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Neurosarcoidosis: Correlation of cerebrospinal fluid findings with diffuse leptomeningeal gadolinium enhancement on MRI and clinical disease activity

Oliver Wengert [a,*], Eva Rothenfusser-Korber [b], Boris Vollrath [a], Georg Bohner [c], Franziska Scheibe [a], Carolin Otto [a], Jörg Hofmann [d,e], Klemens Angstwurm [b], Klemens Ruprecht [a,*]

[a] Department of Neurology, Charité — Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
[b] Department of Neurology, Universität Regensburg, Universitätsstraße 84, 93053 Regensburg, Germany
[c] Department of Neuroradiology, Charité — Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
[d] Labor Berlin Charité-Vivantes GmbH, Sylter Straße 2, 13353 Berlin, Germany
[e] Institute of Medical Virology, Charité — Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

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ABSTRACT

Background: Cerebrospinal fluid (CSF) examination is considered important in the diagnosis of neurosarcoidosis, however, data on whether and how CSF parameters may be related to MRI findings and clinical disease activity of patients with neurosarcoidosis are scarce.
Objective: To correlate CSF findings in patients with neurosarcoidosis with MRI findings and clinical disease activity.
Material and methods: Results of 51 comprehensive CSF examinations of 25 patients with probable or definite neurosarcoidosis according to the Zajicek-criteria were analyzed retrospectively.
Results: Patients with diffuse leptomeningeal gadolinium enhancement on MRI had significantly higher cell counts (≥50 cells/μl in 80%), total protein (≥200 mg/dl in 80%), CSF/serum albumin quotients (Q_{Alb}, ≥30 in 80%), and lactate (≥30 mg/dl in 70%), but significantly lower glucose levels (≤40 mg/dl in 67%) than patients without leptomeningeal enhancement. Irrespective of MRI findings, activated lymphocytes and plasma cells were detected in the initial CSF examination in 60% and 47% of patients, and an intrathecal synthesis of IgG, IgA, and IgM in 22%, 29%, and 22%. Patients with clinically active disease had significantly higher CSF cell counts, total protein, Q_{Alb}, and lactate, but significantly lower glucose levels than patients with stable disease.
Conclusion: CSF abnormalities in neurosarcoidosis are most pronounced in patients with diffuse leptomeningeal enhancement on MRI. CSF analyses may thus aid in the distinction of different radiographic and pathologic manifestations of neurosarcoidosis. Furthermore, CSF examinations may allow monitoring disease activity in patients with neurosarcoidosis.

1. Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized histopathologically by non-caseating epithelioid granulomas, most often localized in the lung or draining mediastinal lymph nodes [1]. Manifestations of sarcoidosis within the nervous system occur in 5–15% of patients with systemic sarcoidosis, but post-mortem studies suggest an even higher incidence of clinically silent nervous system involvement [2–4]. Sarcoidosis can affect the brain, spinal cord, cranial nerves, and peripheral nerves [5]. Current diagnostic criteria for central nervous system (CNS) sarcoidosis (further referred to as neurosarcoidosis) were formulated by Zajicek and co-workers [1,6]. Clinical as well as radiographic features of neurosarcoidosis are highly variable, with MRI findings ranging from multiple parenchymal white matter lesions without uptake of gadolinium to localized dural or diffuse leptomeningeal contrast enhancement [1].

Cerebrospinal fluid (CSF) examination is generally considered a key procedure in the diagnostic work-up of patients with presumed neurosarcoidosis [1,4,5]. Results of CSF examinations, in particular CSF cell counts and total protein levels, were previously reported in various series of patients with neurosarcoidosis (see Supplementary Data 1). Nevertheless, given the variable MRI appearance of neurosarcoidosis, it seems conceivable that CSF findings in patients with neurosarcoidosis may be related to different radiographic disease subtypes. CSF parameters may likewise correlate with disease activity, but both questions have hitherto not been investigated in depth. Furthermore, several potentially relevant CSF parameters, such as CSF lactate levels or intrathecal synthesis of immunoglobulin (Ig)A and IgM, were not studied in detail in patients with neurosarcoidosis so far.

* Corresponding authors. Tel.: +49 30 450 560 343; fax: +49 30 450 560 927.
E-mail addresses: oliver.wengert@charite.de (O. Wengert), klemens.ruprecht@charite.de (K. Ruprecht).

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Here, we comprehensively analyzed results of 51 CSF examinations of 25 patients with definite or probable neurosarcoidosis according to the Zajicek-criteria and correlated them with findings on cerebral MRI as well as with clinical disease activity, including CSF data from individual patients who underwent sequential CSF examinations during active and stable disease phases. We also reviewed the literature on CSF findings in sarcoidosis with neurological manifestations.

2. Patients and methods

2.1. Standard protocol approvals

Lumbar punctures were performed for diagnostic purposes only and with written informed consent of the patients or their guardians. The study was approved by the institutional review board Charité — Universitätsmedizin Berlin (EA1/063/12).

2.2. Patients

Patients with neurosarcoidosis (n = 25; 10 female, 15 male) fulfilling the Zajicek-criteria of either definite (n = 7) or probable (n = 18) CNS sarcoidosis were identified by a retrospective survey of case records of the Departments of Neurology, Charité — Universitätsmedizin Berlin (n = 22; January 1999 to December 2012) and University of Regensburg (n = 3; January 2000 to December 2010). The patients' median (range) age was 39 (23–73) years. Demographic, clinical, radiographic, and laboratory data, including results of tissue biopsies and CSF studies, were extracted from patient records. All patients were of Caucasian origin and had an abnormal cerebral and/or spinal MRI at the time of the initial lumbar puncture. One patient included in the present series was described in detail before [7]. Diagnosis of sarcoidosis was confirmed histologically in all patients. Biopsies were taken from CNS (n = 7), sural nerve (n = 1), lung (n = 9), liver (n = 1), lymph node (n = 7), and skin (n = 1). One patient underwent liver and sural nerve biopsy, hence the total number of 26 biopsies.

Results from the initial CSF examination, i.e. the CSF examination performed at the time of diagnosis, were available from 22 patients, all of whom were untreated. Results of follow-up CSF examinations were available from 24 patients, which were categorized according to their clinical disease activity into patients with active (any new clinical deficit or worsening of a pre-existing symptom; n = 7) or stable disease (no new clinical deficit and no worsening of a pre-existing symptom; n = 17). Fig. 1 provides an overview of patients included in this work. The mean duration between the initial and follow-up lumbar punctures was 5 months for patients with active disease (range 1–17 months) and 14 months for patients with stable disease (range 3–73 months). Of the patients with active disease on follow-up 2 were untreated and 5 received corticosteroid treatment. Of the patients with stable disease on follow-up 5 were untreated, 6 received corticosteroid treatment only, 3 were treated with corticosteroids and azathioprine, 2 were treated with corticosteroids and methotrexate, and 1 received cyclophosphamide treatment.

2.3. CSF studies

CSF white cells were counted manually with a Fuchs–Rosenthal counting chamber. CSF white cell differentiation was performed by microscopic examination of CSF cytospin slides as previously described [8]. Total albumin, IgG, IgM, and IgA concentrations in serum and CSF were measured nephelometrically (BN ProSpec, Siemens Healthcare Diagnostics). CSF-specific oligoclonal bands (OCB) were determined either by isoelectric focussing in polyacrylamide gels and consecutive silver staining or using agarose gels with subsequent in-gel immunofixation (hydrasys, sebia, Fulda, Germany). For all protein analyses, CSF and serum samples were analyzed within the same analytical series.

2.4. Analysis of CSF data

A white cell count ≥5 cells/μl was considered elevated. The upper limit of normal for total CSF protein was 45 mg/dl. Normal values for CSF glucose and lactate were ≥40 mg/dl and ≤20 mg/dl, respectively. Blood–CSF barrier function was assessed by CSF/serum albumin quotients (Q_{Alb}). The age-adjusted upper reference limit of Q_{Alb} was calculated using the formula $Q_{lim(Alb)} = 4 + (\text{age [years]} / 15)$ [9–11]. Dysfunction of the blood–CSF barrier was defined as $Q_{Alb} > Q_{lim(Alb)}$. Quantitative expressions of the intrathecal humoral immune response were based on calculation of the CSF/serum quotients Q_{IgG}, Q_{IgM}, and Q_{IgA}, with $Q_{Ig} = Ig_{CSF[mg/l]}/Ig_{serum[g/l]}$ [9–11]. The upper limits of the respective reference ranges, $Q_{lim(IgG)}$, $Q_{lim(IgM)}$, and $Q_{lim(IgA)}$, were calculated against Q_{Alb} according to Reiber's revised hyperbolic function and intrathecal immunoglobulin synthesis was evidenced by Q_{Ig} exceeding $Q_{lim(Ig)}$ in CSF/serum quotient diagrams [9–11]. Intrathecal production of antibodies against measles virus, rubella virus, and varicella zoster virus, commonly referred to as “MRZ reaction”, was assessed by calculation of antibody indices, as previously described in detail [12,13]. Antibody indices ≥1.5 were considered elevated.

2.5. Statistics

Statistical significance of differences between groups with and without diffuse leptomeningeal gadolinium enhancement on MRI, or with active and remitted disease, was assessed by the non-parametrical Mann–Whitney U test. Differences of frequencies were analyzed by Fisher's exact test. To assess the statistical significance of intraindividual differences in serial CSF examinations the non-parametrical Wilcoxon test was used. P-values <0.05 were considered significant.

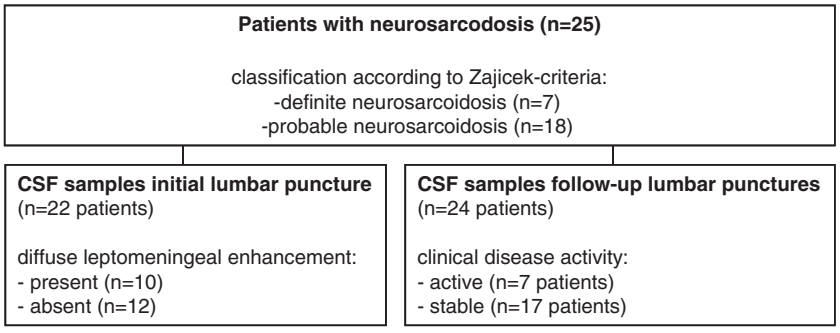

Fig. 1. Overview of patients with neurosarcoidosis included in this study.