Review paper

Neurosarcoidosis

Neurosarkoidoza

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Abstract

Sarcoidosis is a multi-organ granulomatous disease of unknown aetiology. Although it usually affects lungs and hilar lymph nodes, lesions can also affect other organs, including the organs of the nervous system. Five–fifteen percent of sarcoidosis patients are diagnosed with diverse neurological symptoms, in most cases the cranial nerves and meninges. Parenchymal lesions in the cerebrum, spinal cord, peripheral nerves and muscles are less common. Such a complex symtomatology causes numerous diagnostic problems, especially in cases beginning with neurological symptoms. The diagnosis of neurosarcoidosis is based on clinical signs, radiological techniques, examination of cerebrospinal fluid and histopathological examination confirming the presence of non-caseating granulomas. The treatment in neurosarcoidosis is difficult and depends on the manifestation of the disease. Adrenal corticosteroids are commonly used.

Streszczenie

Sarkoidoza jest układową chorobą ziarniniakową o nieustalonej etiologii. Przebiega najczęściej z zajęciem płuc i węzłów chłonnych wnęk, ale zmiany mogą dotyczyć wielu innych narządów, również układu nerwowego. Różnorodne objawy neurologiczne stwierdza się u ok. 5–15% chorych. Najczęściej zajęte są nerwy czaszkowe i opony mózgowo-rdzeniowe, rzadsze są zmiany miąższowe w mózgu i rdzeniu kręgowym oraz nerwach obwodowych i mięśniach. Tak złożona symptomatologia powoduje liczne problemy diagnostyczne, zwłaszcza w przypadkach rozpoczynających się od objawów neurologicznych. Rozpoznanie neurosarkoidozy opiera się na obrazie klinicznym, badaniach radiologicznych i płynu mózgowo-rdzeniowego oraz badaniu histopatologicznym potwierdzającym obecność nieserowaciejących ziarniniaków. Leczenie neurosarkoidozy jest trudne i zależy od przebiegu choroby. Powszechnie stosowane są glikokortykosteroidy.

Introduction

Sarcoidosis (or Besnier-Boeck-Schaumann disease), also called the Scandinavian disease, is an inflammatory multi-system disease of unclear aetiology. As early as in 1877 Jonathan Hutchinson described its characteristic skin lesions. Then, Ernest Besnier in 1889 and Caesar Peter Boeckin 1899 took note of other dermatological manifestations of this disease. Jörgen Nilsen Schaumann (1917) was the first to describe its multi-organ nature and pulmonary and lymphatic involvement [1, 2]. These observations resulted in sarcoidosis being defined as a chronic, generalised, granulomatous disease of unknown aetiology, which most frequently affects the lungs. The pulmonary signs are frequently accompanied by skin lesions, lesions in the area of the eyes, lymph nodes, liver, spleen, heart and other organs, including the neural system organs [1–3].

Epidemiology

Sarcoidosis affects people throughout the whole world. The incidence ranges from 3 to 50 per 100,000 people [4, 5]. Its prevalence, clinical picture, course and prognosis depends on latitude, race, sex and age [3, 4]. There are countries in which sarcoidosis is relatively frequent (50–60 cases per 100,000 people in Scandinavian countries) and others in which it is rare (0.04–1 cases per 100,000 people in the south of Europe) [3–5]. The mean incidence of sarcoidos is in Europe is estimated at approximately 20 cases per 100,000 people, and 7–10 cases per 100,000 in Poland [3, 5]. The disease mainly affects non-smok-

ers (70–80%) [3], and it has been confirmed that it is 10 times more common in the black population than it is in the white population [4]. Sarcoidosis presents most frequently in young adults aged 20–40 years, but can also be diagnosed in children and the elderly [1–5].

Etiopathogenesis

Even though the disease was described for the first time over 140 years ago, the cause of it has not yet been found. It is assumed that the pathogenesis of sarcoidosis involves immunological disturbances, which are a reaction of the body to an unidentified antigen in genetically predisposed patients [3, 6]. However, numerous different hypotheses are taken into account. They include the possible connection between the disease and exposure to insecticides and environmental pollution, as well as allergic and infectious factors [6]. Sarcoidosis is also thought to be associated with HLA phenotypes [3, 7].

One of the characteristics of the disease are granulomas consisting of foam cells with no tendency to caseate, which are present in numerous organs. Active lesions are characterised by epithelial and giant multinucleated cells surrounded by lymphocytes. The mechanism of their formation involves mononuclear phagocytes and T1 CD4+ (Th1) helper lymphocytes infiltrating the area of granuloma formation and locally producing numerous cytokines and chemokines: interleukins, adhesion molecules, interferon γ, tumour necrosis factor α (TNF-α) and transforming growth factor β (TGF-β) [3, 6, 8, 9]. These disturbances lead to the formation of non-caseating granulomas, which are built of giant cells, can contain cytoplasmic inclusion bodies and may be present in various organs of the body [3]. With time, the granulomas undergo fibrosis, which progresses from their periphery to the centre, and/or subsequent hyalinisation [3]. The lesions can involve all organs, especially the lungs, lymph nodes, skin, bones, eyes and salivary glands.

Clinical course

The clinical manifestation of sarcoidosis is extremely diverse. The symptoms depend on the location of granulomas and can involve almost all organs. Thus, there are no symptoms that are specific for this disease. Sarcoidosis is usually diagnosed accidentally, based on a routine chest X-ray, since it is the lungs that are usually affected by the disease. General signs of sarcoidosis include pyrexia, fatigue, general malaise, lack of appetite, loss of body mass and articular pain. If the lungs are affected, patients may also suffer from cough and dyspnea. Skin lesions including papules, nodules and symptomatic erythema are frequent as well. In 12–70% of patients sarcoidosis can be asymptomatic, especially at its initial stage [3, 6]. It may be acute or chronic. The acute form, also called Löfgren's syndrome, is mainly diagnosed in young females. It is characterised by pyrexia or subfebrile body temperature, adenopathy of both pulmonary hila, erythema nodosum and arthritis (most commonly of the ankle) [3]. Also, patients with the acute form of sarcoidosis frequently experience spontaneous recovery; thus it has the best prognosis of all of its forms. The chronic form affects almost 95% of all cases [3, 8–11]. Neurological changes are relatively rare, but the diagnosis of neurosarcoidosis is exceptionally difficult.

Neurosarcoidosis

The nervous system is involved in approximately 5–15% of sarcoidosis patients, but the prevalence of subclinical neurosarcoidosis is much higher [9–11]. Postmortem examinations reveal changes in the nervous system in approximately 27% of cases [12]. Neurological signs can be the first manifestation of sarcoidosis, but additional tests confirm the systemic disease in 97% of cases [8]. Symptoms of sarcoidosis limited only to the nervous system, on the other hand, occur much less frequently (1% of cases) and always constitute a difficult diagnostic problem [9–12]. Neurological complications of systemic sarcoidosis usually occur during the first 2 years from the onset of the disease [11–13].

Sarcoidosis granulomas can be located in the structures of the central and the peripheral nervous system. In about 50% of patients with neurosarcoidosis the nervous system is damaged in more than one location [8–12]. Neurosarcoidosis is usually acute or subacute, but approximately 60% of patients experience spontaneous remission. In the remaining 20–30% of patients, the disease evolves into a chronic progressive form [3, 9–12]. Due to its diverse course and significantly variable clinical picture, neurosarcoidosis is frequently confused with multiple sclerosis (MS) [9–11].

The most frequent location of granulomas are the cranial nerves, especially the facial and optic nerves, the hypothalamus and pituitary gland. Sometimes, cranial neuropathy associated with sarcoidosis results from cerebrospinal meningitis located at the base of the scull. The spinal cord, peripheral nerves and muscles are less frequently involved (Figure 1).

Intracranially, the granulomas are usually located within the area of the cerebrospinal meninges (especially at the base of the brain) and secondarily involve cranial nerves, obstructing cerebrospinal fluid (CSF) flow and resulting in hydrocephalus [14, 15]. In 88% of patients, magnetic resonance (MR) examination reveals hyperintense lesions in the meninges, which are associated with the presence of granulomas [16, 17]. The lesions can spread interstitially along the vessels, involving various brain structures (most frequently the hypothalamus) and the spinal cord. The course

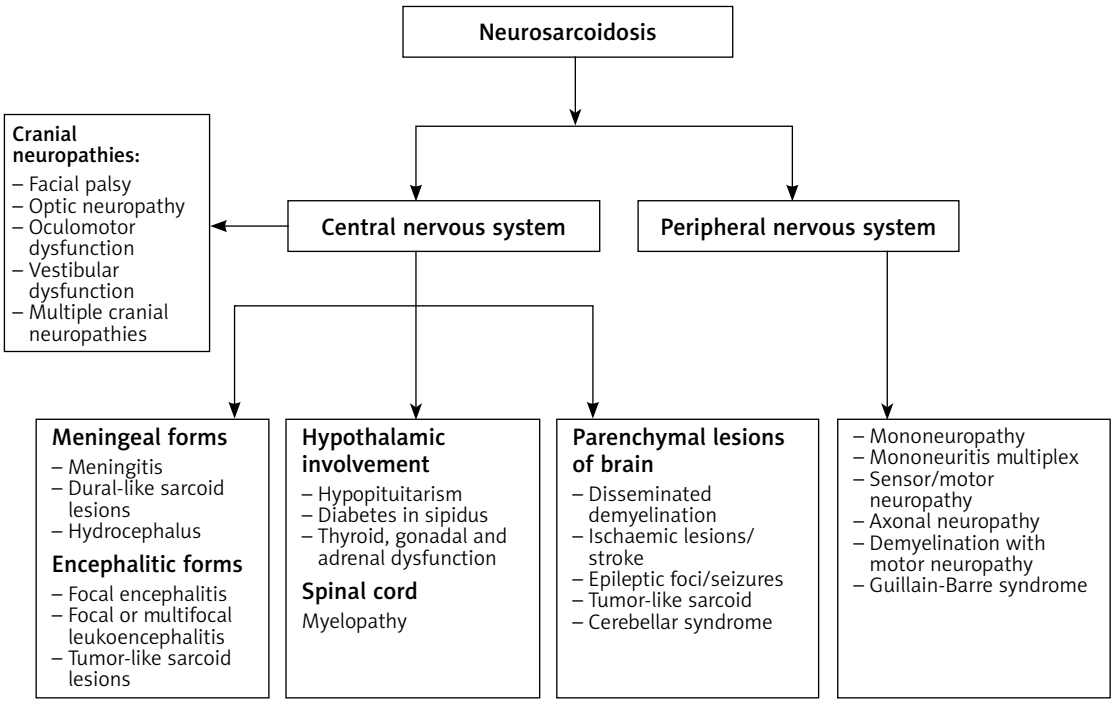

Figure 1. Clinical manifestation of neurosarcoidosis

can be acute, subacute or chronic with an insidious onset. Due to the unpredictable location and extent of the changes, the clinical picture is characterised by wide diversity and variability of symptoms.

According to numerous authors, the most frequent sign is cranial neuropathy, which was reported in 23–73% of patients with neurosarcoidosis [10, 11, 18, 19]. It mainly involves facial nerves (unilateral or bilateral isolated paralyses, monophasic or recurrent after recovery) [18–21]. The disease frequently also involves the visual nerve and the optic chiasm (less frequently the vestibulocochlear nerve and the nerves moving the eyeballs) [18, 20]. In 80% of patients, these symptoms subside spontaneously at the early stage of the disease. In some cases, facial nerve involvement is the only symptom (especially facial nerve paralysis and visual neuropathy). Such an acute or subacute episode is referred to as clinically isolated syndrome (CIS) and must always be taken into account in the differential diagnosis between sarcoidosis and multiple sclerosis [18].

Occurring in almost 50% of all patients, parenchymal damage of the central nervous system is the second most common symptom of neurosarcoidosis [14, 18, 20]. The most common symptoms include disturbances in the functioning of the pituitary gland and hypothalamus and the endocrinological and non-endocrinological dysfunctions associated with them (diabetes insipidus, thermoregulation disturbances, decreased libido, galactorrhoea, amenorrhoea, impotence, hypoglycaemia, sleep and appetite disturbances, obesity, change of behaviour) [9–11]. In 10% of patients, cerebellar signs are observed. Granulomas can be single or multiple – disseminated in various parts of the brain. Magnetic resonance imaging images in T1-, T2- and PD-sequences visualise them as hyperintense lesions suggesting multiple sclerosis [16]. If located subcortically, they may result in convulsive seizures or deficiency signs. Epileptic seizures are reported in 7–22% of patients with neurosarcoidosis [11]. Granulomatous lesions in the form of vasculitis can lead to cerebral stroke [14, 18, 19]. Larger intracranial pathological masses require differentiation with the primary neoplasm of the central nervous system.

Cerebrospinal meningitis is diagnosed in 8–40% of patients with neurosarcoidosis and mainly involves the leptomeninx at the base of the cranium. Leptomeningeal infiltrations can be asymptomatic or symptomatic (cranial nerve paralysis and chronic aseptic inflammation, leading to complications such as hydrocephalus, ependymitis of the ventricular system with encephalopathy or cauda equina damage) [6, 9, 15].

About 10% of patients gradually develop a progressive paresis of the lower limbs, caused by an intramedullary granuloma [11]. Another form of sarcoidosis of the vertebral canal involves the meninges and nerve roots, mainly in the lumbosacral region [9–11]. Magnetic resonance examinations show that lesions in the spinal cord or its meninges occur in 15–28% of patients but are not always clinically manifested [10,

11]. The location of lesions can result in gait disturbances; however, such symptoms can also result from myopathy in the course of neurosarcoidosis [9–11].

Peripheral nerve and muscle involvement is relatively rare; peripheral neuropathy is diagnosed in approximately 2–3% of sarcoidosis patients, myopathy is even more infrequent [9, 11]. In the works of numerous authors, peripheral neuropathy was reported in 4–20% of patients with neurosarcoidosis [11]. The damage of the peripheral nervous system can have the form of a mononeuropathy, multiple mononeuropathy or sensory/motor/sensori motor symmetric polyneuropathy, all acute (similar to Guillain-Barré syndrome) or chronic progressive [22–24]. What distinguishes mononeuropathy in sarcoidosis is the extensive area of sensation loss on the trunk [11].

Diagnostic evaluation of neurosarcoidosis

Due to the unpredictable location and extent of the lesions, the clinical picture of neurosarcoidosis is characterised by a wide diversity and variability of symptoms, which causes many diagnostic problems [25, 26]. Diagnostic evaluation is easier in patients with already-diagnosed sarcoidosis, but in cases beginning with merely neurological symptoms it is a real challenge. Extensive general and neurological diagnostic evaluation is then needed, depending on the symptoms observed.

Computed tomography (CT) and MRI (of various kinds) and CSF examination are usually the most significant diagnostic tools in the diagnosis of neurosarcoidosis. However, the granulomatous changes visualised in T1- and T2-sequences of MRI images as disseminated hyperintense periventricular and interstitial lesions are not specific and can be similar to those characteristic of multiple sclerosis [25–27]. It is the contrast-enhanced lesions in the meninges, hypothalamus, pituitary gland and the hydrocephalus that are typical for sarcoidosis. If the granulomas are located in the spinal cord, spinal fusiform dilation and leptomeningeal enhancement on contrast-enhanced T1-weighted image scan be observed [16, 17].

The examination of the CSF can reveal pleocytosis – up to several thousand white blood cells (lymphocytes prevailing in most cases), increased protein level (> 100 mg/dl), decreased glucose level, increased immunologlobulin level and increased IgG index, as well as the presence of oligoclonal bands (in more than 40% of patients with sarcoidosis) [25–27]. In some patients, the cerebrospinal fluid is of increased angiotensin-converting enzyme (ACE) activity along with increased CD4 : CD8, lysozyme and β_2-macroglobulin ratios [28–32]. Concentrations of calcium in serum, calcium in urine, ACE in serum, γ-globulins in serum and sodium in serum are checked as well, along with endocrinological and tuberculin tests (negative in 2/3 of patients) [26–32]. The Kveim test – a skin test with a sterile supernatant of human sarcoid tissue as the antigen – is positive in 60–80% of cases. However, the test has lost its significance since there is no standardised testing material and lack of specificity [9, 19, 26, 27].

Thus, chest X-ray (asymptomatic enlargement of the hilar lymph nodes of fibrous lesions and nodules), high resolution computer tomography (HRCT), pulmonary function tests and bronchial washing tests evaluating the increase of lymphocyte percentage and CD4 : CD8 ratio still remain the most crucial diagnostic tools [31, 32]. In 95% of patients there are changes visible in the radiological examination of the chest. They served as the basis for distinguishing four types of sarcoidosis, which determine the strategy of treatment, the prognosis and the differentiation [3]:

0 – normal chest X-ray; confirmed sarcoidosis in some other location;
I – enlarged hilar and mediastinal lymph nodes with no changes in pulmonary parenchyma;
II – enlarged hilar lymph nodes and lesions of the parenchyma in the form of nodular, reticular or streaky disseminations;
III – no lymph node enlargement, extensive advanced lesions in the pulmonary parenchyma (including infiltrations);
IV – extensive fibrotic and fibroemphysematous lesions.

The final diagnosis can be established on the basis of a set of characteristic symptoms and after ruling out other possible causes of the abnormalities observed. However, it is the presence of granulomas in histopathological samples (samples of lymph nodes, bronchial mucous membrane, meninges or brain) that is most crucial. It allows diagnosis of definite, probable or possible neurosarcoidosis according to the criteria established by Zajick [19, 27]:

Definite neurosarcoidosis

1. Clinical picture consistent with the course of neurosarcoidosis.
2. Exclusion of other causes of symptoms.
3. Typical histopathological changes in the nervous tissue biopsy (presence of non-caseating granulomas of epithelial cells, with giant Langhans cells)

Probable neurosarcoidosis

1. Clinical picture consistent with the course of neurosarcoidosis.
2. Exclusion of other causes of symptoms.
3. Evidence of inflammation in the cerebrospinal fluid (increased level of protein and/or cytosis, presence of oligoclonal bands) and/or MRI picture consistent with sarcoidosis.
4. Systemic sarcoidosis, confirmed by additional tests (typical histopathological lesions, positive Kveim test and/or at least two positive results of the following tests: chest tomography/HRCT, isotope scintigraphy with gallium, increased ACE in serum).

Possible neurosarcoidosis

When the above-mentioned criteria are not fulfilled, but:

1. the clinical picture is consistent with the course of neurosarcoidosis.
2. other causes of symptoms have been excluded.

Based on the criteria mentioned above, definite clinical diagnosis can be established if there are neurological symptoms suggesting neurosarcoidosis, other diseases of the nervous system are excluded and non-caseating granulomas consisting of epithelial cells, Langhans giant multinucleated cells surrounded by a lymphocyte infiltration, are revealed in the histopathological examination. The differential diagnosis should also include numerous immunological diseases (multiple sclerosis, lupus erythematosus, Behçet's disease, Guillain-Barré syndrome), neuroinfections (tuberculosis, neuroborreliosis, HIV infection, nervous system syphillis, mycosis, Whipple's disease) and neoplasms (lymphomas, leukaemic infiltrations of the meninges, multiple myeloma, meningiomas, metastases).

Similar lesions revealed on chest X-ray, hilar lymph nodes enlargement or interstitial lesions in the lungs require proliferative diseases, especially lymphatic ones, pneumoconiosis, tuberculosis, other interstitial diseases of the lungs to be ruled out, as well as *Pneumocystis jiroveci* and *Mycoplasmae pneumoniae* infections. Revealing a non-caseating granuloma in the histopathological examination with no other symptoms characteristic for sarcoidosis requires conducting differential diagnosis of other disease that may manifest themselves in granuloma formation (mycobacteriosis, allergic pulmonary alveolitis, berylliosis, histoplasmosis, aspergillosis, Crohn's disease or sarcoid reaction at the site of malignant neoplasm) [3, 27].

Treatment of neurosarcoidosis depends on the location and intensification of the lesions [33–35]. In approximately two-thirds of patients it regresses spontaneously after one-phase course. In one-third of cases, the course is chronic with periods of relapse and remission. The treatment is complex and long-lasting [35]. It is based on corticosteroid therapy (corticosteroids relieve the symptoms and limit the size of granulomas); however, their use is highly controversial [33–35]. Although the effect of corticosteroids is temporary, they are always recommended in cases of nervous system involvement. In severe cases, immunosuppression is applied (azathioprine, methotrexate, cyclophosphamide or ciclosporin) [35–38]. Chloroquine and its derivatives are rarely used [34, 35].

Summary

Sarcoidosis is known as one of the so-called *great imitators*, i.e. diseases that feature non-specific symptoms and can be confused with a number of other diseases. Most spectacular diagnostic errors are associated with multiple sclerosis.

The onset of the disease with isolated neurological symptoms, similar picture in MRI, the presence of oligoclonal bands in CSF and improvement after steroid therapy can lead to erroneous diagnosis of multiple sclerosis in patients with sarcoidosis. Consequently, the immunomodulating therapy turns out to be redundant and patients can be at risk of stigmatisation. Introducing this extremely expensive treatment in a disease imitating MS is not only ineffective, but can also aggravate the symptoms of sarcoidosis (e.g. interferon β).

The prognosis for sarcoidosis is definitely more favourable than that for MS; therefore, it is crucial to provide good differential diagnostic evaluation. The diagnostic evaluation of both of these diseases should be based on the diagnostic criteria (according to McDonald, 2010) which are characteristic for MS, sarcoidosis or neurosarcoidosis [27, 39]. If these criteria are not fulfilled, time and the appearance of new symptoms can be the only decisive criterion.

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