Neurosarcoidosis: A Case Report and Literature Review

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Summary. Sarcoidosis is an inflammatory granulomatous systemic disease of unknown origin affecting multiple organ systems. The lungs, ocular, and skin involvement are thought to be the most common presentations of the disease. The diagnosis is established when clinico-radiological findings are supported by histological evidence of noncaseating epithelioid granulomas of the affected organs. Neurosarcoidosis is considered a rare form of sarcoidosis which can be both isolated or have a systemic manifestation. The incidence of clinical involvement of the nervous system in a sarcoidosis population is estimated to be about 5–15%. Generally, neurosarcoidosis can manifest as a cranial neuropathy with unilateral or bilateral VII nerve palsy and optic nerve involvement being the most common manifestations; it can also cause aseptic meningitis, headaches, seizures, and neuroendocrinological dysfunction such as diabetes insipidus, adenopituitary failure, amenorrhea-galactorrhea syndrome, etc. A far less common presentation of neurosarcoidosis is the involvement of the spine. We present a case report of a 49 year old male patient with neurosarcoidosis manifesting itself as a thoracic myelopathy accompanied by mediastinal lymphadenopathy, confirmed histologically and by imaging studies.

Keywords: neurosarcoidosis, intramedullary, systemic, CNS, mediastinum.

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CASE REPORT

A 49 year old male patient was admitted to Respublikinė Vilniaus Universitetinė Ligoninė (RVUL) Neurosurgical department to diagnose and receive treatment for intramedullary tumor *in suspicio* in the Th3-Th7 segments of the anterior spine, confirmed by imaging studies (MRI) on an outpatient basis.

Since other causes of the lesion, such as vascular, inflammatory, demyelinating, and infectious in origin could not be excluded at the time, the patient was transferred to the neurology ward in the same hospital for further testing and examination.

Anamnesis morbi. The patient started to complain of weakness in the left foot followed by heat sensations in the left leg extending to the upper abdomen, mild constant nonradiating back pain in the thoracic and lumbar areas, frequent urination, and urinary incontinence. Close questioning revealed multiple tick bites in the past without any episodes of fever, *erythema migrans.*

On examination. Areflexia in both legs, positive Babinsky sign bilateraly, hypesthesia up to Th10-11 segment, leg muscle strength 4/5.

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Analysis of cerebral spinal fluid (CSF) reveals negative IgM, IgG for Lyme's disease, negative TPHA, RPR reactions for Tr. Pallidum infection, negative HIV antibod-

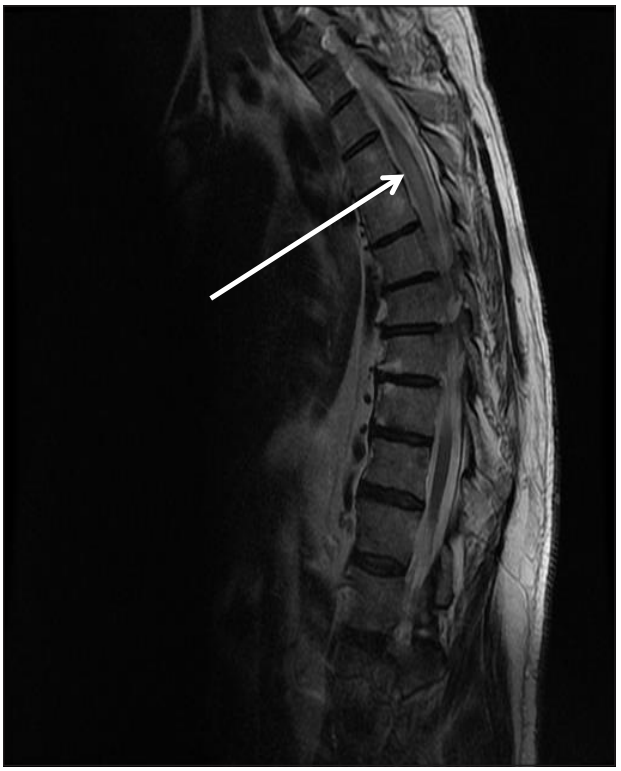

Fig. 1. **Image (T2 frFSE) demonstrates enhanced intramedullary lesion in the thoracic spine Th3-Th7 segment**

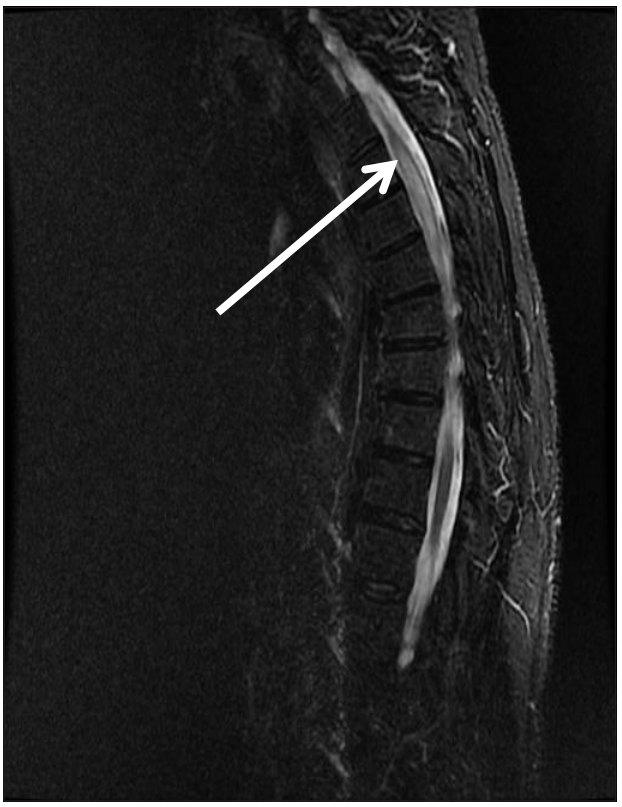

Fig. 2. **Image (T2 STIR) showing even more enhanced intramedullary lesion**

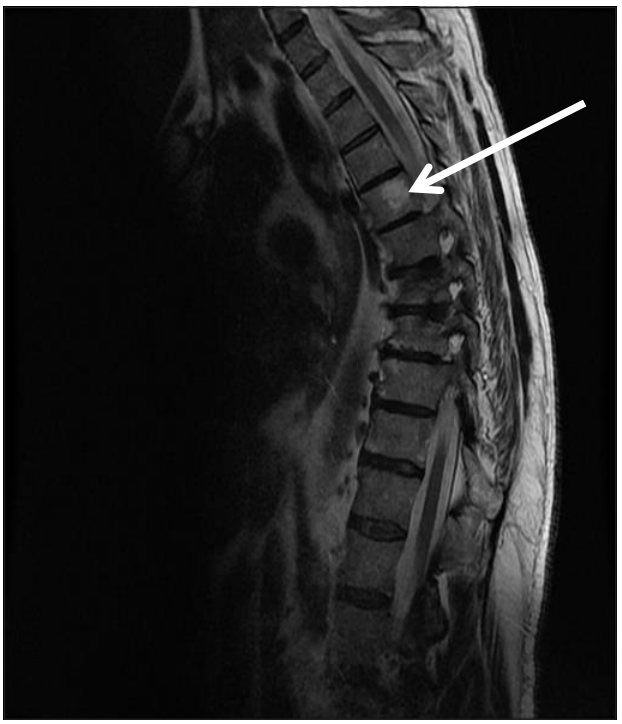

Fig. 3. **Image (T2 frFSE) notes the lesion in the body of the thoracic spinal vertebrae**

ies, but weekly positive oligoclonal bands, elevated protein levels of 0.74 g/L (N 0.15–0.45 g/L) WCC at 0.011×10^9/L with 98% lymphocytes present.

CBC, electrolytes, coagulation profile, and other laboratory tests within normal parameters. ESR within normal range – 29 mm/h (Westergren).

A chest X-ray highly suggestive of right side mediastinal lymphnode envolvement and lymphadenopathy was performed, later to be confirmed by chest CT.

A biopsy of the mediastinal enlarged lymphnodes was performed. Pathological report strongly corresponded to the diagnosis of sarcoidosis with findings of multiple, well defined granulomatous noncaseating lesions with infiltration of lymphocytes, epithelioidal, and Langhans giant cells.

MRI of the brain revealed bifrontal subcortical nonspecific lesions with signs of hydrocephalus. Findings were suggestive of intracerebral course of disease as well as disease of the spine.

A treatment course of prednisolone 60 mg/d per os for one month was administered. Reassessment was scheduled after one month of treatment.

LITERATURE REVIEW

Introduction

Sarcoidosis is a systemic granulomatous disease of still undetermined etiology [1, 2]. Sarcoidosis mainly affects the lungs, but up to 30% of all histologically confirmed cases manifest themselves in other organ systems of the body [3]. The disease may be acute or present itself in a chronic fashion. It may also present itself as an isolated disease of the nervous system, but may be a part of a confirmed systemic illness.

Neurosarcoidosis has protean manifestations and can affect intracranial structures such as leptomeninges, hypothalamus, and cranial nerves, or can involve the spine and its coverings, the peripheral nerves, and the muscles.

The prognosis for neurosarcoidosis is difficult to evaluate due to low prevalence of the disease. Different forms of neurosarcoidosis have different outcomes. Patients with dural lesions, peripheral neuropathy, cranial nerve lesions, and, to a lesser degree, nonenhancing brain lesions seem to fare better than patients with leptomeningeal, brain parenchymal, and spinal lesions [4].

The immunopathogenesis and treatments of neurosarcoidosis are similar to those of systemic disease.

Epidemiology

In the United States, sarcoidosis ranges from 11 per 100,000 in Caucasians to 36 per 100,000 in African Americans and tends to manifest prior the age of 40. The incidence of clinical involvement of the nervous system in a sarcoidosis population is estimated to be about 5–15% [2, 3]. However, one has to keep in mind that not every sarcoidosis case presenting itself with a neurological deficit can be termed as neurosarcoidosis, so it is hard to estimate the true incidence of the disease.

The typical mean age of onset for neurosarcoidosis is estimated to be 33–41 years, that is a few years later than other forms of sarcoidosis. Neurologic manifestations occur within the first two years of the disease [2, 4]. Like in systemic disease, neurosarcoidosis tends to affect more blacks than whites, and women make the majority of these cases. A study carried out by Stern et al. suggested that 85% of the patients who had been diagnosed with neurosarcoidosis were African Americans, and 64% of these patients were female [2]. However, others suggest that this might not be a constant. A study carried out in the United Kingdom stated that 29 of 30 patients with confirmed neurosarcoidosis were Caucasian, and 53% were male [5]. This might suggest that the incidence of neurosarcodoisis depends not so much on race and gender but on the environmental factors in certain geographic areas as well.

Etiology

Many hypotheses have been proposed on the probable causes of sarcoidosis. Researchers suggest that a granulomatous process may arise by infection with mycobacteria and propionibacteria [6]. Other researchers suggest that there might be a genetic predisposition for the immune mechanisms arousing sarcoidosis. It has been proposed that individuals with HLA-B8 and other antigens might be susceptible to the disease or even have a chance for spontaneous remission in some cases [7]. Because sarcoidosis mainly affects the lungs, skin, and the eyes, it is thought by some researchers that exposure to airborne antigens might be one of the etiological factors of sarcoidosis. Recently, associations between sarcoidosis and inorganic particles, such as photocopier dust [8], insecticides, and moldy environments [9] have been established. Occupational studies revealed that some occupations such as serving in the U.S. NAVY [10] and firefighting [11] might set off an immune response consequently leading to sarcoidosis. Recently, it has been reported that firefighters who had worked in the World trade center during 9/11 in 2001 were found to have an increased incidence in sarcoidosis [12]. Though many hypotheses have been proposed and explored, the exact cause of the disease remains unknown.

Pathogenesis

The pathogenesis of sarcoidosis still remains unclear, but it is thought to be a T-cell mediated immune response following an exposure to an antigen via MHC II complex. Activated macrophages and activated CD4+ T-cells release cytokines and chemokines, including interferon , tumor necrosis factor , and interleukin (IL) including IL-2, IL-6, IL-12, IL-15, IL-16, and IL-18. Other cells are then recruited to the site of granuloma formation and become activated.

Following accumulation of mononuclear inflammatory cells in the affected tissues, macrophages tightly aggregate and differentiate into epithelioid histiocytes and multinucleated giant cells. CD4+ and CD8+ lymphocytes and some B cells form a rim around the granuloma. Subsequently, the inflammatory nodule becomes encased in fibroblasts, mast cells, collagen fibers, and proteoglycans, forming a destructive region of fibrosis through an incompletely understood process.

Lesions in the central nervous system are formed in a similar fashion via similar mechanisms as the lesions in the lungs and other organs as well.

Signs and symptoms

Neurosarcoidosis can present in a vast majority of forms. It can involve cranial structures as well as the spine, peripheral nerves or cause myopathy.

Cranial neuropathy

Of a vast array of clinical manifestations, cranial nerve involvement seems to be the most common [2]. Any cranial nerve can be affected, and sometimes multiple cranial nerve involvement is common. Cranial nerves may be injured directly due to formation of granulomas or indirectly via increased intracranial pressure or meningitis.

The most common neurological manifestation seems to be unilateral or bilateral VII nerve (Bell's) palsy [13]. Bilateral palsy may present simultaneously or sequentially. VII nerve palsy is a rather short term complication that in most cases resolves completely.

Optic nerve damage is also a very common presentation of neurosarcoidosis, if not more common than the ones mentioned above. A study carried out on 30 patients with confirmed neurosarcoidosis via brain biopsy showed that optic nerve involvement was suspected in 37% of patients, with 64% bilateral and 36% unilateral involvement of the optic nerve [8]. When optic neuropathy occurs, especially in young patients, multiple sclerosis is considered a likely cause. In these cases, a chest radiograph with evidence of sarcoidosis makes multiple sclerosis highly unlikely [14].

Unilateral or bilateral VIII cranial nerve involvement is sometimes observed and could cause auditory or vestibular dysfunctions, although it can be asymptomatic and can be detected by brainstem auditory-evoked responses.

Heerfordt's syndrome consists of cranial neuropathy (mostly the facial nerve), uveitis, parotid gland enlargement, and fever. This syndrome is highly suggestive of sarcoidosis.

Papilloedema

The diagnosis of neurosarcoidosis should be considered in young adults, particularly females of childbearing age, with rapidly developing papilloedema, especially associated with the seventh or other nerve palsies. In sarcoidosis patients, fundoscopy should always be performed.

Aseptic meningitis

Meningitis may be acute or chronic and present itself with headaches, fever, neck rigidity, and a sterile cerebrospinal

fluid (CSF). Meningeal infiltration preferably involves the basal leptomeninges, which might lead to CSF flow obstruction leading to hydrocephalus, or could involve the cranial nerves as well. By some researchers, meningitis manifests itself in up to 40% of cases [15, 16]. Analysis of CSF reveals pleocytosis, usually with lymphocytes present [17]. Hypoglycorrhachia is observed in about one fifth of patients [18].

Cerebral sarcoid lesions

Cerebral sarcoid lesions may remain small or form large intracranial tumors; they can also be single or multiple in number. The localization of these granulomas varies from meningeal lesions to lesions of the parenchyma [19–22]. Occasionally, periventricular white matter lesions can be observed, which may resemble those found in multiple sclerosis, so it is important to differentiate between the two. Asymptomatic periventricular white matter lesions without meningeal enhancement in sarcoidosis patients aged 50 years are most probably not due to sarcoidosis and can be regarded as age-related small vessel disease.

Hypothalamic dysfunction causing diabetes insipidus, amenorrhea-galactorrhea syndrome, decreased pilosity, changes in libido, hypogonadism, adenopituitary failure, or panhypopituitarism can be observed in some cases. Of the mentioned above, hypogonadism and diabetes insipidus along with hyperprolactinemia are the most common presentations [23].

Lesions of the cerebellum may also be found in some cases. Both supratentorial and infratentorial granulomas can be present, the former being more common than the latter [24].

Seizures

Seizures occur in 7 to 22% of neurosarcoidosis cases [25]. In 10% of cases, seizures are the first manifestation of the disease. They can be either generalized or partial [26]. The etiological mechanisms of seizures include leptomeningeal infiltration with cortical irritation, parenchymal masses, metabolic disturbances related to hypothalamic dysfunction, and possibly small vessel vasculitis associated with granulomatous angiitis. The presence of seizures indicates chronicity and poor prognosis although in some cases they can be easily controlled with anticonvulsant medications [26].

Neuropsychiatric symptoms

Patients with neurosarcoidosis were found to have increased prevalence of significant stress (55% of patients) due to deterioration of physical health. These patients are also more prone to depression (up to 66% of patients) [27]. Encephalopathy or psychosis may also arise. Other mental changes include cognitive changes, memory loss, altered sensory functions, etc [28].

Table 1. **Symptoms suggestive of small fiber neuropathy**

Sensory:
Pain
Parasthesiae
Sheet intolerance
Restless leg syndrome
Autonomic dysfunction:
Hypo/hyperhidrosis
Diarrhoea/constipation
Urinary incontinence/retention
Gastroparesis
Sicca syndrome (xerophtlamia, xerostomia, enlargement of the parotid glands)
Blurry vision
Facial flushes
Orthostatic intolerance
Sexual dysfunction
New-onset arrhythmias without signs of coronary heart disease

Spinal cord lesions

Lesions in the spinal cord can be extradural or intradural (further divided into intramedullary or extramedullary) and can cause arachnoiditis, cauda equina syndrome, and sensory and motor dysfunction in the trunk and limbs as well. Spinal lesions are estimated to make up to 20% of neurosarcoidosis cases both isolated or with systemic involvement [5, 29]. Intramedullary involvement of the spine is considered a rare manifestation of the disease. Diagnosis can be difficult to obtain because granulomas in the spine often resemble and are indistinguishable from a malignant tumor both clinically and radiologically [30, 31].

Peripheral neuropathy

Peripheral neuropathy is considered a rare form of neurosarcoidosis [32], although some authors suggest that the rate of incidence is from 15 to 18% [2, 4] and the manifestations can be as common as lesions in the CNS, but the patients remain asymptomatic or escape detection at times [33]. Peripheral neuropathies have a wide spectrum of clinical and pathological presentations. Large fiber neuropathies include multiple mononeuropathies, polyradiculopathy, Guillain-Barré syndrome, and distal symmetric polyneuropathy which may be sensorimotor, mostly sensory, or mostly motor [4, 34]. A symmetric axonal polyneuropathy is the most common neuropathy [33]. Sensory deficit is more common than motor in patients with sarcoid neuropathy, but chronic pain remains one of the most common symptoms reported in patients with sarcoidosis. A relatively large number of mononeuropathies can be observed in some cases with the ulnar and peroneal nerve mononeuropathies being the most common presenations. Peripheral nerve biopsy is a handy

diagnostic tool displaying typical noncaseating epithelioid granulomas. Necrotising vasculitis and microvasculitis without obvious signs of necrosis is also observed [35].

Small fiber neuropathy

Small fiber neuropathy has only recently been identified as a distinct manifestation of neurosarcoidosis. With a vast array of symptoms and a lack of diagnostic tools, it can both easily be missed and cause life threatening complications to sarcoidosis patients. Sympathetic denervation of the heart, causing arrhythmias and restless leg syndrome has been observed in sarcoidosis patients [36, 37]. Restless leg syndrome is associated with sleep disturbances in some cases. Table 1 presents findings that might suggest small fiber neuropathy in sarcoidosis patients. The pathophysiology and treatment of small fiber neuropathy in sarcoidosis patients are not well understood and need further research.

Myopathy

Muscle involvement in sarcoidosis can be either symptomatic or asymptomatic, the latter being more common. Asymptomatic myopathies are confirmed in autopsies and clinical series from 50 to 80% of cases [38]. Symptoms of muscle disease are far more rare, accounting for only up to 2% of cases [39]. Symptomatic sarcoid muscle myopathy can be classified into nodular sarcoid myopathy, acute or subacute myositis, and chronic sarcoid myopathy [40]. The nodules are palpable, but painless, usually not associated with muscle weakness; serum muscle enzyme levels appear normal in this case [40, 41].

Acute myositis is rare and more frequently seen in women, it may present with acute symmetric weakness and swelling of the proximal muscles of limb, with progressive hypertrophy leading to muscle contractures. Serum muscle enzymes are typically elevated [40, 41]. Chronic myopathy is more common, is slower in progression, and occurs later in life. Diagnosis is established via muscle biopsy and electromyography. Sometimes it is difficult to distinguish myopathic muscle changes in sarcoidosis from myopathic muscle changes due to steroid therapy, especially in cases of chronic myopathy. In these cases, muscle biopsy is most helpful.

Diagnosis

Diagnosis of the disease is rather difficult, because it can mimic other diseases of infectious, vascular, connective tissue, malignant in origin, so other possible causes should always be excluded. The diagnosis should be made when there is a compatible clinical presentation, biopsy of any tissue, preferably the brain, showing noncaseating epithelioid granulomas, and radiological and laboratory findings suggestive of the disease. Zajicek et al. proposed diagnostic criteria with levels of certainty which are now commonly used [42]. *Definite* neurosarcoidosis diagnosis can be made when other possible causes of the lesions are explored and excluded, and a brain biopsy has been performed suggesting pathological changes compatible with sarcoidosis. *Probable* neurosarcoidosis diagnosis is established when there is laboratory support (CSF, MRI) of inflammation of the brain, exclusion of alternative diagnoses together with evidence of systemic disease either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging, and serum ACE. *Possible* neurosarcoidosis diagnosis is established when the clinical picture is suggestive of neurosarcoidosis and other possible causes have been explored and excluded, where the above criteria cannot be met [42]. Adapted diagnostic criteria from Judson et al. propose the same level of confidence in diagnosis, but include revised signs and clinical features in each confidence level.

Adapted from the proposed diagnostic criteria by Judson et al. [43]	
Definite	• Positive MRI with uptake in meninges and the brain stem • CSF with pleocytosis and increased protein • Diabetes insipidus • Bell's palsy • Cranial nerve dysfunction • Positive brain biopsy showing granulomatous infiltration
Probable*	• Other abnormalities on MRI • Unexplained neuropathy • Positive electrodiagnostic studies
Possible*	• Unexplained headaches • Radiculopathy
*Requires an extraneural tissue biopsy with positive results in any other organ affected and assumes all other possible causes of disease have been explored and ruled out	

Diagnostic tests

Histology

A tissue sample taken from the organ affected and histologically confirmed presence of noncaseating epithelioid granulomas is the most specific diagnostic test for sarcoidosis. Although biopsies of central and peripheral nerve tissues are often associated with high morbidity and in some cases mortality, the diagnosis of neurosarcoidosis should be established via biopsies of extraneural tissues with clinical finding suggesting neurosarcoidosis. Because of the reasons mentioned above, brain biopsies account only for 10 to 30% in sarcoidosis patients [2, 8]. Still, in cases where brain biopsies are performed to confirm the diagnosis, tissue samples from the meninges and mass lesions are taken most commonly. The specificity of a biopsy of the meninges increases when paired with imaging studies prior to the biopsy.

The Kveim test is an old diagnostic method to detect sarcoidosis, where the antigens from a sarcoidosis af-

fected spleen are placed intradermally. After 4–6 weeks, if a nodule arises at the site of implantation, a biopsy of the skin is taken for histological examination. If the histology reveals noncaseating epithelioid granulomas, this is highly specific of sarcoidosis [44]. Unfortunately, the test is not very sensitive and is not FDA approved, but could be taken into consideration in cases of isolated neurosarcoidosis, because a biopsy of the skin is much less invasive.

Imaging of extraneural organs

Chest imaging demonstrates abnormalities in cases of suspected neurosarcoidosis and is a strong evidence to support the diagnosis. In patients with normal chest radiographs, chest CT, gallium scant, or a PET scan might be helpful in diagnosing systemic disease. High resolution chest CT is more sensitive, especially for detecting nodules along the bronchovascular bundle and subpleural regions [45].

Whole body Gallium (Ga)-67 scan might be helpful in diagnosing systemic disease. Tracer uptake in the lacrimal and salivary glands, chest, and spleen can be observed in 45% of patients.

PET scans are not routinely used to diagnose sarcoidosis, because they are expensive and may produce false positive results in patients with other inflammatory conditions or malignant diseases. Even though a PET scan is not included in the diagnostic criteria for diagnosing sarcoidosis, it may be helpful in some cases for revealing active inflammatory areas and potential biopsy sites in hardly accessible organs such as the brain [46].

MRI of the brain and spine

MRI is considered a gold standard of detecting lesions in the brain of patients with neurosarcoidosis and is more sensitive than a head CT. The most common findings on scans of the brain are white matter lesions and leptomeningeal involvement. Lesions in the white matter account from 43 to 46% of patients tested [42, 47]. Leptomeningeal involvement account from 36 to 38% of cases reported [42, 47]. It is very important to emphasize that imaging enhanced with gadolinium contrast is advised. Gadolinium enhanced images are more likely to detect multiple lesions in different areas such as the white matter, hypothalamus, optic chiasm, gray mater, leptomeninges, etc, compared with images taken without gadolinium contrast [48]. Leptomeningeal lesions were seen in 85% of patients on MRI with contrast versus 15% of patients on MRI without contrast.

Leptomeningeal involvement is most commonly seen in the suprasellar and frontal basal regions of the brain. Although a common finding in neurosarcoidosis, this is not a specific finding of the disesase. Basal leptomeningeal involvement can be seen in other diseases like Granulomatosis with polyangiitis (Wegener's granuliomatosis), tuberculosis, lymphoma, leptomeningeal carcinomatosis, etc.

Neurosarcodosis can present itself as a solitary or multiple enhancing intraparenchymous tumor or a demyelinating disease which can make the diagnosis difficult on MRI. Lesions in the brain can resemble astrocytoma, meningioma, infectious meningeal lesions, or even multiple sclerosis [51].

The spine

Spinal neurosarcoidosis can cause an array of imaging findings including intramedullary, intradural extramedullary, extradural, vertebral, and disk space lesions.

Intramedullary spinal lesions

A very rare form of neurosarcodosis accounting for less than 1% of all cases. Spinal lesions usually appear in the cervical or thoracic levels of the spine as a high intensity signal in T2-weighted images, low intensity signal in T1-weighted images, and show patchy enhancement after contrast admission on MRI [49].

Leptomeningeal and dural lesions

Leptomeningeal lesions are found in up to 60% of cases and are thought to give rise to intramedullary lesions. Extramedullary dural masses are a rare manifestation [50, 51]. Lesions are described as having a dural base and can involve the cervical, thoracic, or lumbar spine respectively.

Bone involvement

The reported estimation of bone involvement is from about 1 to 13% of cases. The actual frequency might be higher because patients often remain asymptomatic or avoid screening. Small tubular bones of the hands and feet are commonly involved, while the skull, long tubular bones, the spine, and pelvis present less frequent manifestations [52].

Vertebral lesions are rare and usually occur in the lower thoracic and upper lumbar segments of the spine. Clinical symptoms include pain, neuralgia, and tenderness. The imaging findings are usually multiple well-defined lytic lesions with sclerotic margins in the vertebral body. MRI shows multiple lesions with low T1 signal, high T2 signal, and enhancement after contrast administration or low T1 and T2 signal in sclerotic lesions. Bone scintigraphy might be used to locate potential biopsy sites, but radiological findings described above are not sufficient enough to make the diagnosis of sarcoidosis. A biopsy should be considered only if evidence of sarcoidosis elsewhere in the body is absent and to rule out other diseases such as myeloma, lymphoma, metastasis, and tuberculosis causing similar radiological features.

Laboratory studies

CSF

CSF abnormalities are not specific and are not eligible to make the diagnosis alone, because similar findings are present in other diseases such as multiple sclerosis and systemic lupus erythromatosus. The common findings suggesting the diagnosis include mild pleocytosis, elevated protein level, and hypoglycorrhachia. Elevated ACE [53,

Table 2. **Differential diagnosis of sarcoidosis**

Infectious diseases
Leprosy Tuberculosis Whipple's disease Toxoplasmosis Mycosis Helminthic infections Treponemal infections Lyme disease
Granulomatous diseases
Wegener's granulomatosis Churg–Strauss syndrome Lymphomatoid granulomatosis
Tumors
Neurolymphomas Gliomas Meningiomas (Leptomeningeal) metastases
Vasculopathies
Vasculitis Behcet's disease
Systemic diseases
Amyloidosis Chronic subdural haematoma
Neurological diseases
Multiple sclerosis Acute demyelinating encephalomyelitis

Table 3. **Differential diagnosis of spinal myelopathy**

Demyelinating diseases
Multiple sclerosis Transverse myelitis Neuromyelitis optica Acute disseminated encephalomyelitis
Tumor
Astrocytoma Ependymoma Hemangioblastoma Metastases Lymphoma
Vascular
Ischemia Spinal AVM
Inflammatory
Vasculitis Sarcoidosis
Infection
Herpes-VZV HIV-VM-TB Bacteria Toxo-fungus Cysticercosis

54], immunoglobulin G index, oligoclonal bands [55, 56], elevated CD4/CD8 lymphocyte ratio [57], lysosome, and -2 microglobulin [58] levels have been reported in patients with neurosarcoidosis.

Elevated ACE levels are found in more than half of patients with neurosarcoidosis, the test being negative in patients with systemic sarcoidosis without neurological manifestation; increased levels of ACE in CSF were found in malignancies of the brain and infectious diseases of the CNS as well [54]. The usefulness of ACE assay is controversial, because a recent study found the test insensitive (24–55%), but highly specific (94–95%) [59]. Furthermore, when establishing the diagnosis, cultures for fungi and bacteria should be negative and there should not be evidence of neoplasm on cytologic reports.

Differential diagnosis

Differential diagnosis is wide, because in general, sarcoidosis is a rare disease and along with histological evidence other diseases have to be excluded to make the diagnosis. Table 2 shows diseases to differentiate from. Table 3 displays the differential diagnosis of sarcoid myelopathy.

Treatment

In general, neurosarcoidosis does not spontaneously resolve, with the exception of unilateral Bell's palsy, so most authors recommend early treatment. Usually, acute neurological manifestations caused by inflammation respond well to anti-inflammatory treatment, while chronic conditions tend to respond less. Treatment options for neurosarcoidosis match those of other forms of systemic sarcoidosis, and steroid treatment is the first-line option. There are no protocols or guidelines on how to carry out treatment, so recommendations on treatment are based on experience rather than evidence. Recommended treatment doses for neurosarcoidosis are higher than in other forms of disease and usually a dose of 1 mg/kg/d is recommended. Intravenous methylprednisolone can be used in severe cases refractory to standard oral treatment. Bolus methylprednisolone can be used to obtain a high initial dose or intravenous treatment on alternate days is possible to avoid the long term side effects of oral treatment. Only if aggressive steroid therapy fails, surgical removal of CNS masses and lesions should be considered. In general, neurosarcoidosis is not as responsive to steroid treatment as other forms of disease [15]. Some patients are refractory to steroid treatment or relapse after administration of lower doses if on steroids alone [15, 42], so these patients require additional treatment options or trial therapy.

To patients, who do not respond to corticosteroid treatment or it causes severe side effects of long-term use, addi-

tional cytotoxic agents such as methotrexate, azathioprine, cyclophosphamide, and cyclosporine can be administered.

Of the cytotoxic drugs mentioned above, methotrexate has been reviewed [60] and is considered a drug of choice in cases of steroid refractory sarcoidosis. The overall response rate to methotrexate has been estimated to be about 66% in systemic forms without brain damage. In 61% of the patients with neurosarcoidosis, methotrexate was able to maintain the patients in remission or to make the administration of lower doses possible [15, 60]. The major problem with methotrexate is liver toxicity, so liver function has to be periodically reviewed.

Cyclophosphamide is a highly toxic drug, producing negative carcinogenic, teratogenic, and hematopoetic effects and should be considered only if other treatment options fail. Nevertheless, it can be used in short regimens and has produced positive effects in some patients. 8 of 9 patients who failed to respond to steroid monotherapy and combination therapy with methotrexate, showed objective and symptomatic improvement on cyclophosphamide [15]. Another case study of 7 patients with neurosarcoidosis reported that after a 5–6 month cyclophosphamide regimen, 4 showed clinical improvement and 7 showed objective improvement on MRI follow up [61].

Immunomodulating drugs can be considered in some cases. Infliximab is a chimeric monoclonal antibody which blocks TNF- activity which imparts the main role in the formation of sarcoid granulomas. A couple of case reports suggest good results on infliximab when other treatment options fail to stabilize the progression of the disease [62, 63], however side effects on central and peripheral nervous system demyelination have been known to happen.

Other pharmacotherapy options include chloroquine and hydroxychloroquine. The latter has been shown effective in stabilizing the disease in patients who either discontinued treatment with steroids due to side effects or did not want to take prednisone [64].

CONCLUSION

Neurosarcoidosis is a rare form of sarcoidosis affecting the brain, spine, peripheral nerves, and muscles. The least common presentation is a sarcoid myelopathy. Neurosarcoidosis has a vast array of clinical manifestations making it hard to diagnose. Tissue biopsy is a gold standard for diagnosing neurosarcoidosis, but since the procedure itself could cause irreversible neurologic deficit, extraneural diagnostic techniques are often used. The treatment strategy is to use immunosuppressive agents, and corticosteroids are the drugs of choice, but there is lacking evidence for both treatment efficacy and outcomes.

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NEUROSARKOIDOZĖ: ATVEJO ANALIZĖ IR LITERATŪROS APŽVALGA

Santrauka

Sarkoidozė yra sisteminė, nežinomos etiologijos liga, paveikianti daugelį organų sistemų ir pasireiškianti uždegiminiais granuliominiais pokyčiais organuose taikiniuose. Dažniausiai paveikiami plaučiai, akys, oda, o diagnozė patvirtinama histologiškai. Neurosarkoidozė – tai reta ligos forma, galinti pasireikšti izoliuotu CNS pažeidimu arba kartu pažeisti ir kitas organų sistemas. Nervų sistema pažeidžiama 5–15 % atvejų, o klinikinė ligos išraiška būna labai įvairi, tačiau regos nervo ar VII galvinio nervo pažeidimo požymiai pasitaiko dažniausiai. Daug rečiau neurosarkoidozė pasireiškia kaip mielopatija. Pristatome atvejį, kai 49 m. pacientui nustatyta histologiškai patvirtinta neurosarkoidozės intramedulinė forma.

Raktažodžiai: neurosarkoidozė, intramedulinė, sisteminė, CNS, tarpuplautis.

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