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DIAGNOSIS OF NEUROSARCOIDOSIS - NECESSITY OF BIOPSY

DIJAGNOZA NEUROSARKOIDOZE − NEOPHODNOST BIOPSIJE

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Summary

Introduction: Sarcoidosis can affect any part of the central nervous system presenting with an extremely diverse clinical picture. Clinical presentations actually depend on the localization of granulomas in the central nervous system. Making diagnosis according to the localization and the clinical variations is often a clinical challenge. **Diagnosis of Neurosarcoidosis**. Diagnosis is based on the clinical picture, clinical and radiological findings (magnetic resonance imaging with contrast endocranium), laboratory findings (angio-tenzin-converting enzyme and chitotriosidase in cerebrospinal fluid); however, it is necessary first to exclude all other possible causes of granulomatous inflammation. Recent studies in patients with neurosarcoidosis show a high value of at least one marker of the disease. The safest way and the gold standard in diagnosing this disease would be histopathological confirmation, which is rarely performed due to its invasiveness. **Conclusion**. New diagnostic methods will contribute to better methods of bypassing invasive procedures, and they will significantly facilitate the diagnosis of neurosarcoidosis, which is a real challenge even for experienced clinicians who deal with this disease.

Key words: Sarcoidosis; Central Nervous System; Diagnosis; Granuloma; Signs and Symptoms; Biopsy; Magnetic Resonance Imaging; Spinal Puncture

Sažetak

Uvod. Sarkoidoza može zahvatiti bilo koji deo centralnog nervnog sistema i dati izuzetno šaroliku klinički sliku. Kliničke prezentacije upravo i zavise od lokalizacije granuloma u centralnom nervnom sistemu. Dijagnostika, shodno lokalizaciji ove bolesti i kliničkim varijacijama, često je veliki klinički izazov. **Dijagnoza neurosarkoidoze**. Dijagnoza se postavlja na osnovu kliničke slike, kliničkog i radiološkog nalaza (magnetna rezonancija endokranijuma sa kontrastom), laboratorijskih nalaza (angiotenzin-konvertujući enzim i hitotriozidaze u likvoru), s tim što je prethodno neophodno isključiti sve druge moguće uzroke granulomatozne inflamacije. Dosadašnja ispitivanja kod obolelih od neurosarkoidoze pokazuju postojanje povišene vrednosti bar jednog od markera aktivnosti ovog oboljenja. Najsigurnijji način i zlatni standard u postavljanju dijagnoze ove bolesti bila bi patohistološka potvrda, koja se zbog svoje invazivnosti retko radi. **Zaključak**. Nove dijagnostičke metode doprineće zaobilaženju invazivnih procedura i značajno olakšati postavljanje dijagnoze neurosarkoidoze, što je pravi izazov i za iskusne kliničare.

Ključne reči: Sarkoidoza; Centralni nervni sistem; Dijagnoza; Granulom; Znaci i simptomi; Magnetna rezonanca; Lumbalna punkcija

Introduction

Sarcoidosis is a systemic granulomatous disease most frequently affecting lungs and hilar lymph nodes. Recent studies have shown that sarcoidosis can affect any organ including the central nervous system (CNS) [1].

It is difficult to determine the precise number of patients with sarcoidosis because of a great number of subclinical cases. It is believed that only half of the patients are diagnosed during their lifetime [2].

Sarcoidosis may affect any part of the CNS and give a particularly diverse clinical picture. Clinical presentations depend on the localization of granulomas in the CNS. The symptoms are most frequently given by cranial nerves [2]. Making diagnosis according to the localization of this disease and clinical variations is often a big clinical challenge. We have tried to clarify some of the dilemmas in this text, including the question whether pathohistological confirmation is the only way to diagnose this disease and which are diagnostic criteria.

Diagnosis of Neurosarcoidosis

In hospital, the diagnosis of sarcoidosis is made on the basis of the clinical picture, clinical and radiological findings (magnetic resonance imaging of

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Abbreviations

CNS	– central nervous system
NMR	– magnetic resonance
ACE	– angiotensin-converting enzyme

endocranium with contrast-NMR), laboratory findings (angio-tenzin-converting enzyme-ACE and chitotriosidase in liquor), but it is necessary first to exclude all other possible causes of granulomatous inflammation. The safest way and the gold standard in making the diagnosis of this disease would be the pathohistological confirmation, when noncaseating granuloma is present on the pathohistology slide. In everyday practice, biopsy of the CNS is very rarely performed due to its invasiveness and serious complications. Biopsy of nerve tissue is reserved only for vitally threatened patients [3,4].

American National Cardiopulmonary and Hematology Institute has suggested the criteria for sarcoidosis diagnostics in cases when the localization is known and when sarcoidosis of another organ has been pathohistologically confirmed [5,6].

Criteria of A Case Control Etiologic Study of Sarcoidosis (ACCESS) group in neurosarcoidosis diagnostics are classified in the following way:

I Definite diagnosis of neurosarcoidosis
II Probable diagnosis of neurosarcoidosis
III Possible diagnosis of neurosarcoidosis

I Definite Diagnosis of Neurosarcoidosis

1. Positive NMR finding with characteristic piling up of contrast in meninges or the brain stem
2. CSF with lymphocytosis and/ or an increase in protein level
3. Diabetes insipidus
4. Bell's palsy
5. Dysfunction of some of cranial nerves
6. Biopsy of peripheral nerve

II Probable Diagnosis of Neurosarcoidosis

1. Other pathological finding on NMR
2. Neuropathy of inexplicable cause
3. Positive electromyogram finding

III Possible Diagnosis of Neurosarcoidosis

1. Persistent headaches of unknown cause
2. Radiculopathy of peripheral nerves

According to this classification, the definite diagnosis includes the pathohistological finding, and excludes any other granulomatosis of CNS.

In practice, the most frequently used criteria for making the diagnosis of neurosarcoidosis are those suggested by Zajcek et al.[7]. They are very simple and applicable for doctors who meet, diagnose, and treat these patients in practice. These criteria are based on levels of safety in diagnostics of neurosarcoidosis. They are classified in three categories and each of them includes the clinical presentation indicating the diagnosis of neurosarcoidosis and excludes any other diagnosis in the CNS. They are divided into definite, probable and possible diagnosis of neurosarcoidosis, but *definite diagnosis* is the only pathohistological confirmation of this disease. The criteria for *possible* neurosarcoidosis include: clinical symptoms and diagnosis suggesting neurosarcoidosis, but infections and malignancy are not excluded or there is the pathohistological confirmation of systemic sarcoidosis.

For diagnosis of *probable* neurosarcoidosis, clinical symptoms and diagnostic evaluation suggest neurosarcoidosis. Alternative diagnoses are excluded and there is also the pathohistological confirmation of systemic sarcoidosis.

Lumbar puncture is recommended in all patients for diagnostic purposes. Nonspecific anomalies of liquor described in patients with neurosarcoidosis include lymphocytic pleocitosis, increased protein level, decreased glucose concentration, and increased intracranial pressure. Some studies revealed increased immunoglobulin, lysozome and concentration of beta 2 microglobulin, as well as the ratio of lymphocytes CD4+:CD8+ higher than 5. It is important to know that one third of patients suffering from neurosarcoidosis have no abnormalities in CSF. It is also important to have in mind that the patients having some diseases, such as multiple sclerosis and lupus, have similar finding in CSF as the patients with neurosarcoidosis [8, 9].

Specificity and susceptibility of ACE in CSF is still the subject of research. High values of ACE are non-specific and may appear in some other diseases such as infections and tumors. In addition, patients with neurosarcoidosis may have the normal level of CSF. A study has shown that 55% of patients with neurosarcoidosis, 5% of patients with systemic sarcoidosis, and 13% of patients with other diseases have increased values of ACE in CSF. In general, ACE values in CSF are not sensitive enough (24%-55%) for diagnosis of sarcoidosis of CNS, although they may be relatively specific (94%-95%). Based on these results, increased ACE value in CSF is not enough for making the diagnosis [10, 11]. In recent research, chitotriosidase is used as a sensitive marker for sarcoidosis, as well as neurosarcoidosis, the values of which are determined in CSF [12,13]. Determination of chitotriosidase enzyme values in CSF is the method being just introduced into clinical practice and it is the subject of further research. Previous investigations of patients with neurosarcoidosis show the existence of increased value of at least one activity marker of this disease.

Conclusion

Pathohistological diagnostics of this disease is very difficult; therefore, it is necessary to develop other diagnostic methods in diagnosing neurosarcoidosis. New clinical research dealing with bi-

omarkers in cerebrospinal fluid, such as chitotriosidase, will be helpful in everyday management of these patients. New diagnostic methods will make it possible to avoid invasive procedures and they should considerably facilitate making the diagnosis of neurosarcoidosis, which is a real challenge even for experienced clinicians dealing with this disease.

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