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Neurosarcoidosis Without Systemic Sarcoidosis

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Summary. Neurosarcoidosis is a well-recognised complication of systemic sarcoidosis but diagnosis may be difficult if there is no clear evidence of an extracerebral manifestation of the disease. We present the case of a 42-year-old woman with clinical features characteristic of cerebral sarcoidosis including tetraparesis, diabetes insipidus, diencephalic hyperphagia, personality changes, and memory loss. Diagnosis was supported by cerebrospinal fluid (CSF) findings and magnetic resonance imaging (MRI): CSF showed mild lymphocytic pleocytosis, intrathecal production of IgG without oligoclonal bands, and a raised level of lysozyme. MRI revealed multiple contrast-enhanced granulomas at the base of the brain with partial involvement of diencephalic and mesencephalic structures and parts of the spinal cord. There was no evidence of systemic manifestation of sarcoidosis. Administration of corticosteroids led to improvement of the symptoms.

Key words: Sarcoidosis – Cerebrospinal fluid – Lysozyme – Magnetic resonance imaging

Introduction

Neurological manifestations are found in about 5% of patients with systemic sarcoidosis [22, 26] and are the presenting symptoms in 48% of those affected [15, 22]. The major pathological features are aseptic granulomatous basal meningitis or focal lesions due to granulomas; common neurological symptoms are facial palsy, other cranial neuropathies, and involvement of central nervous system (CNS) parenchyma causing hypothalamic-pituitary dysfunction, encephalopathy, seizures, and lesions of the corticospinal tract [5, 10, 15, 19, 22, 26]. Cerebral sarcoidosis without systemic manifestation is rare [15, 22, 26] and difficult to diagnose. This has been facilitated by magnetic resonance imaging (MRI) [11], and recent findings of raised levels of cerebrospinal fluid (CSF) lysozyme (LZM) and angiotensin converting enzyme (ACE) [16–18] in those patients.

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Case Report

A 42-year-old woman presented with progressive spastic gait, personality changes, and memory loss. Past medical history revealed complex partial seizures from the age of 6 years, which had been treated effectively with 400 mg carbamazepin daily. Intellectual development had occurred normally until the age of 18, when she had an episode of delusional paranoia and a second episode 5 years later. After that, she worked as a housemaid. Twelve months before admission she fell ill with difficulty in walking, impairment of memory, and polydipsia. She also had difficulty emptying her bladder with episodes of incontinence and had been amenorrhoeic for several years.

General examination revealed an overweight female (55 kg, 140 cm) with pale, dry skin. Body and pubic hair was almost absent. The remaining physical examination was normal. Neurological examination showed increased tone in the legs, and she was unable to walk owing to spasticity. Tendon stretch reflexes were brisk throughout and plantar responses were extensor. Hand movements were clumsy but strength of the arms was normal. There were no sensory disturbances detectable. There was no stiff neck or papilloedema and cranial nerves were unremarkable. Neuropsychological testing revealed an infantile personality, and gross loss of short- und long-term memory. Ophthalmological examination was normal.

Routine blood tests were normal. At admission, erythrocyte sedimentation rate was raised to 80 mm/h. Testing of endocrine functions revealed mild hypothyroidism; the thyroid-stimulating hormone level was normal before and after stimulation. Plasma cortisol was decreased (2.9 μg/dl at 8 a.m., normally 7–25 μg/dl) with adrenocorticotropic hormone in the normal range. Serum prolactin level was increased to 3.3 μg/dl (normally less than 2.5 μg/dl). Serological testing gave no evidence of any kind of viral, bacterial, fungal, or parasitic infection. A tuberculin test was nonreactive. Serum levels of IgG, IgM, IgA, and immunoelectrophoresis were normal; no tissue-specific antibodies (by immunofluorescence) were detected (including antineutrophil cytoplasmic antibodies). There was no evidence of metachromatic leukodystrophy or other neurolipidoses.

CSF was examined on admission and 1, 6, and 11 months thereafter (Table 1). ACE and LZM were determined by commercial kits (Testomar-Lysozym Mono, Behring, Marburg, FRG; ACE Color FS 116 Mast Diagnostica, Hamburg, FRG), but normal ranges for CSF were not available. We therefore tested a series of patients with other neurological diseases (Fig. 1). In our patient, LZM in serum was slightly raised on two of three occasions but markedly increased in three CSF samples; the patient's and controls' ($n = 23$) values are shown in Fig. 1. ACE was normal in the patient's serum and not detected in CSF; also, CSF ACE was below a detectable level in 19 controls tested (less than 1 unit/l, not

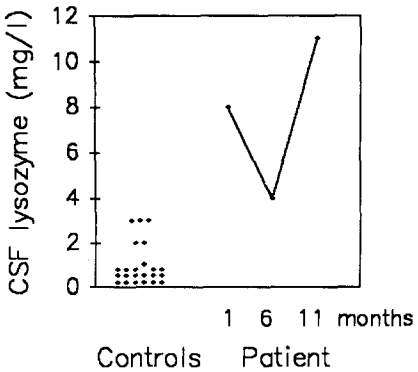


Fig. 1. CSF lysozyme in the sarcoidosis patient (1, 6, and 11 months after the first presentation) and 23 controls with other neurological diseases (5 multiple sclerosis, 2 meningiosis carcinomatosa, 2 Guillain-Barré syndrome: cell counts up to 50/μl; remaining patients with non-inflammatory conditions and normal CSF)

shown). Soluble interleukin-2 receptor (sIL-2R) was quantified using a commercially available ELISA kit (IBL, Hamburg, FRG) and was increased in serum, but not detected in CSF (Table 1).

MRI of the brain and the cervical spinal cord showed irregularly shaped hyperintensities of the white matter, especially the basal temporal lobes, and the diencephalon on T2-weighted series. Also, there was enlargement of the left temporal horn. T1-weighted spin-echo images after intravenous injection of gadolinium diethylene triaminepentaacetic acid (Gd-DTPA, 0.1 mmol/kg) revealed multiple contrast-enhanced superficial nodules along the basal CSF spaces (Fig. 2a). The lesions were pronounced in the suprasellar, mesencephalic, and callosal cisterns, as well as in the regions of the brain stem and upper spinal cord. Some were also located in the sylvian fissure and along the ventricular walls and the convexity of the brain. Predominantly in the diencephalon and in a few locations of the hemispheres, intraparenchymal lesions were seen, too. The appearances were considered to be those of superficial leptomeningeal and intraparenchymal granulomas (Fig. 2c). No sign of brain oedema or impaired CSF circulation was seen.

On the grounds of clinical signs, CSF, and MRI findings the diagnosis of cerebral sarcoidosis was made and the patient was treated with corticosteroids (initially 60 mg prednisolone). There was no evidence of an extracerebral manifestation of sarcoidosis in radiographs and CT of the chest, CT of the abdomen, and skin biopsy of a suspect area (described as pseudolymphoma). Brain biopsy was not done. Bronchoscopy showed no abnormality suggestive of sarcoidosis; at a later date transbronchial biopsy was attempted but not tolerated by the patient. No Kveim test was done. Duodenal biopsy was performed to exclude Whipple's disease and was unremarkable.

Three months after starting steroid therapy the patient's clinical appearance was much improved. She was able to walk short distances and perform simple everyday tasks. Nevertheless, there was still a marked memory deficit, diabetes insipidus which could be controlled by desmopressin, and excessive hyperphagia which improved somewhat with diphenfluramine. MRI follow-up showed a marked reduction in the size of the multiple granulomas, though their actual number was unchanged (Fig. 2b).

Discussion

Sarcoidosis with solely intracranial manifestations is a rare condition and diagnosis must not be made without clear laboratory or neuroradiological evidence, also carefully excluding other treatable conditions. In this case diagnosis was suspected clinically because of diencephalic dysfunctions, spastic tetraparesis, and personality changes with memory loss.

Hypothalamic lesions leading to diabetes insipidus, raised serum prolactin levels, and hyperphagia are found in 15–32% of patients with neurosarcoidosis [5, 9, 13, 15, 22, 25, 26]. In combination with involvement of the corticospinal tract and encephalopathy a diffuse inflammatory process had to be assumed in this case; multiple sclerosis or neurodegenerative disease seemed less likely.

There is no single CSF finding specific for neurosarcoidosis, but typical features have been described. Most cases show mild lymphocytic pleocytosis up to 50 cells/μl [2, 23]. Intrathecal production of IgG was found in 4 out of 6 patients with neurosarcoidosis in a recent study by Borucki et al. [2], but earlier investigations had not suggested such an association [12, 23]. In any case, these would be unspecific findings more often found, for example, in multiple sclerosis and CNS infections.

An important diagnostic feature in our case was the absence of oligoclonal bands in any of the four consecutive CSF samples. In multiple sclerosis, detection of bands is highly diagnostic and of greater value than a raised IgG index. However, the few data available on a total of 15 patients show that in neurosarcoidosis bands are typically absent [2, 12, 23], whether or not the IgG index is raised. There has been one exceptional case reported

Table 1. Summary of CSF findings in the case presented

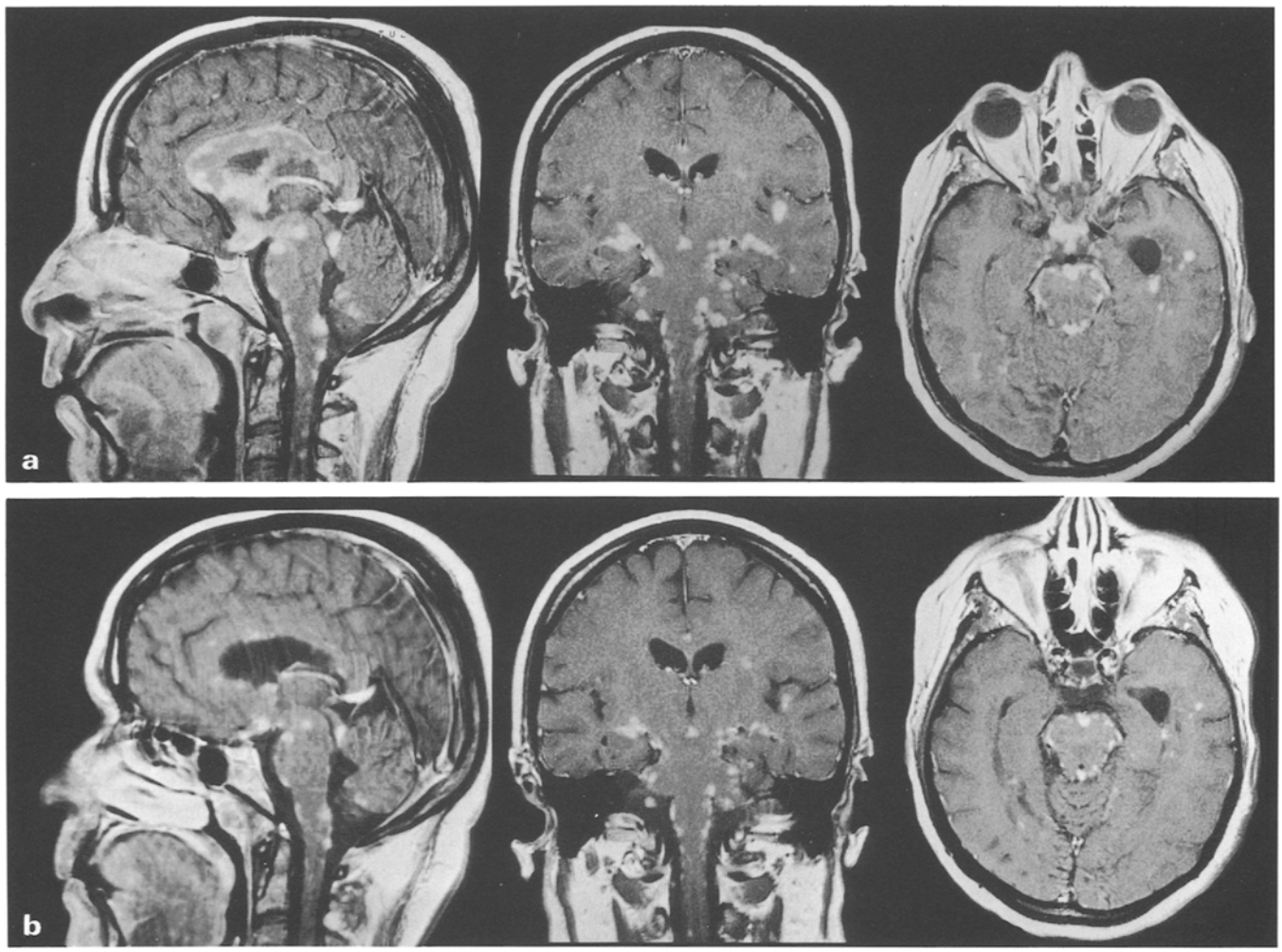
CSF sample[a]	Cells (/μl)	Albumin (mg/l)	IgG (mg/l)	IgG index	Glucose[b] (mg/dl)	Lactate[b] (mmol/l)	Lysozyme[c] (mg/l)		ACE[c] (units/l)		sIL-2R[c] (units/ml)	
							CSF	Serum	CSF	Serum	CSF	Serum
0	4	862	456	1.36							--	663.2
1	9	1250	219	0.62	330	2.2	8	14	1	20		
6	3	654	85.5	0.69			4	9	<1	10		
11	7	564	129	0.75	406	2.6	11	13	<1	9		

ACE, Angiotensin converting enzyme; sIL-2R, soluble interleukin-2 receptor

[a] Months after the first presentation

[b] Normal range: glucose 320–820 mg/dl (depending on blood glucose), lactate less than 2.1 mmol/l

[c] Parallel CSF and serum values are given. Normal ranges: serum lysozyme 3.0–9.0 mg/l; serum ACE 8–28 units/l; sIL-2R in serum less than 200 units/ml. For CSF lysozyme see Fig. 1; CSF sIL-2R was not detectable



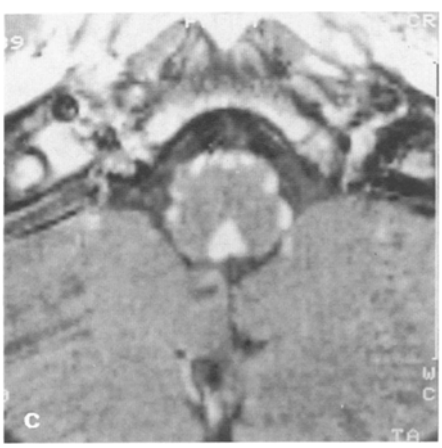


Fig. 2a–c. T1-weighted post-contrast MRI: spin-echo images in sagittal, coronal, and axial planes (1.5 T, TR 0.6 s, TE 15 ms, 4 mm, Gd-DTPA 0.1 mmol/kg). **a** Initial investigation: multiple enhanced leptomeningeal granulomas along the basal CSF spaces. Intraparenchymal infiltrations in the diencephalon and the hemispheres. **b** Follow-up investigation 6 weeks after onset of steroid therapy, showing marked reduction of size of the enhanced granulomas. **c** Primary leptomeningeal nodules infiltrating the surface of the brain stem

with oligoclonal IgM and IgG bands in CSF persisting after steroid treatment and clinical remission [7]. Also, in a recent study of 7 cases, oligoclonal bands in CSF were detected in 2 patients with normal IgG indices [20], however, the authors failed to state whether bands were also positive in the parallel serum samples, which would indicate an unselective B-cell activation.

CSF LZM has been proposed as a helpful marker for detecting CNS involvement in systemic sarcoidosis. Raised levels were found in 15 of 20 patients with neurosarcoidosis and in only 4 of 12 with extraneural sarcoidosis [18]. CSF LZM was also raised in bacterial meningitis and in syphilis in this study, and the authros pointed out that the enzyme is produced intrathecally mainly by macrophages. In our study, the control group consisted of patients with CSF cell numbers less than 50/μl; thus, the highly elevated LZM level with only mild pleocytosis in the sarcoidosis patient seemed rather specific. Since the raised CSF LZM was a major finding to support the diagnosis, we suggest that an improved assay for measur-

ing low concentrations of LZM in the CSF should be more widely available [18]. Moreover, ACE and β_2-microglobulin have been shown to be valuable markers in neurosarcoidosis. However, they are less specific and sensitive than LZM and also elevated in bacterial meningitis, cerebrovascular disease, and CNS tumours [16–18]. In our case, ACE was slightly raised in serum but not detectable in CSF. β_2-microglobulin could not be assessed. Furthermore, a raised serum level of sIL-2R is a marker of T-cell activation and may be increased in patients with systemic sarcoidosis as well as other inflammatory diseases [8]. In sarcoidosis, it does correlate with disease activity and seems to be more sensitive than ACE [24]. The raised level in our patient thus gave evidence of a generalised T-cell activation, typical of sarcoidosis; in CSF, sIL-2R was too low to be detected.

MRI (Fig. 2) revealed multiple contrast-enhanced granulomas at the base of the brain, infiltrating the hypothalamus, the surface of the brain stem, and the spinal cord. In addition, the ventricles and the foramina of the fourth ventricle were lined with nodules. MRI was clearer than CT (not shown) in showing the disseminated, leptomeningeal spread that suggested a granulomatous-inflammatory process.

MRI is the imaging investigation of choice in detecting parenchymal changes in the brain in sarcoidosis [4, 11]. Typically, periventricular and multifocal white matter lesions are found on T2-weighted images (not shown) and the number of lesions detected is greater than by CT [11]. However, these findings are not specific, and by T2-weighted MRI alone it may generally be difficult to differentiate neurosarcoidosis from multiple sclerosis [21]. CT is less accurate in delineating hypothalamic involvement and periventricular white matter disease in some patients [6], but contrast-enhanced CT may reveal diffuse meningeal involvement [11]. Using Gd-DTPA as a paramagnetic contrast medium for MRI leptomeningeal granulomas show a characteristic pattern of superficial enhancement (Fig. 2c), which is highly suggestive of sarcoidosis [14] and would rule out multiple sclerosis. Leptomeningeal spread of tumour cells, as well as fungal or other inflammatory or granulomatous conditions needs to be excluded by other diagnostic methods.

Differential diagnosis included histiocytosis X, Whipple's disease, lymphoma, and fungal meningitis. CSF cytology, however, gave no specific findings for any of them. Duodenal biopsy revealed no changes typical of Whipple's disease. The long duration of the illness and the relatively slow response to steroids were not indicative of a lymphoma. There was no evidence of fungal infection in CSF smears, serology, or culture. Moreover, any infectious process would almost certainly have exacerbated during the long-term steroid treatment; instead, the patient showed some clinical improvement paralleled by improvement of MRI appearances (Fig. 2b).

Interestingly, our MRI findings are strikingly similar to those in a case of fungal meningitis due to *Trichosporon beigelii* [3]. This infection is almost exclusively found in immunocompromised hosts and the chronic course with no response to antifungal therapy in that patient might lead one to speculate that neurosarcoidosis was a concomitant condition. Also, cryptococcal abscesses were associated with systemic sarcoidosis in two other patients [1], indicating that a simultaneous occurrence of fungal infection and sarcoidosis is possible and must be considered.

We suggest that in the case presented CSF and MRI findings provided strong support for the diagnosis of cerebral sarcoidosis, despite the fact that histological evidence could not be obtained.

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