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ORIGINAL COMMUNICATION

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Neurosarcoidosis

Clinical description of 7 cases with a proposal for a new diagnostic strategy

Abstract *Objective* Chronic involvement of the nervous system is relatively rare in sarcoidosis. We describe 7 cases that fulfil Zajicek's criteria for neurosarcoidosis (NS) and propose some modifications to such criteria. *Materials and methods* The patients were admitted for various neurological syndromes: 2 cases presented with chronic lymphocytic meningitis, 4 with spinal cord symptoms, one case was initially confused with multiple sclerosis. Serological tests, immunological screening, cerebrospinal fluid (CSF) analysis, bacteriological and viral testing were performed in all patients. Spinal and cerebral MRI, gallium scan, bronchoscopy with biopsy and bronchoalveolar-lavage fluid analysis, high-resolution computed tomography (HRCT) of the chest, biopsy of the lungs, skin, mediastinal lymph-node and meninges, were useful in diagnosing NS. *Results and discussion* Laboratory tests showed serum inflammatory abnormalities, but were negative for infectious diseases, while CSF showed inflammatory signs in all patients. MRI revealed meningeal enhancement or hypertrophic pachymeningeal lesions in 4 patients, white matter abnormalities and mass lesions in 2 patients, and a spinal mass lesion in 1 patient. Gallium scan, HRCT, bronchoscopy were positive in most cases. Patients were treated with steroid and immunosuppressive therapy, with improvement in six cases. One patient died from infectious complications. *Conclusion* A definite diagnosis of NS requires demonstration of non-caseating granulomas affecting nervous tissues. In most cases, histological evidence of systemic disease (probable NS) is sufficient in the presence of compatible alterations in the CNS. In our patients the bronchoalveolar-lavage fluid analysis, gallium scan, and chest HRCT were important for diagnosis, while serum ACE was always normal and chest radiographs were not suggestive of sarcoidosis.

Key words neurosarcoidosis · CNS diseases · inflammatory

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Introduction

Sarcoidosis is a chronic, granulomatous, systemic disease of unknown aetiology, which can only be diagnosed with certainty by histological analysis. In the absence of positive histology, the diagnosis may be supported by other types of investigation, as broncheoalveolar lavage (BAL) with analysis of the lymphocyte subpopulations. A prevalence of CD4 lymphocytes on BAL, with a CD4:CD8 ratio higher than 3.5, has a positive, predictive value of 76 %, with 53 % sensitivity and 94 % specificity [Costabel et al. 1992]. Another non-invasive procedure for diagnosing sarcoidosis is scintigraphy with gallium-67 (Ga scan), which yields a "panda pattern" on the face and a "lambda pattern" on the mediastinum [Sulavik et al. 1990]. Some centres still adopt the Kveim-Siltzbach intradermoreaction test based on inoculation of granuloma homogenate. This test is only used in a limited number of cases owing to the risk of infectious-agent transmission.

Central and peripheral nervous system involvement is estimated to be 5 % [Stern et al. 1985], but other studies have reported an incidence of 15–16 % [Ferreby et al. 2000; Mayock et al. 1963].

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Neurological symptoms are the primary manifestation of the disease in 62–74% of cases of neurosarcoidosis (NS) [Zajicek et al. 1999; Ferreby et al. 2001]. Thus most patients with NS only develop systemic symptoms after presenting with neurological signs of disease. The clinical course may be acute, subacute or chronic with insidious onset. Reviewing 68 diagnosed cases of NS, Zajicek and colleagues (1999) formulated a series of diagnostic criteria for NS. These criteria envisaged: "certain NS", when the diagnosis was supported by positive nervous tissue histology; "probable NS", when there were signs of inflammation in the central nervous system (CNS), positive histology for a systemic lesion, or a positive Kveim-Siltzbach test and/or positive results for at least 2 of the following tests: Ga scan, serum angiotensin-converting enzyme (ACE) level and chest radiology; "possible NS", in the absence of histological confirmation and after ruling out other inflammatory pathologies.

We report the case histories of 7 patients with NS (1 certain, 4 probable and 2 possible), highlighting the neurological clinical characteristics, the instrumental tests used to exclude other CNS pathologies and the ones used to diagnose NS. In particular, our case set stresses the importance of high resolution computed tomography (HRCT) of the chest in demonstrating lung lesions accessible to biopsy, the Ga scan in revealing lymph nodes or areas of inflammation enhanced by the radionuclide, and BAL in detecting an elevated CD4:CD8 ratio. Cerebrospinal fluid (CSF) analyses are frequently altered, albeit not specifically (blood-brain barrier damage, IgG oligoclonal bands (OB), lymphocytic pleiocytosis). In one case of suspected sarcoidosis-related meningitis, detection of an elevated CD4:CD8 ratio in the CSF was helpful.

We did not use the Kveim-Siltzbach test because of the risk of transmitting infection. Finally we propose that Zajicek's (1999) diagnostic criteria for "Probable NS" should be modified to include HRCT, analysis of BAL and the CD4:CD8 ratio in the CSF, and to exclude the Kveim-Siltzbach test and ACE.

Patients and diagnostic procedure

The patients presenting to our Department between 1989 and 2003 with symptoms suggestive of CNS inflammatory pathology were referred for the following tests: biochemical, blood and immunological profile, electrocardiography (ECG), chest radiology. CSF analysis with cell count, detection of glycorrhachia, protein assay, IgG assay, isoelectrofocusing (IEF) for IgG OB, cytological test, extensive bacteriological and viral tests, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) and angiotensin-converting enzyme (ACE) assays. Examination of the CSF CD4:CD8 lymphocyte ratio was performed, in the presence of a sufficient number of lymphocytes. Magnetic resonance imaging (MRI) with gadolinium (Gd) of the spinal segment involved and brain (to reveal any spatial spread of the pathology) together with visual evoked potential tests (VEP) were also performed.

In order to rule out other inflammatory and infectious diseases of the CNS, tests continued with a Ga scan, HRCT and bronchoscopy with BAL, transbronchial biopsy or biopsy of other tissues (when possible).

Patients with NS, treated with corticosteroid and/or immunosuppressive therapy were then followed-up radiologically and in the outpatient clinic. for at least one year (range: 1–10).

The clinical data are summarised in Table 1, while the CSF data are reported in Table 2. Therapy and follow-up are summarised in Table 3.

Case reports

Case no. 1

This female presented at 22 years with an episode of pulsing headache with nausea, intentional tremor, paraesthesia and paresis of the left upper extremity, polyuria and polydipsia, with spontaneous improvement. At 23 years, she had a recurrence associated with fever and laterocervical lymphoadenopathy that again regressed spontaneously. At 24 years, the neurological symptoms relapsed and the patient was admitted to our ward (Table 1).

Laboratory tests yielded erythrocyte sedimentation rate (ESR) of 36 (normal value < 20) and serum C-reactive protein (CRP) of 0.63 (normal value 0.0–0.50 mg/dl). CSF analysis revealed lymphocytic pleiocytosis, raised protein level, and hypoglycorrhachia. Cultures and the Mantoux test were negative (Table 2).

Brain CT showed slight ventricular dilatation and chest radiographs disclosed thickening of the hilar structure. Bronchoscopy with BAL revealed lymphocytic alveolitis with CD4:CD8 of 3.3 (normal value > 2.4).

The outcome of transbronchial biopsy was "isolated epithelioid granulomatous foci and lung sarcoidosis".

The patient was initially treated with antituberculous therapy, and then with a low-dose corticosteroid, without benefit (Table 3). Application of a ventriculo-peritoneal shunt for worsening hydrocephalus led to brief improvement but the device later became obstructed. Motor and cognitive skills deteriorated, with onset of epileptic seizures and subsequent death. Autopsy was not performed.

Diagnosis: Probable NS with chronic lymphocytic meningitis.

Table 1 Clinical and instrumental characteristics in 7 patients with Neurosarcoidosis

Patient	1	2	3	4	5	6	7
Neurological syndrome	Chronic meningitis	Subacute myelitis	Pachy-meningitis	Uveitis and focal deficits	Chronic meningitis	Recurring myelitis	Meningo-myelitis
Systemic syndrome	Lymph Adenopathy,	–	–	Uveitis, erythema nodosum, glomerulonephritis, polyarthralgia	–	–	–
Chest radiograph	N	N	N	N	N	N	N
Serum ACE	N	N	N	N	N	N	N
Ga scan	–	+	+	+	–	N	+
HRCT(stage)	–	II	II	II	N	N	I
Biopsy	Lung +	Lymph node Mediastinum +	Meninges +	Skin +	–	Conjunctiva –	Lymph node Mediastinum +
CT/MRI CNS	+	+	+	+	+	+	+
CSF	Barrier lesion	Barrier lesion Mirror pattern	Barrier lesion	IgG OB+	Barrier lesion IgG OB+	IgG OB+, then IgG OB–	IgG OB+, then IgG OB–

ACE Angiotensin converting enzyme; *HRCT* High resolution chest CT; *N* normal; *I* bilateral hilar lymphadenopathy; *II* bilateral hilar lymphadenopathy + lung infiltrate; *III* lung infiltrate (without lymphadenopathy); *IV* pulmonary fibrosis

Table 2 CSF data on 7 patients with Neurosarcoidosis

	Aspect	Cell/mm^3	Glucose g/l	Protein mg/dl	IgG index	IEF
1	Opalescent	105 Lymph.	0.11	2240	–	IgG OB+
2	I: clear	4 Lymph.	N	1228	–	Mirror pattern
	II:clear	6 Lymph.	N	N	N	N
3	Clear	11 Lymph.	N	484	N	N
4	Clear	5 Lymph.	N	N	1.6	IgG OB +
5	I: clear	90 Lymph.	0.31	260	–	–
	II^a: opalescent	146 Lymph.	0.32	302	–	–
	III: clear	14 Lymph.	N	697	N	IgG OB+
6	I: clear	31 Lymph.	N	N	–	IgG OB+
	II: clear	1 Lymph.	N	N	N	N
7	I: opalescent	200 Lymph.	N	99	–	IgG OB+
	II: opalescent	49 Lymph.	0.40	152	0.693	N

N normal; *I* before therapy; *II* after steroid therapy; *II^a* after anti-TUBERCULOUS therapy; *III* after immunosuppressive and steroid therapy

Case no. 2

This female, aged 70 years, had developed subacute myelopathy with bilateral T6 sensory level. Spinal MRI showed an intramedullary lesion from D5 to D8 enhancing with gadolinium. The patient was treated with high-dose i. v. corticosteroid therapy with benefit. Spinal symptoms recurred on reduction of the corticosteroid and again partially regressed with i. v. corticosteroids. Subsequently paresis and astereognosis also appeared in the right arm. The patient presented to our attention with steroid-sensitive relapsing myelopathy (Table 1).

Laboratory tests yielded ESR 113, CRP 4.9, and fibrinogen 670 mg/dl (normal value 200–400 mg/dl). CSF analysis showed raised proteins, normal glucose, an IgG mirror pattern on IgG IEF. A subsequent control, performed after corticosteroid therapy, was normal (Table 2).

A control spinal MRI showed an alteration in the signal from C2 to C6 and tiny syringomyelinic cysts from C7 to D11. In the dorsal segment, the spinal cord was compressed by an elongated, irregular area with hypointense signal in T1 and hyperintense in T2 (hypertrophy of the meninges) (Fig. 1a and b).

A Ga scan revealed numerous areas of hyperactivity with large nodules in the hila, right lung, mediastinum and cervical rachis. Bronchoscopy with BAL showed lymphocytic alveolitis with a CD4:CD8 ratio of 5.1. HRCT showed pleural thickening, diffuse enhancement of the interstitium, and swollen mediastinal lymph nodes.

Table 3 Therapy and clinical course

Patient	Follow-up (years)	Treatment	Follow-up
1	2	Antituberculous therapy Deflazacort 30 mg	Progressive disease/exitus
2	3	MP 500 mg x 12 days Prednisone 25 mg x 2 yrs + CFX i. v./montly x 2 yrs.	Clinical improvement Stabilization
3	4	MP 1000 mg x 3 days, 500 mg x 6 days Prednisone 25 mg x 2 yrs	Clinical improvement Asymptomatic
4	8	MP 500 mg + CFX i. v./monthly x 1 yr Prednisone 25 mg + IFN β1b MP 1 g for 6 days, then prednisone 50 mg + MTX 22.5 mg/week	Stabilization Worsening Stabilization
5	5	Antituberculous therapy for 9 months MP 500 mg for 6 days Dexamethasone 16 mg/day followed by prednisone 100 mg + CFX i. v./monthly MTX 25 mg/week + prednisone 50 mg + chloroquine 200 mg x 2/day	No response to anti-TUBERCULOUS therapy Clinical improvement Complete regression Asymptomatic
6	10	MP 500 mg x 6 days Prednisone 32.5 mg/day	Improvement Asymptomatic
7	1	MP 1000 mg x 6 days, 500 mg x 6 days No Therapy Prednisone 50 mg + MTX 10 mg/week + chloroquine 200 mg/day	Improvement Worsening Improvement

MP Methylprednisolone; *MTX* methotrexate; *CFX* cyclophosphamide; *IFN* interferon β1b

Mediastinal lymph node biopsy revealed "sarcoid-type granulomatous lymphoadenopathy".

Treatment was started with corticosteroids associated with cyclophosphamide i. v. (CFX), with partial benefit (Table 3).

Diagnosis: Probable NS with hypertrophic pachymeningitis and myelopathy.

Case no. 3

A female, aged 57 years, presented with subacute paraparesis with sensory level T9, regressing after i. v. corticosteroid therapy. Recurrence after a few months was associated with dysphagia, paresis of the XII cranial nerve and dysphonia owing to blocked left hemilarynx (Table 1).

Laboratory tests yielded: ESR 102, fibrinogen 739 mg/dl, CRP 9.9. CSF analysis showed moderate lymphocytic pleiocytosis, albumin 484.1 mg/l (normal value 10–40 mg/l) (Table 2).

Myelography and a myelo-CT scan revealed pathological peridural tissue, concentrically arranged causing dural-sac stenosis from the atlanto-occipital passage to D9. MRI was not performed because the patient had a pace-maker.

Meningeal biopsy disclosed: "fibroadipose tissue with lymphocytic infiltration grouped in nodules with predominantly perivascular distribution, consisting prevalently of T and B lymphocytes and giant cells (granulomatous inflammation)".

A Ga scan showed areas of intense hyperfixation in the right lung, dorsolumbar vertebrae and left sacrum. HRCT showed slight patches of thickening in the middle lobe and right inferior lobe. CT-guided biopsy was not indicative (performed after starting corticosteroid therapy).

Symptoms disappeared completely on high-dose corticosteroid therapy (Table 3). At follow-up the patient remained asymptomatic.

Diagnosis: Certain NS with hypertrophic pachymeningitis.

Case no. 4

This female patient, aged 34 years, presented with relapsing anterior uveitis, asthenia of the lower extremities, and polyarthralgia. Proliferative mesangial glomerulonephritis onset at 35 years, during the postpartum period, but completely regressed with corticosteroids. At 36 years, uveitis recurred, with the appearance of paraparesis. Systemic lupus erythematosus was diagnosed (ANA test positive for anti-Ro) and treated with CFX i. v. for one year, with stabilization of the clinical picture. Erythema nodosum appeared on suspension of therapy.

A skin biopsy revealed "lymphogranulocytic infiltrate associated with an abundant gigantocellular granulomatous component. No microorganisms were grown in culture".

The patient was admitted to a neurological ward to treat onset of cerebellar syndrome and discharged with a diagnosis of Multiple Sclerosis. Treatment was started

with interferon β1b but the clinical picture worsened progressively during the following two years, with the reappearance of erythema nodosum and recurring uveitis (Table 1).

Laboratory tests yielded ESR of 39. CSF analysis showed an IgG index of 1.6, and IgG OB were present on IEF (Table 2).

Encephalic MRI with Gd showed diffuse signal hyperdensity in DP and T2 in the semioval centres, thalamus and right pons. VEP revealed a prolonged latency of bilateral conduction. HRCT showed interstitial thickening and some hilar lymph nodes measuring around one centimetre.

A Ga scan revealed areas of abnormal uptake in large nodules in the lungs, mediastinum, right laterocervical area, coxofemoral joints, lacrimal glands, left parotid, arm and skin.

Corticosteroid therapy was started for 6 days with partial, temporary benefit. Three months later, the patient developed optical neuritis and erythema nodosum, which regressed with corticosteroids associated with methotrexate. After 2 years' follow-up, the patient was stationary (Table 3).

Diagnosis: Probable NS with multifocal involvement (MS-like).

Case no. 5

A male patient, aged 23 years, presented with a history of headache, vomiting, fever, slight nucal rigidity, hearing loss, with a subacute course. Brain MRI revealed two small lesions enhanced by contrast medium in the suprasylvian cortico-subcortical area and in the right cerebellar hemisphere. Angio-NMR and echocardiogram were normal. CSF analysis disclosed lymphocytic pleiocytosis, hypoglycorrhachia. Bacterioscopic tests, cultures for mycobacteria and cryptococcus, and polymerase chain reaction (PCR) for Koch's bacillus were repeatedly negative. The immunological profile and Mantoux test were negative. Antituberculous therapy was started, without benefit (Table 1).

Repeated lumbar punctures documented clear, hypertense CSF, pleiocytosis, hypoglycorrhachia and IgG OB (Table 2). The Lymphocyte subpopulations in the CSF had a CD4:CD8 ratio of 8.7. The test for cell clonality proved negative.

Brain MRI revealed diffuse uptake of contrast medium in the leptomeningeal spaces, particularly at the skull base (Fig. 1c). Chest, abdominal, cranial CT were negative.

Antituberculous treatment was associated with 25 mg prednisone per day with slight improvement. On suspending the corticosteroid, the patient worsened and developed partial epileptic motor seizures. The antituberculous treatment was stopped and dexamethasone introduced at a dose of 16 mg i.v./die, with regression of the symptoms and improvement of the CSF profile (Table 2). Brain MRI revealed a reduction in post-contrast enhancement in the meningeal spaces.

Steroid therapy was associated with CFX i. v., later replaced by methotrexate and chloroquine, with normalization of the clinical and CSF picture. Two years later the patient remained asymptomatic, although treatment was still administered (Table 3).

Diagnosis: Possible NS with chronic lymphocytic meningitis.

Case no. 6

This 37-year-old female developed right hypaesthesia from C4 downwards, subacute triplegia and urinary in-

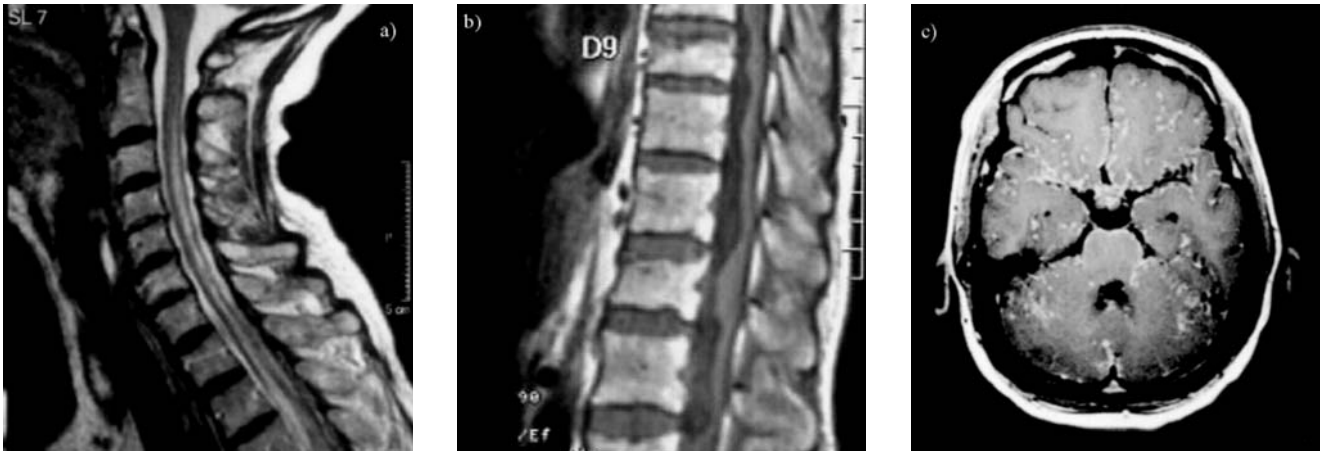

Fig. 1 **a)** Case 2: cervical syringomyelia in a patient with meningeal sarcoidosis at the thoracic level; **b)** Case 2: extensive and irregular hypertrophy of dorsal meninges with spinal cord compression; **c)** Case 5: brain MRI T1-weighted with diffuse uptake of gadolinium mostly at the leptomeningeal level. The non Gd enhanced MRI was negative

continence onsetting 10 days after presenting high temperature (Table 1).

ESR was 29, fibrinogen 533 mg/dl, lymphocyte subpopulations had a CD4:CD8 ratio of 4.5. CSF was clear with lymphocytic pleiocytosis and IgG OB on IEF (Table 2).

Spinal cord MRI disclosed multiple lesions of the cervical spinal cord, with Gd enhancement, probably of inflammatory origin.

Corticosteroid therapy was started with clinical improvement. The control spinal cord MRI was normal. Recurrences occurred in the following two years when the corticosteroid dose was reduced. The patient was thus treated on several occasions with 500 mg/day methylprednisolone, with benefit. A control MRI revealed swelling of the spinal cord between C2 and C4 and post-contrast alteration in signal with quite well-defined margins (suspected glial tumour). At the latest recurrence, after 2 years, CSF was normal. A lymphoproliferative form was ruled out and HRCT and Ga scan were unremarkable. A control MRI showed thin syringomyelia from C1 to C6. Given the presence of inflammatory CNS disease, long-term oral prednisone therapy was started. At 10-year follow-up, the patient remained asymptomatic (Table 3).

Diagnosis: Possible NS with myelitis and secondary syringomyelia.

Case no. 7

This male patient, aged 39 years, developed subacute myelopathy with bilateral T12 sensory level and paraparesis. Dorsal MRI exhibited an intramedullary lesion from T10 to T12 Gd positive. The patient was treated with high-dose i. v. corticosteroid therapy with partial benefit. After 5 months the patient developed subacute paraplegia (Table 1).

The CD4:CD8 ratio of the lymphocyte subpopulations was 4.3.

CSF analysis revealed clear CSF, lymphocytic pleiocytosis, and elevated protein. Glucose was normal and IgG OB were revealed on IEF. Bacterioscopic tests and cultures were negative. Subsequent control after steroid therapy showed clear CSF, lymphocytic pleiocytosis, raised protein. Glucose was normal and there were no OB on IEF (Table 2).

Spinal MRI revealed an alteration in spinal cord signal from D10 to D12 and diffuse uptake of contrast in the cauda equina.

A Ga scan disclosed areas of hyperactivity in the hila and lacrimal glands. Bronchoscopy with BAL showed lymphocytic alveolitis with a CD4:CD8 ratio of 3.0. HRCT revealed swollen mediastinal lymph nodes. A mediastinal lymph node biopsy reported "sarcoid-type granulomatous lymphoadenopathy".

Therapy was started with oral corticosteroids associated with methotrexate and chloroquine, with partial benefit (Table 3).

Diagnosis: Probable NS with meningomyelitis.

Results

The patients described were admitted to our hospital ward between 1989 and 2003 and followed up for a period of between one and ten years through outpatient check-ups and control MRI of the spinal segment involved plus the brain tract.

One patient was diagnosed as "certain NS" (Case 3), 4 patients as "probable NS" (cases 1–2–4–7) and 2 patients as "possible NS" (cases 5–6), in accordance with Zajicek's diagnostic criteria.

Five of the 7 patients showed no signs of systemic inflammation and the neurological symptoms were the first manifestations of the disease. Two patients presented with chronic tuberculous-like lymphocytic meningitis, 3 with steroid-responsive, but relapsing myelitis. One patient had compressive myelitis with hypertrophic pachymeningitis and 1 patient was affected by a disease resembling MS, but with previous systemic inflammatory manifestations (uveitis, glomerulonephritis). In 2 cases presenting as subacute myelitis, a thin syringomyelic cavity was detected at the control MRI (Fig. 1)

The CSF was abnormal in all 7 patients (Table 2). Lymphocytic pleiocytosis was present in 5 out of 7 patients in the first CSF sample. An increased protein level was present in 5 out of 7 patients, IgG OB in 5 and an IgG mirror pattern in 1 case. In one patient with lymphocytic meningitis, the CSF CD4/CD8 ratio was 8.7 (normal value < 5).

The chest radiological examination and the serum ACE were normal in all cases (Table 1).

The HRTC of the chest was performed in 6 cases and showed abnormalities in 4. In 2 cases the HRCT was useful in indicating a biopsy site. Ga scan was performed in 5 cases and was positive in the ones in which the HRCT showed abnormalities.

In 3 cases the BAL was examined and lymphocytic alveolitis was always present, in 2 cases with a CD4/CD8 ratio > 3.5.

In 2 patients the biopsy specimens indicated granulomatous inflammation with multinucleated giant cells on the skin (case 4) and cervical meninges (case 3). However, the pathologist's report did not include the specific term "sarcoidosis" and therefore the neurologist did not initially consider this diagnosis. Only reconsideration of the biopsy material after clinical worsening permitted the diagnosis.

All patients, save the first case, were initially treated with i. v. corticosteroid therapy with 500 or 1000 mg bo-

luses for a duration of between 6 and 12 days (Table 3). On achieving the first signs of functional recovery, corticosteroid therapy was tapered and in 4 cases associated with an immunosuppressant drug to stabilise the clinical picture and reduce side effects of steroid. Case 1 was treated with the standard therapy for lung sarcoidosis, but the neurological syndrome progressed to the death of the patient.

Discussion and conclusions

We describe the clinical and laboratory data of 7 cases of NS, classified according to the diagnostic criteria of Zajicek et al. (1999). The therapy and follow-up data are also reported. From our data we propose some modifications to the diagnostic criteria for "Probable NS".

Sarcoidosis has a variable natural course: two-thirds of cases show spontaneous remission, while disorders become chronic in 10–30 % of cases [Hunninghake et al. 1999]. One to five percent of patients die, mainly from respiratory insufficiency, myocardiopathy or CNS lesions. Excepting paresis of the VII cranial nerve, due to proximate inflammation of the parotid gland [Nowak et al. 2001], nervous system involvement is not conducive to spontaneous remission, as confirmed by several authors. In fact high disability and mortality rates in patients with CNS lesions are reported [Chapelon-Abirc 1991; Ferriby et al. 2001].

The prognosis may be negatively influenced by various factors, including genetic factors and onset after 40 years of age [Manà et al. 1994; Takada et al. 1993]. In the Italian population, systemic diffusion of the disease is often associated with HLA-B22 [Hunninghake et al. 1999].

Neurological manifestations are manifold and depend on localization of the inflammation. Hence differential diagnosis includes chronic and subacute meningitis, multiple sclerosis, myelopathies and tumour-like lesions [Kelly RB et al. 1988; Howard Jaster J 1997; Levivier M 1991].

Systemic inflammatory indices are altered only occasionally in NS. This inconstant alteration of inflammation indices may be explained by the pathogenetic mechanism proper to sarcoidosis, in which the immune system is activated, particularly at the point of the lesion, often without evident signs of systemic inflammation. T CD4+ lymphocytes, which infiltrate the granulomatous area, express the Th1 profile and locally produce cytokines, which promote granuloma growth [Moller DR 1999]. Host organism susceptibility may bring about a switch from Th1 to Th2 profile and onset of the fibrous stage of the disease through the production of cytokines as TGFβ [Agostini et al. 1998].

Alterations in the CSF are varied and change over time; they may be marked and dictate differential diagnosis with tuberculous meningitis, or exhibit oligoclonal bands and orient diagnosis towards a demyelinating disease. CSF analysis proved normal on various occasions, but only after cycles of treatment with corticosteroids and/or immunosuppressants (Table 2).

In 2 cases of NS-related lymphocytic meningitis with hypoglycorrhachia, tuberculous meningitis was initially suspected. However, a number of elements may help to differentiate NS from tuberculous meningitis: failure to identify bacteria, negative cultures and PCR in 3 consecutive samples, persistently negative tuberculin tests, less aggressive clinical course, failure to respond to anti-tuberculous therapy. The MRI lesions in NS are, in our cases, more diffuse and smaller than those usually seen in tuberculous meningitis (Fig. 1c).

Sarcoidosis should be suspected after ruling out other inflammatory pathologies, including cases of cryptogenetic subacute meningo-myelopathies, especially when they respond to corticosteroids but tend to recur on suspending the drug.

The diagnostic procedure should always aim to locate a site of disease that is accessible to biopsy. HRCT, BAL and Ga scan are valuable means of suspecting the diagnosis and authorizing immunosuppressant therapy, when diagnostic biopsy is not possible.

Conventional treatment of pulmonary sarcoidosis is based on oral corticosteroids, but no studies have been published that define optimum dose or duration [Paramothayan et al. 2002]. Hence, therapy is generally adjusted to patient response.

Most patients affected by NS responded to corticosteroids only partially, prompting the need to associate an immunosuppressant drug [Agbogu et al. 1995; Lower 1997; Ferriby et al. 2001]. Our patients responded well to high-dose corticosteroid therapy. Early drug reduction led to a return in symptoms in all described cases. Intravenous corticosteroid therapy was replaced by oral administration, lasting for a period of at least two years at the dosage required to control symptoms. Association with another immunosuppressant was necessary in 4 cases to improve symptom control and reduce corticosteroid-related side effects.

In our experience, making a diagnosis of NS was therapeutically essential, since corticosteroid and immunosuppressant treatment must be started and continued for years in order to prevent, or at least limit, otherwise permanent disability. Neurological impairment results not only from florid inflammation, but also from progression of the fibrosis, which entraps the roots, and compresses and deforms the spinal cord profile and brain base structures. This late stage may also benefit from immunosuppressant therapy (see cases 2 and 3).

NS is difficult to diagnose, partly because the neurological picture is polymorphic and nonspecific. Our cases suggest that diagnosis is facilitated by some tests, i. e. HRCT and Ga scan. HRCT, in particular, may prompt

transbronchial or transthoracic biopsy. BAL also proved to be a valuable diagnostic test, especially when biopsy was not possible. The CD4:CD8 ratio in the CSF may be important when it exceeds 5 [Wrethem et al. 1998]. The study by Stern and colleagues (1987) indicated an increase in the CD4:CD8 ratio in 2 out of 8 patients affected by NS, with findings of 6.8 and 7.6.

Serum and CSF ACE, as well as plain chest radiography proved to be of no diagnostic value.

The Kveim-Siltzbach test was abandoned by our centre some years ago. The material for the test is made of human spleen extracts and is generally no longer available. Consequently, it was never used in our patients and, in our opinion, is not essential for diagnosis.

The main goal of our study was to verify the diagnostic criteria of Zajicek et al. (1999). We propose to modify the diagnostic criteria of Zajicek et al. (1999) for "Probable NS" as follows: to exclude the Kveim-Siltzbach test, chest radiography and serum ACE and include, as indirect indicators, chest HRCT, BAL with a CD4:CD8 ratio >3.5 and a CD4:CD8 ratio >5 in the CSF.

Finally it must be stressed that our cases of NS do not include lesions of the peripheral nervous system or cranial nerves, in which the clinical course and laboratory data may be different.

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