

early-onset Parkinson's Disease and mutations in the *parkin* gene. *N Engl J Med* 2000;342:1560–1567.

7. Klein C, Pramstaller PP, Kis B, et al. Parkin deletions in a family with adult-onset, tremor-dominant parkinsonism: expanding the phenotype. *Ann Neurol* 2000;48:65–71.
8. Tassin J, Dürr A, Bonnet AM, et al. Levodopa-responsive dys-

tonia: GTP cyclohydrolase I or parkin mutations? *Brain* 2000; 123:1112–1121.

9. Maruyama M, Ikeuchi T, Saito M, et al. Novel mutations, pseudo-dominant inheritance, and possible familial affects in patients with autosomal recessive juvenile parkinsonism. *Ann Neurol* 2000;48:245–250.

Long-term follow-up of neurosarcoidosis

Article abstract—The authors evaluated the long-term clinical outcome of neurosarcoidosis and determined predictive factors of disease course. Twenty-seven patients with neurosarcoidosis were followed for at least 5 years from the onset of neurologic symptoms. Patients with CNS involvement during the course of the disease had a higher Modified Oxford Handicap Scale score than those with peripheral nervous system involvement ($p < 0.02$). CNS involvement may be a predictive factor for a less favorable disease course. Early and intensive treatment should be considered in such cases.

NEUROLOGY 2001;57:927–929

D. Ferriby, MD; J. de Seze, MD; T. Stojkovic, MD; E. Hachulla, MD; B. Wallaert, MD; A. Destée, MD; P.Y. Hatron, MD; and P. Vermersch, MD

Neurosarcoidosis occurs in approximately 5% to 15% of sarcoidosis cases.^{1,2} Because of its clinical heterogeneity, diagnosis is often difficult, especially in patients without systemic manifestations. Long-term clinical follow-up has rarely been studied and the natural history of the disease remains uncertain.³ Furthermore, treatment of neurosarcoidosis is not yet well defined. The aim of this study was to evaluate the long-term clinical outcome of neurosarcoidosis and to determine predictive factors for disease course to propose treatment guidelines.

Patients and methods. We retrospectively reviewed the clinical and laboratory data of 52 patients diagnosed between 1968 and 1999 with neurosarcoidosis according to the criteria of Battesti⁴ modified by Oksanen⁵ as follows: Inflammatory systemic pathology consistent with a diagnosis of sarcoidosis diagnosis or typical granulomatous proliferation (biopsy) and compatible neurologic signs. Twenty-seven of these patients (13 men and 14 women) had a follow-up period of 5 years or more since the first neurologic symptoms and were included in the study: 25 were white, one was North African, and one was Asian. Mean age at onset of neurologic symptoms was 42.6 years (range, 17 to 61 years).

Disease onset was classified as progressive or acute. At final examination, disease course was studied by assigning patients to two groups based on the classification proposed by Luke et al.³: Group 1, remission (complete regression of symptoms with normal clinical examination) or improve-

ment (regression of symptoms with a sustained disability considered as sequellar, persisting more than 12 months) and Group 2, stable (no modification of clinical examination) or worsening (progressive worsening of symptoms or physical handicap). Clinical outcome at the end of follow-up was assessed according to the Modified Oxford Handicap Scale (MOHS)⁶: 0 = No symptoms; 1 = minor symptoms that do not interfere with lifestyle; 2 = minor handicap with symptoms leading to some restriction in lifestyle but not interfering with the patient's capacity to look after himself or herself; 3 = moderate handicap with symptoms that significantly restrict lifestyle and prevent totally independent existence; 4 = moderately severe handicap with symptoms that clearly prevent existence though not needing constant attention; 5 = severe handicap leading to total dependence and requiring constant attention during night and day; 6 = death. Patients were then classified into two groups corresponding to "Minor disability" (MOHS score ≤ 2) and to "Severe disability" (MOHS score > 2). Cranial nerves involvement (except for the optic nerve) was classified under PNS involvement.

CSF analysis was performed in 19 cases. Angiotensin conversion enzyme (ACE) level was evaluated in blood in 24 patients and in CSF in 11 patients. A brain CT scan or MRI was performed in 21 cases.

Statistical evaluation was performed by using the Spearman rank correlation coefficient and a χ^2 test or Fisher's exact test ($p < 0.05$ for degree of significance).

Results. The mean clinical follow-up time was 6.6 years (range, 5 to 18 years). Neurologic symptoms were the first clinical manifestation of sarcoidosis in 74% of cases. Thirteen (81.2%) of the 16 patients with isolated neurologic involvement at the beginning of the disease showed one or more extraneurologic localizations during the follow-up (eight mediastinal or pulmonary, two cutaneous, four ocular, and one hepatic). Only two patients presented further neurologic involvement in addition to the initial symptoms

From the Departments of Neurology (Drs. Ferriby, de Seze, Stojkovic, Destée, and Vermersch), Internal Medicine (Drs. Hachulla and Hatron), and Pneumology (Dr. Wallaert), CHRU de Lille, France.

Received January 4, 2001. Accepted in final form April 24, 2001.

Address correspondence and reprint requests to Dr. D. Ferriby, Clinique Neurologique, Service de Neurologie D, Hôpital Roger Salengro, CHRU Lille, 59037 Lille Cedex; e-mail: d-ferriby@chru-lille.fr

Table Clinical data, treatments, and laboratory and radiologic findings of 27 patients with neurosarcoidosis

| Case no./age at onset, y/sex | Initial symptoms | Treatment | | Initial MRI or CT scan | | | Relapses per unit time, mo | Clinical outcome | Systemic ACE level at onset (normal < 55 UI/L) | MOHS score |
|------------------------------------|----------------------------------------|-----------|-------------------------------------------------------|------------------------|--------------|-------------------------|----------------------------------|---------------------|---------------------------------------------------------|---------------|
| | | Initial | During follow-up | Lesion topography | | Contrast enhancement | | | | |
| | | | | Supratentorial | Subtentorial | | | | | |
| 1/40/M | CN (II, V) | OC | OC | + | - | + | - | Improvement | 25 | 0 |
| 2/61/M | Motor deficit | OC | OC | - | - | ND | - | Stabilization | 30 | 2 |
| 3/54/F | CN (VI) | OC | OC | ND | ND | ND | - | Remission | ND | 0 |
| 4/53/F | CN (VII) | OC | OC | ND | ND | ND | - | Remission | 22 | 0 |
| 5/47/F | CN (VII, X) | OC | OC | - | - | ND | - | Remission | 36 | 0 |
| 6/61/M | Partial seizure | OC | OC | - | - | - | - | Remission | ND | 1 |
| 7/39/M | CN (VII) | OC | OC | ND | ND | ND | - | Remission | 28 | 0 |
| 8/27/F | Amenorrhea-galactorrhea | OC | OC | ND | ND | ND | - | Remission | 33 | 0 |
| 9/45/F | Headache, potomania | OC | OC | - | - | - | - | Stabilization | 65 | 2 |
| 10/42/M | Paresthesia | IVC | OC | + | - | + | M30, M48 | Improvement | 37 | 1 |
| 11/35/M | Generalized seizure, cerebellar | OC | OC | + | - | - | M92 | Worsening | 38 | 4 |
| 12/46/F | Muscle weakness | OC | OC | + | - | - | M35 | Improvement | 34 | 1 |
| 13/44/F | Sensorimotor deficit | OC | OC | + | - | - | M36 | Remission | 30 | 1 |
| 14/54/M | Headache, motor deficit, CN (IX, X) | OC | OC | + | - | - | M120, M192 | Worsening | 37 | 5 |
| 15/29/M | Hemiparesia, aphasia | OC | OC | + | - | + | - | Stabilization | 33 | 3 |
| 16/27/M | Headache, motor deficit, CN (VI) | IVC | OC | + | + | - | - | Remission | 104 | 0 |
| 17/30/M | CN (II) | IVC | OC + MTX | + | - | + | M54 | Stabilization | 24 | 2 |
| 18/57/M | Neuropathy | IVC | OC | ND | ND | ND | - | Stabilization | 100 | 2 |
| 19/45/M | Multiple mononeuritis | IVC | OC + MTX followed by CYCLOP, AZA, and CICLOS | - | - | - | - | Stabilization | 27 | 2 |
| 20/41/M | Headache, CN (V) | OC | OC + MTX | + | - | + | - | Stabilization | 82 | 2 |
| 21/42/F | Sensorimotor deficit | OC | OC + MTX | - | - | - | M98 | Stabilization | 40 | 3 |
| 22/32/F | Hemiparesia | IVC | OC + CYCLOP followed by AZA | + | + | - | - | Stabilization | ND | 3 |
| 23/60/F | Muscle weakness | OC | OC | - | - | - | - | Remission | 52 | 0 |
| 24/17/F | CN (VII) | OC | OC | - | - | - | - | Remission | 60 | 0 |
| 25/31/F | CN (VII) | OC | OC | - | - | - | - | Remission | 35 | 0 |
| 26/39/F | Partial seizure | OC | OC | + | - | + | - | Stabilization | 60 | 1 |
| 27/52/F | Neuropathy | IVC | OC | ND | ND | ND | - | Remission | 40 | 3 |

ND = not done; MOHS = Modified Oxford Handicap Scale; CN = cranial nerves; ACE = angiotensin-converting enzyme; OC = oral corticotherapy; IVC = IV corticotherapy; AZA = azathioprine; CICLOS = cyclosporine; CYCLOP = cyclophosphamide; MTX = methotrexate.

during follow-up. Sixty-two percent of patients had CNS involvement, and 48% had peripheral nervous system (PNS) abnormalities. Meninges and muscles were involved in 30% and 20% of cases, respectively. The mean level of systemic ACE at the onset of the disease was 44.6 (range, 22 to 104).

The clinical, therapeutic, laboratory, and radiologic data of patients are summarized in the table.

Fifteen patients were in the remission (12 patients)/improvement (three patients) group (Group 1). Twelve patients were in the stabilization (10 patients)/worsening

(two patients) group (Group 2). The clinical outcome was poorer in the patients with CNS involvement ($p < 0.05$). Twenty-one patients (77.7%) had an MOHS score of 2 or lower ("Minor disability" group), and six had an MOHS score of more than 2 ("Severe disability" group). The mean MOHS score was 1.4 (range, 0 to 5) for the 27 patients, and 0.8 in the "Minor disability" group and 3.5 in the "Severe disability" group. None of the patients died. At the end of the follow-up period for each of the patients included in the study, 16 patients (59.2%) had one or more neurologic sequelae (three patients [25%] in the remission group). Only

20% of patients with PNS involvement had an MOHS score superior to 2. In contrast, 62.5% of patients with CNS involvement had an MOHS score superior to 2 ($p < 0.02$). The number of relapses is indicated in the table. The existence of extraneurologic manifestations was not associated with a poorer clinical course. There was no correlation between presenting CNS lesions or contrast enhancement on imaging and clinical outcome or MOHS score. We did not find any correlation between the form of disease onset (progressive or acute) and clinical course, nor did we find any correlation between clinical scores and CSF abnormalities or blood or CSF ACE. There was no clinical manifestation carrying a higher risk of disability in the "Severe disability" group. Concerning treatments, most of the patients initially received oral or IV corticotherapy, depending on the severity of the clinical signs. Immunosuppressive drug therapy was initiated in association with corticotherapy in most cases in which no clinical improvement was observed after 2 months or in the event of clinical worsening. Where one type of immunosuppressive drug was found to be ineffective, it was replaced by another. There was no correlation between treatment and clinical outcome.

Discussion. Long-term clinical outcome of neurosarcoidosis has rarely been evaluated in previous studies. The low prevalence of the disease makes large follow-up studies difficult.¹ To our knowledge, our study is the first to evaluate the clinical and laboratory findings of a large group of patients with neurosarcoidosis followed-up for at least 5 years. We found that the CNS involvement at onset was associated with a less favorable disease course compared with PNS involvement.

A previous study noted that one third of patients had refractory illness associated with higher morbidity and mortality.⁷ In patients with aseptic meningitis, cranial polyneuropathies, myopathy, or peripheral neuropathy, neurosarcoidosis seems to have a protracted course but tends not to be fatal. In contrast, the group with CNS involvement have more severe conditions and higher morbidity and mortality.¹ Our results partially confirm these data as patients with clinical CNS involvement at disease onset had a significantly higher MOHS score and increased morbidity after follow-up. Compared with previous studies, we observed fewer relapsing forms during the follow-up.³ Laboratory findings (including CSF and blood) are not a predictor for developing refractory neurosarcoidosis. Furthermore, the commonly acknowledged markers of disease activity (blood and CSF ACE, gallium scintigraphy) were not correlated with MOHS score or clinical outcome. Similar data have previously been reported, but the mean follow-up time was shorter than in our study.^{7,8} We did not find any correlation between the evidence

of lesions on brain MRI or CT scan (location or contrast enhancement) and MOHS score or clinical outcome. These data could be attributable in part to the polymorphism of brain lesions.^{9,10} The form of neurosarcoidosis onset (acute or progressive) was not associated with the treatment response, as previously reported.⁵ Our results show that clinical course is more closely related to initial localization (CNS or PNS) than to clinical mode. The association between PNS involvement at onset and a favorable clinical outcome or lower MOHS score is in line with these data. No correlation between extraneurologic manifestations and clinical outcome or MOHS score was found, suggesting that systemic involvement is not a predictive factor for the evolution of neurosarcoidosis. We did not find any correlation between treatment and clinical outcome. However, a prospective study is warranted to evaluate more clearly the effects of the various therapies in neurosarcoidosis.

Our study shows that patients with clinical CNS involvement had increased morbidity after a long follow-up. We did not find any other significant predictive factor of disease course. This finding may influence therapeutic strategy. Early intensive immunosuppressive treatment could be proposed in cases with CNS involvement. However, neurosarcoidosis is a complex disease, and its course remains uncertain. Multicenter prospective studies are now needed to confirm these results and develop optimal treatment strategies.

References

1. Chapelon-Abrie C, Ziza JM, Godeau P. Neurosarcoidoses. *Ann Med Interne* 1991;142:601–608.
2. Ferriby D, de Seze J, Stojkovic T, et al. Manifestations cliniques et approche thérapeutique de la Neurosarcoidose: 40 cas. *Rev Neurol (Paris)* 2000;156:965–975.
3. Luke RA, Stern BJ, Krumholz A, Johns CJ. Neurosarcoidosis: the long-term clinical course. *Neurology* 1987;37:461–463.
4. Battesti JP. Critères de diagnostic de la sarcoidose. *Nouv Presse Med* 1981;10:673–674.
5. Oksanen V. Neurosarcoidosis. In: James D.G, ed. *Sarcoidosis and other granulomatous disorders*. New York, NY: Marcel Dekker Inc; 1994:285–309.
6. Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community. *J Neurol Neurosurg Psychiatry* 1988;51:1373–1380.
7. Agbogbo B, Stern BJ, Yang G. Therapeutic considerations in patients with refractory neurosarcoidosis. *Arch Neurol* 1995; 52:875–879.
8. Sharma OP. Neurosarcoidosis: a personal perspective based on a study of 37 patients. *Chest* 1997;112:220–228.
9. Caparros-Lefebvre D, Wallaert B, Girard-Buttaz I, et al. MRI aspect and course of supra-tentorial sarcoidotic lesions. *Rev Neurol* 1996;152:196–201.
10. de Seze J, Caparros-Lefebvre D, Pruvo JP, Petit H. Sarcoidosis of the central nervous system: clinical and radiological polymorphism. *Rev Med Interne* 1996;17:482–487.