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REVIEW

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Neurosarcoidosis: a review of its intracranial manifestation

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Abstract Sarcoidosis is a multisystem disease of unknown cause and with a worldwide distribution. Involvement of the central nervous system occurs in a relatively small number of patients with sarcoidosis. Isolated neurosarcoidosis without signs of systemic disease is a rarity. Because of its non-specific clinical presentation and neuroradiological imaging characteristics, intracranial neurosarcoidosis remains a very difficult diagnosis, particularly in the absence of systemic signs of the disease. Intracranial neurosarcoidosis has a predilection for the basal leptomeninges commonly affecting the cranial nerves, but any part of the brain may be involved, resulting in a wide spectrum of clinical syndromes. Cranial nerve involvement is the most common single symptom. Intracranial sarcoid manifests as nodular or diffuse leptomeningeal thickening and extra- or intra-axial parenchymatous lesions. Intracranial sarcoid may mimic various forms of meningitis, including carcinomatous and intracranial mass lesions such as meningioma, lymphoma and glioma, based on neuroradiological imaging. Magnetic resonance imaging is a very sensitive diagnostic tool for detecting intracranial abnormalities due to neurosarcoidosis. Lumbar puncture is useful in ruling out other neurological disorders, in particular infectious, but cerebrospinal fluid findings are not specific. Angiotensin-converting enzyme in serum and cerebrospinal fluid may be increased, decreased or normal. Therapy consists of immunosuppressive agents and should be initiated with corticosteroids. Other immunosuppressive drugs should be added in severe cases or after frequent recurrences. We review here all aspects of intracranial neurosarcoidosis from the clinical point of view, with special emphasis on presentation, diagnostic procedures, differential diagnostic considerations and treatment.

Key words Central nervous system · Intracranial neurosarcoidosis · Solitary neurosarcoidosis · Review

Introduction

The effects of sarcoidosis (Besnier-Boeck-Schaumann disease) on the nervous system are protean. They include involvement of the meninges, brain parenchyma, peripheral nerves and spinal cord [7, 10, 12, 16, 17, 26, 37, 38, 43, 47, 50, 55, 57, 58, 62, 67]. Differentiation of intracranial neurosarcoidosis from other neurological disorders may be difficult, especially in the absence of extracranial disease. Isolated intracranial neurosarcoidosis has occasionally been reported [3, 7, 8, 12, 17, 29,

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37, 44, 47, 50, 59]. Systemic signs of sarcoidosis include bilateral hilar lymph adenopathy, diffuse pulmonary infiltration, skin, liver and eye lesions [13]. In suspicious cases thorough clinical, laboratory and imaging investigations should be carried out to determine involvement of these organ systems. The diagnosis of neurosarcoidosis is made on the basis of clinical features in conjunction with clinical and biopsy evidence of intracranial sarcoid lesions and sarcoid granulomas in other tissues (lymph nodes, lungs, bones, uvea, skin and muscle).

Magnetic resonance imaging (MRI) is a useful mean of detecting meningeal involvement, and periventricular and intra- or extra-axial white matter lesions [11, 32, 35, 48, 65]. Due to the wide spectrum of neuroradiological findings [5, 11, 21, 28, 30, 31, 32, 35, 40, 48, 56] and non-specific clinical signs and symptoms intracranial sarcoid granulomatosis can be mistaken for primary brain tumours, such as glioma [11, 48, 49], meningioma [5, 17, 26, 30, 31, 32, 33, 42, 44, 47, 50], and intrasellar masses [15, 53] as well as infectious disorders of the central nervous system (CNS) [37, 48, 50].

The diagnosis of intracranial neurosarcoidosis is challenging, especially when systemic signs of the disease are missing. In this review we discuss the clinical signs and symptoms, neuroradiological findings on the basis of MRI, and differential diagnostic aspects with emphasis on MRI and histopathology. A diagnostic programme from the clinician's point of view is proposed.

Frequency

Sarcoidosis is a systemic granulomatous disease of unknown origin, most commonly affecting young adults, with predominance in women and North Americans of African descent [35, 43]. Sarcoidosis is usually diagnosed between the ages of 20 and 40 years [16, 43]. The prevalence is estimated at 20–50 per 100,000 in the Caucasian population, and the incidence at 20 per 100,000 among Caucasians [62].

Neurological symptoms due to CNS involvement develop in about 5 % of patients with systemic sarcoidosis [7, 10, 16, 38, 43, 51, 58, 62]. Mayock et al. [38] reported 10 cases of CNS sarcoid in a series of 145 patients with systemic sarcoidosis (7 %). Chen and McLeod [10] observed 14 cases of CNS manifestation among 285 sarcoid patients (5 %), and Stern et al. [62] reported 33 cases of CNS sarcoidosis in a series of 649 patients with systemic spread of the disease (5 %). Ricker and Clark [51] found a 14 % prevalence of CNS involvement in a series of 300 autopsy cases with premortal diagnosis of systemic sarcoidosis. Thus silent CNS involvement is present in at least 10 % of patients with systemic disease.

The majority of patients are diagnosed as having systemic sarcoidosis when clinical signs and symptoms of CNS neurosarcoidosis become manifest [7, 10, 16, 38, 55, 57, 58, 62]. In 10–30 % of patients with systemic sarcoidosis there are initial signs and symptoms of neurosarcoidosis at presentation [62]. In more than 95 % of cases the initial neurological symptoms lead to the diagnosis of systemic sarcoidosis on further clinical and other investigations [10, 34, 51, 57, 58, 62, 67]. Very rarely sarcoid granulomatosis is strictly confined to the CNS [3, 7, 8, 12, 17, 26, 29, 37, 44, 47, 50, 59]. The incidence of isolated neurosarcoidosis is estimated at less than 0.2 per 100,000 among Caucasians. Table 1 presents an overview of the distribution and frequency of systemic and neurological sarcoid manifestation and of isolated CNS sarcoidosis.

Tab. 1 Distribution and frequency of systemic sarcoidosis and CNS neurosarcoidosis in the Caucasian population

Spread of the disease	Frequency
Systemic sarcoidosis	Estimated incidence: 20 per 100,000
CNS neurosarcoidosis	
With multiorgan involvement and additional neurological signs and symptoms	Approx. 5 % of cases with systemic sarcoidosis; estimated incidence: 1 per 100,000
With systemic sarcoidosis and clinically *silent* CNS manifestation	Approx. 10 % of cases with systemic sarcoidosis; estimated incidence: 2 per 100,000
Strictly confined to the CNS without systemic spread of the disease	Estimated incidence: fewer than 0.2 per 100,000

Sarcoidosis may also be accompanied by peripheral nerve involvement, giving rise to subacute or chronic neuropathy, plexopathy of asymmetrical type, and polyneuropathy. Delaney [16] found the frequency of neurological involvement in cases of sarcoidosis to be equally distributed between peripheral and central nervous systems.

Pathogenesis

There is still no precise understanding of the pathogenesis of sarcoidosis. The origin of the disease remains unknown, although it seems that a genetic predisposition for an exaggerated immune response to specific antigens causes inflammatory granuloma formation and progressive fibrosis [43]. There have been several cases of familial sarcoidosis and a higher incidence is observed in monozygotic than in dizygotic twins [13, 43].

Clusters of sarcoidosis among firefighters and nurses have been reported, suggesting a causative environmental exposure [24, 27]. Immunological studies have revealed increased expression of a specific T-lymphocyte receptor, indicating a single antigen of unknown origin [22]. Other studies implicate various sarcoid antigens [2, 19, 20]. Newman et al. [43] emphasise the particular role of T-lymphocytes in the development of sarcoidosis. These authors suggest that following exposure to an un-

known antigen and acquisition of a cellular immunity directed against the antigen, T-lymphocytes amplify the local cellular immune response.

Mycobacterial DNA has been found in bronchial washings of patients with pulmonary sarcoidosis, indicating a potential mycobacterial causative contribution to the pathogenesis of sarcoidosis [52]. However, the role of mycobacteria in the pathogenesis of sarcoidosis remains controversial as both disorders may occur in predisposed individuals. One patient with neurosarcoidosis who received antituberculous medications showed clinical improvement that was correlated with decrease in *Mycobacterium tuberculosis* DNA in the CSF [54]. A recent study found DNA of propionibacteria in sarcoid lesions of Japanese patients suffering from sarcoidosis [25]. The authors suggested that proprionibacteria should be considered a more likely cause of sarcoidosis than mycobacteria, as genetic material from proprionibacteria was detected more frequently in sarcoid lesions than mycobacterial DNA.

Histopathogenesis of CNS sarcoidosis is thought to be primarily leptomeningeal with inflammatory exsudate extending from the subarachnoid space along the Virchow-Robin spaces into brain parenchyma [41, 65]. The Virchow-Robin spaces are especially large at the base of the brain, which may explain the predilection of sarcoid lesions for the basal leptomeninges with frequent involvement of the hypothalamus, third ventricle, and optic and other cranial nerves [6, 7, 16, 51, 57, 58, 62, 67]. The pattern of granulomatous inflammation spreading from the Virchow-Robin spaces into the brain can be analysed histologically and visualised on contrast-enhanced MRI [41, 65].

Clinical presentation

In 1905 Winkler [66] described the first case of CNS sarcoidosis, and the first tumour-like cerebral sarcoid granulomatosis was described by Everts [18] in 1947. Intracranial masses as a manifestation of neurosarcoidosis are occasionally seen [5, 9, 12, 15, 17, 21, 23, 26, 30, 31, 33, 42, 47, 50, 56, 59, 64]. Intracranial CNS sarcoidosis presents a variety of manifestations such as intraparenchymal, extra-axial and diffuse leptomeningeal lesions [5, 11, 12, 28, 32, 35, 37, 40, 48, 56, 65, 67]. Meninges of the skull base, hypothalamus and pituitary gland are the most common sites [5, 6, 11, 16, 32, 48, 51, 55, 58].

Clinical symptoms of intracranial neurosarcoidosis depend on the location of the lesion. Patients may present with signs of meningitis [37], subarachnoid haemorrhage [3], cerebrovascular ischaemia [39], cranial nerve palsy (50 %) [3, 15, 17, 21, 23, 29, 30, 33, 35, 38, 42, 50, 64, 67], aseptic meningitis [36, 37, 50], sensory and motor deficits (10 %) [5, 21, 31, 39, 50], neuropsychological deficits (10 %) [21, 26, 64, 67], hydrocephalus (5 %) [18, 36, 67], headache [5, 17, 25, 42, 44, 47, 50], seizures (10 %) [31, 42, 44, 47, 49, 50], hypothalamic [6] and pituitary dysfunction (10 %) [6, 15, 53]. The most common neurological symptoms are cranial nerve deficits, headache and seizures [10, 16, 34, 48, 51, 55, 57, 58, 62, 67]. Table 2 summarises the neurological signs and symptoms of intracranial CNS sarcoidosis.

Tab. 2 Clinical signs and symptoms of CNS neurosarcoidosis; frequencies of occurrence of individual signs and symptoms refer to percentages of affected cases

Symptoms	%
Cranial nerve palsies	50
Headache	30
Seizures	10
Pituitary dysfunction	10
Sensory and motor deficits	10
Neuropsychological deficits	10
Cerebellar symptoms	10
Hydrocephalus	5
Symptoms and signs of meningitis	5

Cranial nerve palsies can be observed in one-half of the patients with intracranial neurosarcoidosis [11, 16, 43, 55, 57, 58, 67]. The facial nerve is most frequently affected, either due to a meningitic reaction or secondary to inflammation in the parotid gland. Facial palsies may occur unilaterally and simultaneously or sequentially bilaterally [43, 67]. Deficits of the trigeminal nerve (sensory deficits and neuralgia), auditory nerve and cochlear nerve (vertigo) are less common. In a recent series of 68 patients with neurosarcoidosis involvement of the optic nerve (optic neuritis and papillitis) and chiasm was the most common clinical presentation, affecting 26 patients (38 %) [67]. Hydrocephalus, diabetes insipidus and other endocrinological disturbances may result from involvement of the skull base leptomeninges [6, 16, 32, 48, 51]. In general, symptoms of isolated intracranial neurosarcoidosis do not differ from symptoms of additional intracranial manifestation in cases of systemic spread of the disease.

Clinical symptoms may develop acutely or subacutely and may also progress in a chronic way. Spontaneous regressions are more frequent than progressive neurological deterioration [10, 16, 34, 58, 62]. Patients in whom neurological signs resolve spontaneously may develop further neurological symptoms years later [16, 57, 58, 62, 67]. This indicates that sarcoid granulomas within the CNS can subsequently occur and disappear at various intracranial locations and thus mimic the clinical and radiological pictures of multiple sclerosis [32, 40]. Every part of the brain can be involved, and intracranial neurosarcoidosis substantially increases both morbidity and mortality compared to sarcoidosis with exceptional extracranial manifestation.

Diagnostic work-up

In the clinical setting of systemic sarcoidosis and additional neurological symptoms the diagnosis of intracranial neurosarcoidosis is relatively straightforward. When CNS involvement is the first or even only manifestation of sarcoidosis, diagnosis is a real challenge to the clinician and radiologist. Today there are no radiological features, serum and cerebrospinal fluid findings or additional methods specific to the preoperative detection of intracranial neurosarcoidosis. Thus patients presenting with intracranial tumour-like masses due to isolated neurosarcoidosis are frequently operated upon, because a neoplasm is suspected [7, 12, 16, 23, 26, 29, 30, 33, 42, 47, 50, 59].

Neuroradiological findings

Intracranial neurosarcoidosis has a predilection for the leptomeninges and commonly presents with single and multiple nodular and/or diffuse infiltrative growing lesions, which are attached to the leptomeninges [5, 11, 16, 28, 31, 32, 35, 40, 51]. It is quite unusual for neurosarcoidosis to present as a solitary intracranial mass [11, 12, 16, 17, 21, 23, 26, 30, 33, 44]. Earlier reports noted the value of computed tomography [5, 8, 10, 12, 15, 16, 23, 49, 62] in the diagnostic process of intracranial neurosarcoidosis, but MRI is the neuroradiological imaging modality of choice today [11, 28, 30, 31, 32, 35, 39, 40, 43, 48, 56, 65, 67].

MRI before and after administration of Gd-DTPA has been shown to be highly sensitive in detecting intracranial abnormalities due to neurosarcoidosis [11, 28, 32, 35, 40, 48, 65, 67]. Table 3 presents an overview of the wide spectrum of intracranial pathologies due to neurosarcoidosis. In particular, pathological enhancement of brain parenchyma and leptomeninges, and evidence of periventricular and white matter disease are important clues to the diagnosis [11, 32, 35, 40, 67].

Tab. 3 Spectrum of MRI abnormalities due to intracranial neurosarcoidosis; frequencies of individual MRI findings refer to percentages of affected cases

MRI findings	%
Nodular and/or diffuse meningeal involvement	40
Periventricular and white matter lesions	40
Multiple supra- and/or infra-tentorial lesions	35
Solitary intra-axial mass	10
Solitary extra-axial mass	5

Following Gd-DTPA administration, a homogeneous nodular or diffuse enhancing thickening of the affected meninges, usually in the basal cisterns and hypothalamic regions, can be found. Disturbances of the blood-brain barrier are frequently detected after Gd-DTPA administration. Large sarcoid masses within the brain parenchyma are isointense on T1-weighted images and hyperintense on T2-weighted images. Figure 1 illustrates MRI in a case of solitary intracranial neurosarcoidosis [44]. Smaller parenchymatous lesions are usually visualised after intravenous administration of Gd-DTPA. Intracranial sarcoid granulomas may present with nodular or annular enhancement. MRI aids in *narrowing* the differential diagnosis and can be used to demonstrate therapeutic response to immunosuppressive medication [11, 32, 35].

Laboratory findings

Elevated levels of serum and/or CSF angiotensin-converting enzyme (ACE) are not specific for neurosarcoidosis and are found in a variety of disorders, such as Guillain-Barré syndrome, infectious diseases and certain cerebral tumours [45, 46]. ACE is produced by epitheloid cells of the sarcoid granulomas, and serum ACE

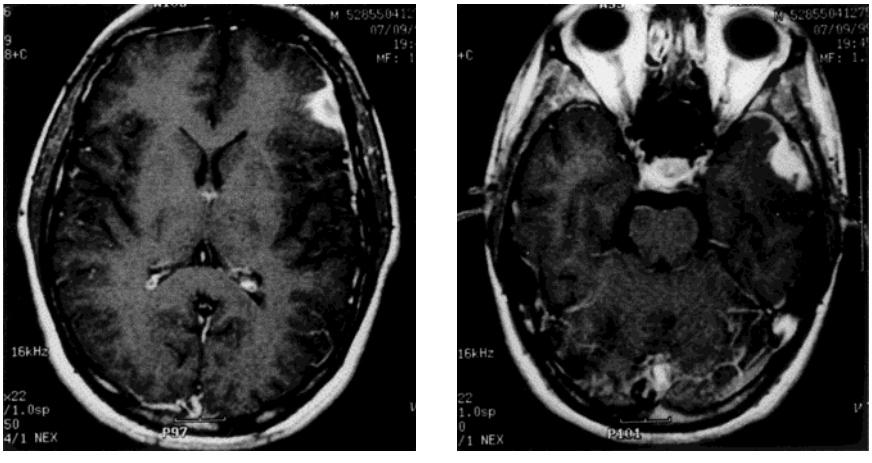

Fig. 1 Axial T1-weighted MRI following Gd-DTPA administration. Two nodular masses of the left frontal (1.5 x 2.0 cm, *left*) and temporal (2.0 x 2.5 cm, *right*) lobes are demonstrated. The lesions are attached to the leptomeninges and show homogeneous enhancement. In addition, diffuse leptomeningeal enhancement is illustrated

is elevated in 70–80 % of patients with systemic sarcoidosis [13].

CSF ACE level has been reported to be increased in about 55 % of patients with neurosarcoidosis, 5 % of those with sarcoidosis, and 13 % of those with other neurological diseases [45, 46]. Oksanen et al. [46] reported increased CSF ACE levels in 11 of 20 patients with neurosarcoidosis and in 1 of 12 cases with systemic sarcoidosis. However, CSF ACE levels were within normal limits in several individual cases [16, 26, 44, 47, 50]. In contrast, other investigators have recently pointed out that the CSF ACE level is not a very useful clue for the diagnosis of neurosarcoidosis [14]. Serum and CSF ACE levels may be used to control therapeutic efforts after the onset of steroid medication. CSF analysis may show lymphocytic pleocytosis of about 10–200 cells per µl (50–70 %), elevated protein levels (40–70 %) or both [10, 16, 17, 49, 55, 58, 67]. CSF glucose level may be decreased. CSF immunglobulines may be elevated [37] and oligoclonal banding may be present (70 %). The intraspinal pressure is occasionally found to be increased.

Elevated ionised calcium in serum and urine result from 1,25-dihydroxy vitamin D secretion by epitheloid cells of the sarcoid granulomas. Serum chemistry is usually unremarkable [16, 49, 55, 58, 67, 47], and an elevated erythrocyte sedimentation rate may be noted [3, 29, 47]. Elevated polyclonal immunoglobulines due to B-lymphocyte stimulation are occasionally observed [37]. Changes in the T-lymphocyte population may cause a negative tuberculin reaction (anergic immunoreaction type IV) [13].

Additional investigations

Diagnostic screening procedures directed to evaluating the systemic spread of sarcoidosis include ophthalmological examination, conjunctival biopsy, radiological investigation with chest and hand radiographs, bronchial lavage with determination of the T4/T8 lymphocyte ratio (CD4/CD8 > 5), bronchoscopy including biopsy specimens, pulmonary function tests and abdominal ultrasonogram [13]. In the case of abnormal findings, biopsy of lymph nodes, liver and skin may be performed. The ^{67}Ga-labelled scintigraphy (the radioactive nuclide gathers in active sarcoid granulomas) is sometimes used to assess the present activity of the disease and to identify extracranial granuloma available for biopsy [67]. The Kveim-Siltzbach-Nickerson test, a skin reaction test with human Boeck granulomatous tissue as antigen, is no longer generally available [13, 43], but it has recently been reported to be positive in a large amount of affected cases [67]. Insertion of Kveim-Nickerson antigen during the administration of steroids may produce a negative Kveim result, as corticosteroids reduce the systemic granulomatous inflammation activity.

Stereotactic biopsy

The difficulty in the diagnostic process of intracranial neurosarcoidosis is the lack of specific clinical and other findings. Diagnosis can be presumed if other causes of intracranial lesions are ruled out, and additional extracranial sarcoid manifestation is present. In the particular case of isolated intracranial sarcoidosis the diagnosis remains a surgical matter [3, 7, 8, 12, 17, 26, 29, 37, 44, 47, 50, 59]. However, indication for biopsy should be derived from the accessibility of the intracranial lesion. Some patients with intracranial sarcoid masses require neurosurgical intervention due to threatening hydrocephalus or herniation with clinical signs of raised intracranial pressure and failure of immunosuppressive therapy, but stereotactic biopsy is a possible choice to permit histopathological diagnosis and exclude other granulomatous infectious diseases (in particular tuberculosis), vasculitis and neoplasms in cases with no history or signs of systemic sarcoidosis.

Zajicek et al. [67] have recently proposed criteria for the diagnosis of *definitive* and *probable* neurosarcoidosis. *Definitive* diagnosis of neurosarcoidosis was mainly based on the exclusion of other possible diagnosis and the presence of positive nervous system histology. *Probable* diagnosis of neurosarcoidosis included laboratory signs of CNS inflammation, such as elevated CSF protein, CSF pleocytosis and presence of oligoclonal bands, MRI findings compatible with neurosarcoidosis and exclusion of other possible diagnoses. In addition, evidence of systemic sarcoidosis through positive histology or indirect indicators, such as ^{67}Ga-labelled scintigraphy, chest radiography and serum ACE should be present [67].

Histopathology

Hutchinson [59] reported the first clinical case of sarcoidosis in 1875. Boeck [4] is credited with the first histopathomorphological description of the pathognomonic sarcoid granuloma in 1899. Non-caseating epitheloid granuloma is the striking histopathological feature of this chronic inflammatory disorder. The epitheloid granuloma consists of focal collections of epitheloid cells surrounded by a rim of lymphocytes. Multinucleated giant cells of Langhans' type are frequently present. After a certain time a fibrotic response develops in sarcoidosis, and collagen and proteoglycans form a diffuse network around the granulomas [43]. Figures 2 and 3 illustrate the typical histopathomorphology of sarcoid-like granulomas.

Nevertheless, the histological picture is not specific for sarcoidosis. Caseating necrosis, foreign bodies and organisms should be excluded. Special stainings and cultures for acid-fast bacilli and fungi should be per-

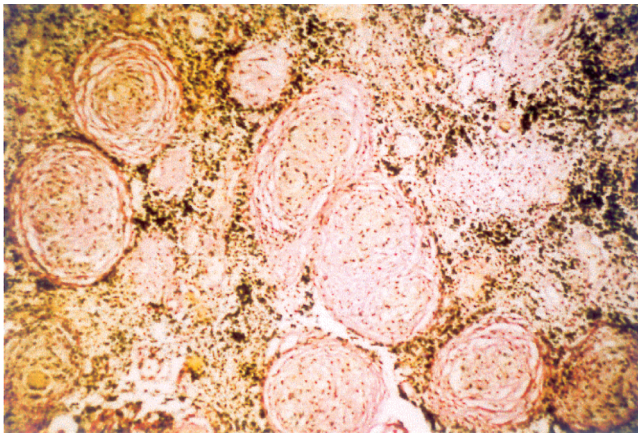

Fig. 2 Characteristic noncaseating sarcoid granulomas embedded within a fibrous stroma. Van Gieson, original magnification x80. (From [44])

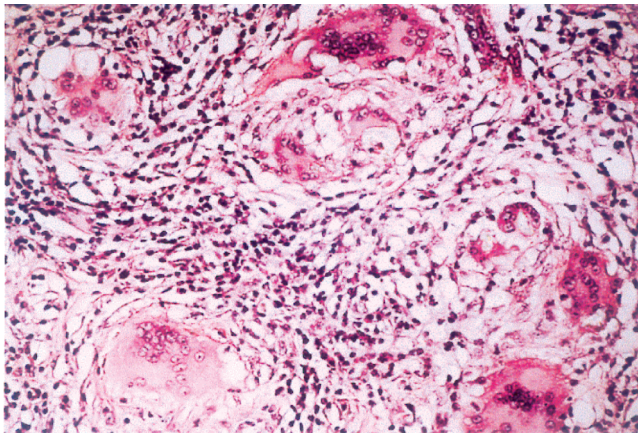

Fig. 3 Sarcoid granulomas consisting of follicles with central multinucleated giant cells (some with polymorph conchoid inclusion bodies) surrounded by epitheloid macrophages and fibroblasts. Haematoxylin & eosin, original magnification x200. (From [44])

formed to rule out other granulomatous infections. The diagnosis is usually definitive with haematoxylin and eosin staining of sections, but misdiagnosis during perioperative histological examination has been reported [17].

Differential diagnostic considerations

In patients diagnosed with systemic sarcoidosis and suspected of having intracranial sarcoid manifestation, other neurological disorders, such as autoimmune inflammatory diseases (e. g. multiple sclerosis, systemic lupus erythematosus), infectious diseases (e. g. neuroborreliosis, neurolues, human immune deficiency) and neoplasms (e. g. lymphoma, meningioma, glioma) should be excluded. In patients with intracranial sarcoid manifestation without known systemic sarcoidosis thorough clinical examination of typically involved organ systems and purposefully guided investigation should be performed to diagnose or rule out sarcoidosis.

Clinical symptomatology

Neurological signs and symptoms of intracranial neurosarcoidosis are protean and may mimic various neurological disorders [10, 12, 16, 34, 55, 57, 58, 62, 67]. Facial nerve dysfunction is probably the most common single presentation of neurosarcoidosis [16, 57]. Facial nerve palsy may occur uni- and bilaterally. In particular, synchronous bilateral manifestation should warrant differential diagnosis from neuroborreliosis, Guillain-Barré syndrome and Miller-Fisher syndrome. In unilateral manifestation idiopathic facial palsy should be considered, which usually manifests with a more acute onset. When dysfunctions of additional cranial nerves are present, other infectious and tumorous disorders of the basal meninges should be considered in the differential diagnosis [34, 35, 50, 51, 62]. Viral and fungal meningitis, lues, tuberculosis and carcinomatous meningitis share the prevalence for the basal meninges with neurosarcoidosis. Cerebello-pontine angle tumours may result in a combination of trigeminal, facial and vestibulocochlear nerve palsies [11, 12, 17, 32, 56].

Pituitary and hypothalamic dysfunction should be differentiated from other lesions in this area, such as pituitary adenoma, Rathke cleft cyst and craniopharyngeoma [53]. Involvement of the hypothalamus and clinical symptoms due to both anterior and posterior pituitary insufficiency (panhypopituitarism) and diabetes insipidus may help in the differential diagnosis [6]. Tumours do not commonly result in combined insufficiency of the anterior and posterior pituitary lobes.

Due to the variability in neuroradiological findings and the periodical course of symptoms in some cases, multiple sclerosis remains a particular problem given the age of the cohort affected [32, 57, 65]. Intracranial sarcoidosis most frequently occurs between the second and fourth decades [16, 38, 67]. Seizures, motor and sensory deficits or progressive intracranial mass effects in severe cases are further symptoms, which should be distinguished from tumorous, ischaemic and infectious disorders by additional laboratory and imaging investigation.

Differential diagnosis based on MRI

Gross pathological studies reveal two forms of intracranial neurosarcoidosis: (a) poorly demarcated sarcoid tumour growth within brain parenchyma and (b) mat-like meningocortical thickening due to granulomatous in-

flammation [49, 51]. The MRI abnormalities of intracranial neurosarcoidosis, especially white matter lesions, periaqueductal involvement and abnormal enhancement of brain parenchyma and meninges offer a wide spectrum of differential diagnostic considerations [5, 11, 28, 30, 31, 32, 35, 40, 56, 65]. MRI features of intracranial sarcoid masses include isointensity with brain on T1-weighted images, homogeneous contrast enhancement of the lesion and/or affected meninges and low signal intensity on T2-weighted images [11, 32, 33, 48, 56, 65].

Intracranial parenchymatous sarcoid lesions should be distinguished from neoplasms, such as lymphoma, glioma, meningioma and metastasis. Lymphoma has a similar affinity for the basal leptomeninges and periventricular white matter as does sarcoid; however, it appears hypointense to the surrounding oedema on T2-weighted MRI. Primary CNS lymphoma has an affinity for the subcortical white matter, especially periventricular brain parenchyma, whereas secondary intracranial lymphoma with multiorgan distribution preferentially involves the leptomeninges. CSF analysis for malignant lymphocytes, chest radiography, abdominal ultrasonography and bone marrow aspiration are additional investigations for distinguishing between the two entities.

Periventricular and diffuse white matter lesions are characteristic of multiple sclerosis and constituted one of the most common MRI abnormalities of neurosarcoidosis in a recent series [32]. Enhancement of the lesions and additional leptomeningeal enhancement patterns following Gd-DTPA administration are useful in distinguishing sarcoid from multiple sclerosis [65]. CSF analysis and electrophysiological investigation narrow the differential diagnosis.

Intra-axial masses with central necrosis, progressive mass effect and garland-like enhancement are more typical of primary or secondary cerebral neoplasm, such as glioma, glioblastoma and metastasis. Intra-axial sarcoid lesions frequently present with multifocal distribution. Enhancement characteristics of intra-axial sarcoid masses vary from homogeneous to a more irregular pattern [32, 65]. Extra-axial sarcoid masses are commonly indistinguishable from meningiomas on MRI [9, 17, 26, 30, 44, 47, 50]. Multifocality and additional meningeal enhancement may aid in the differential diagnosis of these cases (see Fig. 1).

Differential diagnosis of meningeal sarcoid lesions is even more difficult than in cases of intra- and/or extra-axial sarcoid lesions of brain parenchyma. There are no specific MRI features to distinguish definitively between bacterial, mycotic and tuberculous infections of the meninges, or leukaemic infiltration or carcinomatous meningitis [11, 37, 40, 48, 65]. Circumscribed meningeal enhancement following intravenous Gd-DTPA injection may be an additional key to the diagnosis. The following is an overview of neurological disorders to be considered in the differential diagnosis of cerebral intra- and extra-axial as well as meningeal neurosarcoidosis on the basis of MRI:

- **Involvement of brain parenchyma**
  - Multiple sclerosis
  - Cerebral metastasis
  - Cerebral lymphoma
  - Neurotuberculosis
  - Fungal infections of the brain
  - Low- and high-grade glioma
- **Meningeal involvement**
  - Bacterial meningitis
  - Tuberculous meningitis
  - Carcinomatous meningitis
  - Meningioma
  - Leukaemic infiltration
  - Meningeal lymphoma
  - Meningeal plasmocytoma

Histopathological differential diagnosis

The striking histopathological features of sarcoid-type noncaseating granulomas embedded within a fibrous stroma is revealed by microscopic examination (Figs. 2, 3). Disruption of leptomeningeal vessel walls, characteristic of granulomatous angiitis, should be excluded. Clinically granulomatous angiitis may present with sudden multifocal stroke-like symptoms. MRI may reveal multiple ischaemic lesions in various vascular territories or a meningeal involvement with thickened enhancing leptomeninges. Angiography shows typical signs of angiitis with segmental artery stenosis and occlusions.

Another vasculitis with ulcerative granulomas to be distinguished from sarcoid lesions is Wegener's granulomatosis. This inflammatory disorder may initially manifest with localised granulomatous lesions of the head, lungs and kidneys. Rhinitis, otitis, oropharyngeal ulcera, pseudocavernous ulcera of the lungs and microhaematuria are typical symptoms. In a subsequent multisystemic spread of the disease eye, muscle and CNS symptoms may occur. Anti-neutrophil cytoplasmatic antibodies, microhaematuria and renal arteriography lead to the correct diagnosis.

Necrosis or micro-organisms must be sought, and special stainings for fungi and fast acid bacteria (Ziehl-Neelsen staining) should be performed to exclude other leptomeningeal inflammatory diseases, in particular tuberculosis, which shares the affinity for the base of the brain with sarcoidosis. Clinical symptoms, chest radiography and polymerase chain reaction analysis for the detection of mycobacteria in CSF may aid in narrowing the differential diagnosis. Further histopathomorphological differential diagnosis of inflammatory granulomatous disorders with intracranial manifestation in-

Tab. 4 Differential diagnostic considerations of intracranial granulomatous diseases from the histopathological point of view

Disease	Aetiology	Histopathological description
Sarcoidosis (Besnier-Boeck-Schaumann's disease)	Unknown	Granuloma arranged of epitheloid cells, giant cells (Langhans' type) with inclusion bodies (asteroid, conchoid); lymphocytes and plasma cells in the periphery; fibrosis of granuloma beginning in the peripheral corona
Syphilis (lues)	*Treponema pallidum*	Gumma of rubbery consistence: perivascular granuloma formation; central necrosis; plasma cells in the periphery
Tuberculosis	*Mycobacterium tuberculosis*	Tuberculous granuloma: palisade of epitheloid cells with interspersed giant cells; lymphocytes and plasma cells in the periphery; central caseating necrosis
Leprosy (Hansen's disease)	*Mycobacterium leprae*	Hyperergic tuberculoid appearance with tuberculoid granuloma: corona of epitheloid and giant cells; lymphocytes in the periphery; central necrosis
Wegener's granulomatosis	Autoimmune dysregulation	Tuberculoid granuloma: corona of epitheloid and giant cells; lymphocytes and polynucleated cells in the periphery; central necrosis
Granulomatous angiitis	Unknown	Extensive disruption of blood vessel walls; sarcoid-like granuloma: palisade of epitheloid cells, macrophages and giant cells; lymphocytes and plasma cells in the periphery
Foreign-body granulomatosis	Traumatic, iatrogenic, per injection (intravenous drug abuse)	Granuloma consisting of giant cells with incorporated foreign bodies, macrophages, lymphocytes and fibroblasts; neovascularisation with diffuse capillary spread

cludes leprosy, cryptococcosis and syphilis. Most of these leptomeningeal diseases can be diagnosed by lumbar puncture and additional microbiological CSF analysis.

Foreign-body granulomatosis, which features giant cells with polymorph inclusion bodies within their cytoplasm, is another potential histopathological differential diagnosis. Sarcoid granulomas often present with asteroid and conchoid inclusion bodies, in contrast to other granulomatous inflammations (see Fig. 3). Inclusion bodies of microbiological origin are uniform in shape and appearance, unlike the polymorph forms found in foreign-body granulomatosis. A history of traumatic brain injury or other sources of foreign body inoculation, such as intravenous drug abuse, should be excluded. Table 4 summarises various granulomatous diseases which should be considered in the differential diagnostic process from the histopathological point of view.

Therapy

There have been no controlled prospective studies to identify useful therapeutic options. Corticosteroids are the therapy of choice for intracranial neurosarcoidosis as they have been reported to improve neurological symptoms [43, 45, 55, 58, 62, 67] and cause reduction in intracranial sarcoid spread confirmed by the means of MRI [11, 32, 48, 58, 67]. However, response to steroids is variable; some patients improve rapidly [32] while others do not respond at all. Early studies reported spontaneous regression of intracranial sarcoid tumour size [16, 49]. Tentative administration of steroids should be avoided until definitive histological diagnosis is established. In particular, microbiological infections must be ruled out and primary or secondary CNS lymphoma shows a similar response to steroid therapy.

Failure of response to steroids and clinical deterioration during late reduction after long-term administration of oral corticoids warrant additional immunosuppressive agents, such as azathioprine, methotrexate, cyclophosphamide and cyclosporine [1, 56, 60, 63, 67]. In cases resistant to immunosuppressive treatment CNS radiation therapy with 20 Gy has been recommended [1, 55, 61].

In addition, symptom-oriented therapies may be necessary in certain clinical situations. Examples include hormone substitution therapy in cases of pituitary dysfunction, anticonvulsive therapy for seizures, permanent surgical shunt drainage for hydrocephalus and neurosurgical intervention in cases of progressive intracranial mass effect.

Principles of pragmatic therapy

In cases of histopathologically diagnosed intracranial neurosarcoidosis 0.5–1 mg/kg prednisolone is initially administered orally [60]. The dose is reduced in parallel with clinical improvement in neurological symptoms. Facial nerve palsies commonly improve after a few weeks therapy with oral steroids. The majority of cases, especially those with involvement of the basal leptomeninges and diffuse parenchymal lesions, require long-term administration of oral steroids. Repeat MRI is needed to determine steroid dose reduction [32, 65]. After long-term administration of oral steroids over several months the dose reduction should not exceed 5 mg within 4 weeks. High-dose intravenous steroid infusion therapy is recommended in patients with acute severe clinical deterioration [67], for example, 1000 mg/day methylprednisolone over 3–5 days.

If steroid therapy is insufficient, additional immunosuppressive drugs should be added. Methotrexate, at an oral dose of 10 mg per week, has recently been reported

to be of value in cases of poor response to steroids [67]. Azathioprine is administered at 2–2.5 mg/kg per day [60]. Blood count and liver parameters should initially be checked weekly and after 8 weeks of therapy in monthly intervals. Azathioprine therapy must be limited in 5–10 % of patients due to nausea and vomiting. Cyclosporin A should be initiated at a dose of 2 mg/kg twice a day [60]. Dosage should be adapted to the individual basal level and the therapeutic range in serum. Side effects include arterial hypertonus and nephropathy. Table 5 summarises the content of immunosuppressive agents proposed for the therapy of neurosarcoidosis.

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Tab. 5 Immunosuppressive agents and their dosage proposed for the therapy of neurosarcoidosis

Generic	Dosage
Prednisolone	0.5–1.5 mg/kg orally per day, stepwise reduction according to clinical improvement in symptoms
Methylprednisolone	1000 mg per day intravenously, for 3–5 days in cases of acute and severe clinical deterioration
Azathioprine	In combination with steroids: 2–2.5 mg/kg orally per day, weekly blood count and control of liver parameters within first 8 weeks of therapy, then monthly follow-up
Cyclosporin A	In combination with steroids: 2x2 mg/kg orally per day, individually adapted according to the therapeutic range in serum, regular renal function tests and blood pressure control

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