microhemorrhage-related hemosiderin deposits and engorgement of medullary veins. b) T2/FLAIR sequence shows subcortical and periventricular hyperintensities. c) The contrast-enhanced T1-weighted MPRAGE sequence depicting diffusely dilated medullary veins. d) Sagittal plane – contrast-enhanced T1-weighted MPRAGE sequence shows contrast enhancement of the floor of the 3rd ventricle.*

tensity, also present on the left side around the anterior horn of the lateral ventricle and putamen. The postcontrast T1-weighted MPRAGE sequence revealed diffuse dilatation of medullary veins, accompanied by nodular enhancement situated predominantly in the supratentorial and infratentorial cortex as well as at the bottom of the third ventricle. Multiple small areas of subcortical signal loss were detected on the SWI sequence, located in both cerebellar hemispheres, pons, and supratentorial subcortical regions consequently to microhemorrhage-related hemosiderin deposits. MRI findings are demonstrated in Figure 1.

In January 2023, the patient underwent an endocrine evaluation where hypogonadism was detected (total testosterone 0,2 nmol/L) following gonadotropic hypophysis insufficiency. All of these findings were attributed to NS leading to the patient's methylprednisolone-based therapy prescription. A compressive vertebral fracture developed in April 2023 was suspected to be a consequence of hypogonadism and corticosteroid treatment. X-ray finding that demonstrated compressive fracture is depicted in Figure 2. Due to corticosteroids, side-effect therapy was slowly decreased, and azathioprine was introduced. In July 2023, the patient was scheduled to undergo a brain biopsy; however, the pre-biopsy brain MRI revealed disease remission, thereby confirming the effectiveness of the administered therapy and the initial diagnosis.

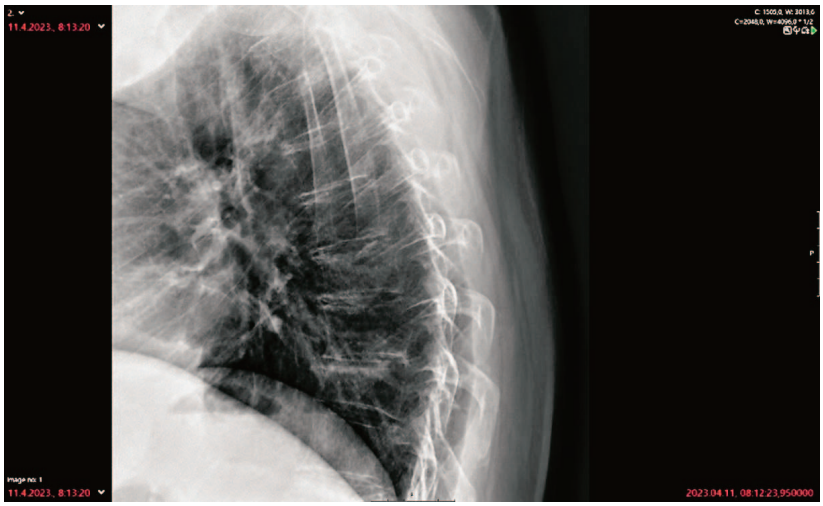


Fig. 2. *Compressive vertebral fracture due to developed osteoporosis as a complication of corticosteroid treatment and hypogonadism.*

Consequently, the patient opted to forego the biopsy procedure.

## DISCUSSION

We reported a patient with an unusual presentation of NS without any specific systemic non-neurological sarcoidosis characteristics in association with negative serum biomarkers. Even though sarcoidosis is classically considered a multisystem disease, according to recent studies, approximately 10%-20% of patients with NS do not have recognizable systemic sarcoidosis (7, 8, 9). Neurosarcoidosis-related optic neuropathy commonly affects up to 35% of patients with NS and arises through several different processes (10, 11), such as subacute optic neuritis, optic perineuritis, or compressive optic neuropathy. A subacute optic neuritis, which presents identically to demyelinating optic neuritis in most respects, is after facial nerve neuropathy, the most common form of cranial neuropathy (10-14). Our patient developed blurred vision, accompanied by bilateral temporal and upper quadrant visual field defects, which are suspected to be a consequence of the chiasmal involvement due to infiltration of the hypothalamus and adjacent structures. Noted by several studies, the prevalence of peripheral neuropathy is around 10%-14% of all NS patients, usually concomitant with central neurological disorders without neurophysiological proof of peripheral involvement (15, 16). In those with manifest peripheral neuropathy, the clinical symptoms are sensorimotor or purely sensory, and the electrophysiological investigations point to an axonal pathology predominantly, although there may be conduction slowing, focal conduction block, and multifocal conduction block (15, 16). Despite normal nerve conduction findings documented in 2017 and 2023, our patient presented with occasional symptoms of sensory polyneuropathy which came along in irregular intervals lasting never more than 30 minutes. Hypothalamic and pituitary involvement has been verified on the first MRI performed in our center and confirmed through hormone analysis. Gonadotropin and thyroid insufficiency coinciding with diabetes insipidus are often identified during endocrine evaluations (17, 18). Despite a radiological response, most of these do not improve with treatment, but complete recovery still occurs (18). Significantly decreased levels of total testosterone (0,2 nmol/L) were noticed in our patient which later contributed with corticosteroids to the osteoporosis-related thoracic vertebral compressive fracture. At the onset of systemic sarcoidosis, lymphopenia is usually noticed due to the accumulation of activated T-cells at the inflammation sites (3). Also, raised serum calcium occurs in 10% of cases because of the upregulation of an enzyme that converts 25 – hydroxy vitamin D to 1,25 dihydroxy vitamin D (3). However, none of these laboratory abnormalities were found in our patient. Furthermore, elevated levels of ACE are noticed in 60% of patients with systemic sarcoidosis, but it is not a useful disease monitor biomarker since it does not always rise in relapse and is not associated with disease progression (19). A recent comparative study of ACE and chitotriosidase revealed that a raised serum chitotriosidase had a specificity of 85% in sarcoidosis (20). Not any of these serum biomarkers were detectable in our patient which

also makes this case unusual. Regarding CSF analysis, in a recent series of 128 patients with NS affecting the CNS, the median CSF protein was 0,8 (0,19 – 8,35) g/L and raised in 76% of 89 samples. The CSF to plasma glucose ratio was reduced in 81% of patients. Moreover, the median CSF white cell count was 5 (0-395) cells/μL and raised in 51% of samples. Finally, oligoclonal bands were negative in serum and CSF in 73% of this series (9,21-23). Comparatively, our patient presented with an increased CSF total cell count, significantly elevated levels of proteins (1,55 g/L), lower glucose levels (2,10 mmol/L) combined with present intrathecal oligoclonal bands, and elevated CSF to plasma chitotriosidase ratio Q (3,30). Meanwhile, those findings are nonspecific and could be also identically manifested in some other CNS conditions such as multiple sclerosis (MS) or CNS infections. MRI is the most important imaging method and in a recent series, MRI findings were abnormal in 35% of those with cranial neuropathy excluding optic neuropathy, and 100% of those with central neurological disease (11). Performing MRI imaging with paramagnetic contrast administration is essential due to its capacity to provide visualization of specific pathological conditions. Meningeal enhancement, which often corresponds with the site of the disease, including affected vessel walls, can be accurately evaluated through the utilization of this technique. Furthermore, in instances of leptomeningeal disease, the approach proves to be invaluable in delineating enhancement patterns within the adjacent cortex and white matter, thereby offering critical insights for accurate diagnosis and subsequent treatment strategies. In the context of isolated NS, the identification of vein wall enhancement and venous engorgement can provide invaluable diagnostic insights (6), especially in challenging clinical cases like this one. One recent study involving 32 patients demonstrated a sensitivity of 71.4% and specificity of 92.3% for the deep medullary vein sign which substantiates that this MR finding effectively bridges diagnostic gaps in the prior extensive diagnostic evaluation (24). However, in a very recent paper, the deep medullary vein sign was entirely absent in 14 patients with confirmed NS on histopathological examination (25). This finding complicates the diagnostic process of isolated NS, particularly when considering that venous engorgement can also be present in certain brain neoplasms, arteriovenous malformations, venous thrombosis, or Struge-Weber syndrome (26). Nonetheless, in those specified conditions, a favorable response to our therapy would not be anticipated. Our patient developed multifocal lesions on the T2/FLAIR sequence, multiple areas of signal loss on the SWI sequence, and medullary veins enhancement on the postcontrast T1-weighted MPRAGE sequence. The combination of these MRI findings, along with the patient's response to prescribed therapy for NS, played a pivotal role in confirming isolated NS.

## CONCLUSION

Even though that is a rare entity, it should be kept in mind while evaluating patients with multiple non-specific CNS symptoms of longer duration. Sometimes, despite many diagnostic procedures, MRI is one of the most important methods to confirm our suspicion of NS.

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