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# Neurosarcoidosis: symptoms, diagnosis, and treatment – current state of knowledge

## Neurosarkoidoza: objawy, diagnostyka i leczenie – obecny stan wiedzy

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### Abstract

Neurosarcoidosis is an inflammatory disease of unknown aetiology, characterised by the presence of non-caseating granulomas within the nervous system. Its prevalence in patients diagnosed with sarcoidosis is estimated to be approximately 10%. The clinical presentation is ambiguous, with symptoms that may manifest acutely or progress gradually over time. Many of these symptoms mimic those of other diseases, making neurosarcoidosis a diagnostic challenge. No sufficiently sensitive or specific biomarkers are available to enable an accurate diagnosis. A range of diagnostic tests must be performed to exclude other conditions. Histopathological confirmation via biopsy is necessary to make a definitive diagnosis, which is not always possible due to the location of lesions and the potential risk of complications associated with performing a biopsy. Once a diagnosis is established, regular follow-up examinations are necessary to monitor disease activity and assess the progression of changes. The optimal treatment strategy depends on the patient's current clinical status and the potential risk of side effects. Three main lines of treatment for neurosarcoidosis have been described. Treatment selection should also take into account the ability of medications to cross the blood–brain barrier. Treatment response, severity of the disease at the time of diagnosis, and lesion location within the nervous system all influence the prognosis. With appropriate treatment, the majority of patients achieve either complete or partial remission. Therefore, neurosarcoidosis requires multidisciplinary specialist care and a comprehensive approach to each patient.

**Keywords:** neurosarcoidosis, neuroinflammation, immunosuppressive treatment, nervous system disease

### Streszczenie

Neurosarkoidoza jest chorobą zapalną o nieznaną etiologię, w której ziarniniaki nieserowaciejące znajdują się w układzie nerwowym. Częstość jej występowania u chorych na sarkoidozę szacowana jest na około 10%. Choroba ma niejednoznaczny obraz kliniczny o ostrym lub powoli postępującym charakterze. Wiele objawów upodabnia ją do innych jednostek chorobowych, co prowadzi do wyzwania diagnostycznego. Nie istnieją wystarczająco czułe i swoiste biomarkery, by można było trafnie ustalić rozpoznanie. Należy wykonać szereg badań diagnostycznych, które pozwolą wykluczyć inne jednostki chorobowe. Żeby postawić definitywną diagnozę, potrzebne jest potwierdzenie histopatologiczne z biopsji, co nie zawsze jest możliwe ze względu na lokalizację zmian i potencjalne ryzyko powikłań po wykonaniu biopsji. Po postawieniu diagnozy należy wykonywać badania kontrolne, które pozwolą monitorować aktywność choroby i ewentualną progresję zmian. Wybór optymalnego leczenia podyktowany jest obecnym stanem klinicznym pacjenta oraz potencjalnym ryzykiem działań niepożądanych. Opisane zostały trzy główne linie leczenia neurosarkoidozy. Wybór leczenia powinien także uwzględniać penetrację przez barierę krew–mózg. Odpowiedź pacjentów na leczenie, stopień zaawansowania choroby przy postawieniu diagnozy, a także lokalizacja zmian w obrębie układu nerwowego mają wpływ na rokowanie pacjentów. Po zastosowaniu odpowiedniego leczenia u większości chorych udaje się osiągnąć całkowitą lub niecałkowitą remisję. Neurosarkoidoza wymaga multidyscyplinarnej opieki specjalistów i szerokiego spojrzenia na pacjenta.

**Słowa kluczowe:** neurosarkoidoza, zapalenie tkanki nerwowej, leczenie immunosupresyjne, choroba układu nerwowego

## INTRODUCTION

Sarcoidosis is a systemic disorder of unknown aetiology, characterised by the formation of non-caseating granulomas in lymph nodes and various organs. It may also involve the brain and peripheral nervous system. According to multiple studies, neurosarcoidosis occurs in 3% to 15% of patients diagnosed with sarcoidosis (Basheer et al., 2023; Bradshaw et al., 2021; Pirau and Lui, 2023; Sarac et al., 2022; Sève et al., 2021; Ungprasert et al., 2016).

## EPIDEMIOLOGY

According to research, neurosarcoidosis is most commonly diagnosed in middle-aged women (Lord et al., 2020; Sarac et al., 2022). The condition is rare in children. In a study by Young et al. (2022), 30 children were identified with neurosarcoidosis. Of these, 30% had primary neurosarcoidosis, while 70% had systemic sarcoidosis.

## SYMPTOMS

The spectrum of symptoms in neurosarcoidosis is broad and very often non-specific. Some patients may develop acute symptoms, while in others, neurological deficits progress gradually over time (Sinha et al., 2024). One of the most common symptoms mentioned in the literature is cranial neuropathy, caused by infiltration of cranial nerve nuclei, especially the optic nerve (resulting in visual disturbances such as blurred or double vision), the facial nerve (leading to palsy), and the vestibulocochlear nerve (causing vestibular dysfunction and hearing loss) (Børhaug and Vedeler, 2021; Bradshaw et al., 2021; Kleinschmidt-DeMasters, 2023; Sambon et al., 2022; Schilke et al., 2024; Voortman et al., 2024; Young et al., 2022). Neurosarcoidosis may also manifest as headache, fever, and neck rigidity, resembling infectious meningitis (Dorman et al., 2019; Fritz et al., 2016; Kleinschmidt-DeMasters, 2023; Lord et al., 2020; Mijajlovic et al., 2014). Neurosarcoidosis can cause leptomeningitis or pachymeningitis, which may resemble tuberculosis (Basheer et al., 2023; Bradshaw et al., 2021; Fritz et al., 2016; Lord et al., 2020; Pandey et al., 2021; Sambon et al., 2022;

Schilke et al., 2024; Voortman et al., 2024). Neurosarcoidosis often causes non-specific symptoms, which makes the condition difficult to diagnose. Tab. 1 presents the symptoms and relevant differential diagnoses.

## DIAGNOSIS

The diagnosis of neurosarcoidosis remains a major challenge. Up to 25% of sarcoidosis cases involving the nervous system are clinically silent and detected only during autopsy (Bradshaw et al., 2021). Diagnostic criteria for neurosarcoidosis were published in 2018 and categorised as possible, probable, and definite. The criteria were based on clinical presentation and the results of various diagnostic tests (magnetic resonance imaging – MRI, cerebrospinal fluid – CSF, electromyography, nerve conduction studies). Clinical symptoms and diagnostic evaluation must indicate typical granulomatous inflammation of the nervous system. An important diagnostic criterion is the exclusion of other disorders that may produce the same symptoms (Stern et al., 2018). It has been emphasised that a biopsy is needed to increase confidence in the diagnosis. However, it is important to recognise that the histological picture of granulomatous inflammation can be found in other diseases such as tuberculosis (Bradshaw et al., 2021). The above-mentioned criteria must be satisfied to make a diagnosis of neurosarcoidosis. When there is no pathological confirmation of granulomatous disease, the diagnosis is considered possible. When there is pathological confirmation of systemic granulomatous disease consistent with sarcoidosis, the diagnosis is probable. When nervous system pathology is consistent with neurosarcoidosis, the diagnosis is definite. Type A refers to cases where extraneural sarcoidosis is evident, while type B means isolated central nervous system sarcoidosis (Stern et al., 2018).

No sufficiently specific or sensitive biomarker is known for the diagnosis of neurosarcoidosis. Therefore, the main aim of serum studies and CSF analysis is to exclude diseases with a similar course, such as infectious meningitis, tuberculosis, multiple sclerosis, Guillain-Barré syndrome, and cancerous processes (Bradshaw et al., 2021; Stanowska et al., 2019). Tab. 2 shows the

Symptom/Manifestation	Percentage of prevalence	Differential diagnosis
Cranial neuropathy	50–75%	Infections, tumour demyelinating conditions
Optic nerve involvement (blurred/double vision)	7–35%	
Facial nerve involvement (palsy)	11–35%	
Vestibulocochlear nerve (hearing, balance issues)	3–17%	
Headache, fever, neck rigidity Leptomeningitis/Pachymeningitis	10–20%	Infectious meningitis (tuberculosis, Lyme disease, fungal)
Hydrocephalus	10%	–
Seizures	15%	Epilepsy
Peripheral neuropathy, sensory/motor abnormalities	2–86%	Guillain-Barré syndrome, neurological infections, diabetes
Pituitary-hypothalamic dysfunction	2–8%	–

Tab. 1. Symptoms and differential diagnosis (Bradshaw et al., 2021)

	Laboratory tests	Abnormalities
Blood chemical tests	Calcium	Hypercalcaemia
	Morphology	Anaemia, leucopenia
	ESR	>20 mm/h
	Serum angiotensin-converting enzyme (ACE)	Increased activity
Cerebrospinal fluid analysis	Cell count	Pleocytosis (usually <100 cells/ $\mu$ l) Lymphocyte predominance
	CD4/CD8 ratio	Elevated (higher than in other inflammatory neurological disorders)
	IL-6 concentration	Elevated
	Protein	Increased
	Glucose	Hypoglycorrhachia
	Immunoglobulin G (IgG) index with corresponding serum	Elevated
	Oligoclonal bands	Present
	Tuberculin test	Negative

Tab. 2. Basic tests and abnormalities in neurosarcoidosis (Basheer et al., 2023; Baughman et al., 2021; Gupta et al., 2023)

basic tests and abnormalities observed in patients with neurosarcoidosis.

Soluble interleukin-2 receptor (sIL-2R) was analysed for its usefulness as a biomarker in sarcoidosis. Serum and CSF levels of sIL-2R were tested, and an index was calculated. Published studies indicate the possible benefit of assessing levels of sIL-2R. CSF sIL-2R levels differentiated neurosarcoidosis from vasculitis or multiple sclerosis, whereas sIL-2R index differentiated patients with neurosarcoidosis from those with meningitis or neurotuberculosis (Chanpura et al., 2024). Elevated levels of serum angiotensin-converting enzyme (ACE) were observed in 60% of sarcoidosis patients, but the published study showed poor sensitivity and specificity, making this marker clinically unreliable (Ungprasert et al., 2016). Examination of the CSF showed abnormalities, but they were not specific to neurosarcoidosis. Repeated CSF examinations were useful to monitor disease activity and response to treatment. Changes in parameters such as cell count, glucose, protein, IgG index, oligoclonal bands, and opening pressure may indicate remission or progression of the disease (Bradshaw et al., 2021). Interleukin 6 (IL-6) levels are higher in active disease, and a CD4/CD8 ratio above 5 also indicates an active form of neurosarcoidosis. Furthermore, studies show that an IL-6 concentration above 50 pg/mL is associated with disease progression and shorter relapse-free survival (Basheer et al., 2023; Voortman et al., 2024). Increasing levels of biomarkers such as ACE,

lysozyme, and neopterin in follow-up CSF analysis indicate disease progression (Chanpura et al., 2024). However, research is needed to identify reliable biomarkers with sufficient specificity and sensitivity to simplify the diagnosis of neurosarcoidosis (Sinha et al., 2024). Serum chitotriosidase, an enzyme produced by activated macrophages may be promising. It showed high sensitivity and specificity in patients with sarcoidosis, including those with nervous system involvement. Serum chitotriosidase levels were elevated and correlated with disease severity, activity, and extent. Its clinical utility is still being evaluated (Bennett et al., 2020).

The sarcoid process usually affects many organs and is not limited to the nervous system; therefore, it is important to perform various examinations and seek specialised consultations. Tab. 3 presents a list of potential biomarkers that may aid in the diagnosis of neurosarcoidosis.

The best choice for neuroimaging is contrast-enhanced MRI performed using various sequences. This non-invasive technique may be useful for diagnosis, monitoring of disease activity, and assessing response to treatment (Shen et al., 2023). Imaging findings are not specific to neurosarcoidosis, and may also mimic other disease entities (Imsirovic et al., 2023). In a published study, 70% of patients diagnosed with neurosarcoidosis had abnormalities on MRI brain examination (Fritz et al., 2016).

According to diagnostic criteria, a nervous system biopsy is needed to make a definite diagnosis (Stern et al., 2018).

Soluble interleukin-2 receptor (sIL-2R)	CSF sIL-2R levels help differentiate neurosarcoidosis from vasculitis and multiple sclerosis
	Serum sIL-2R levels are elevated but not diagnostically specific
	$sIL-2R \text{ index} = (CSF_{sIL-2R} / Serum_{sIL-2R}) / (CSF_{albumin} / Serum_{albumin})$
	sIL-2R index helps differentiate neurosarcoidosis from neurotuberculosis and bacterial/viral meningitis. Additionally, the index is higher in active neurosarcoidosis than in remission
Angiotensin-converting enzyme (ACE)	Serum ACE levels are elevated – a marker of granulomatous inflammation
Beta-2 microglobulin	Cerebrospinal fluid (CSF) ACE levels have poor sensitivity and specificity
Lysozyme	Elevated levels of these biomarkers in CSF may support the diagnosis, but are not specific to neurosarcoidosis

Tab. 3. Markers useful in the diagnosis of neurosarcoidosis (Basheer et al., 2023; Baughman et al., 2021; Fournier et al., 2023)

When neurosarcoidosis affects the central nervous system, biopsy is often not possible because of its invasiveness. The histopathological findings are typically non-caseating granulomas, but they are not specific to sarcoidosis and do not differentiate it from other granulomatous diseases (Shen et al., 2023). When sarcoidosis involves other organs of the body, such as the lungs, lymph nodes, or skin, these sites are preferred for biopsy (Bradshaw et al., 2021). One published study analysed the usefulness of minor salivary gland biopsy as a minimally invasive procedure to diagnose neurosarcoidosis. Due to the low sensitivity of this method, minor salivary gland biopsy should only be performed after analysing the patient's clinical situation. Patients with spinal cord sarcoidosis may benefit more from this type of biopsy (Fournier et al., 2023). Evidence of the importance of biopsy in the diagnosis of neurosarcoidosis was presented in a case report by Gupta et al. The diagnosis was made after a biopsy of prefrontal swelling and supra-trochlear nerve. Previously, no diagnosis could be made for two months despite numerous laboratory and radiological tests (Gupta et al., 2023).

A combined fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) examination may be helpful in determining the site for biopsy. It can reveal metabolically active lymph nodes or other lesions that may not be visible on other radiological examinations (Bradshaw et al., 2021). It is possible to monitor disease activity and response to the treatment by comparing the results of repeated PET/CT with fluorodeoxyglucose (Sinha et al., 2024).

## TREATMENT

The European Respiratory Society presented specific treatment guidelines for physicians to ensure the best possible outcomes for patients with neurosarcoidosis. Based on the available studies, it is recommended to use glucocorticoids, either intravenous or oral (in doses depending on the severity of symptoms), for patients with clinically significant disease – as the first line treatment, as well as adding methotrexate for patients already treated with glucocorticoids – as the second line (Baughman et al., 2021; Bradshaw et al., 2021). It has been suggested that infliximab be added in the third line for patients who do not respond to previous therapies; however, allergic reactions caused by infliximab can be life-threatening (Baughman et al., 2021). Although patients treated with infliximab at a dosage of 5 mg/kg combined with an appropriate dose of glucocorticoids (depending on the patient's condition) were more prone to serious infectious complications like sepsis, due to a severely immunocompromised state (Fritz et al., 2020). According to Sambon et al. (2022), nearly all patients started treatment with glucocorticoids, and 73% required intensification with methotrexate, mycophenolate mofetil, azathioprine, or hydroxychloroquine. Adding infliximab to the above-mentioned therapies was necessary in two cases. Papanikolaou et al. (2022) confirmed that infliximab

is effective in neurosarcoidosis and may be considered a third-line treatment. Bekkour et al. (2023) reported that 64% of patients started first-line treatment with glucocorticoids, but over 96% received glucocorticoids at some point during treatment. The aim of therapy in neurosarcoidosis is to minimise neurological consequences that may affect the patient's quality of life; therefore, not only pharmacological therapy, but also rehabilitation is necessary (Bradshaw et al., 2021). The choice of appropriate pharmacological treatment should be considered depending on the patient's clinical condition and comorbidities to ensure the best possible option for the patient. The involvement of the nervous system in neurosarcoidosis necessitates the use of appropriate treatment methods penetrating through the blood-brain barrier (Sinha et al., 2024).

## PROGNOSIS

Response to treatment in patients is variable. It depends on the severity of the disease and on the areas of the nervous system involved (Bradshaw et al., 2021). Prognosis also depends on the timing of diagnosis and initiation of treatment (Sinha et al., 2024). In a published study, Fritz et al. (2016) reported that total remission was achieved in 27% of patients, incomplete remission in 32%, stable disease in 24%, and deterioration in 6%. When the first line of treatment was ineffective and additional lines were required, each subsequent therapy was associated with a lower overall likelihood of a favourable outcome. In published studies, the mortality rate ranged from 0% to 33%. Fritz et al. (2016) in their meta-analysis, reported a 5% mortality rate among patients.

## CONCLUSIONS

Sarcoidosis is a multifaceted disease. The diverse manifestations of neurosarcoidosis necessitate an individualised selection of diagnostic tests to exclude other disease entities (Bradshaw et al., 2021; Shen et al., 2023). Due to the complex presentation of neurosarcoidosis and its non-specific symptoms, diagnosis is often challenging and may be delayed (Gupta et al., 2023). When a patient is diagnosed with sarcoidosis, neurological symptoms are often mistakenly attributed to neurosarcoidosis, which may lead to overlooking other potential diagnoses (Shen et al., 2023). Conversely, when neurological symptoms are the first and only manifestations, neurosarcoidosis is often not initially considered in the differential diagnosis (Gupta et al., 2023). Once neurosarcoidosis has been diagnosed and appropriate treatment instituted, any worsening of the patient's condition or lack of response to treatment should prompt re-evaluation of the differential diagnosis to consider alternative causes (Bradshaw et al., 2021; Shen et al., 2023). In diagnosed patients, repeated examinations are needed to monitor disease activity, response to treatment and possible rapid detection of disease progression (Sinha et al., 2024).

Neurosarcoidosis remains a disease of unknown aetiology; therefore, there is a need to explore this topic, as identifying the etiological factors could help in prevention and the development of improved treatment methods (Sinha et al., 2024).

### Conflict of interest

*The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.*

### Author contribution

*Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: MAM, ISS.*

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