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Original article

Neurosarcoidosis ☆
Report of 30 cases and a literature survey

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ABSTRACT

Introduction: Neurosarcoidosis accounts for approximately 5% of cases of sarcoidosis.
Objective: To determine the frequency of Neurosarcoidosis in our setting and analyze the clinical–radiological findings and evolution of 30 patients consecutively diagnosed.
Methods: The medical records of patients with a diagnosis of Neurosarcoidosis were reviewed, and data regarding the clinical features, ancillary tests performed, treatment, and outcome were recorded. We revised the literature to summarize and discuss the previous clinical series of Neurosarcoidosis.
Results: It accounted for 6.7% of all cases of sarcoidosis. Seven patients had definite diagnosis and 23 had probable diagnosis. The mean age at onset of Neurosarcoidosis was 48.3 years and 66.7% of patients were women. Neurologic clinical features were the first manifestation of Neurosarcoidosis in 70% of cases. Cranial neuropathy was present in 17 patients and 14 of them had facial palsy. The central nervous system was affected in 10 patients and the peripheral nervous system in 5. Chest disease, the most common extraneurologic manifestation, was present in 20 patients. All patients were treated with corticosteroids, and all those with central nervous system involvement had poor outcome.
Conclusion: Neurosarcoidosis requires a high degree of suspicion to establish the diagnosis. Central nervous system involvement is associated with a poor prognosis.

1. Introduction

Sarcoidosis is a multisystemic disease of unknown cause, characterized by non-caseating granulomas in affected organs. It has a predilection for young adults and most commonly affects the lung, lymph nodes, skin, and eyes. Neurosarcoidosis accounts for approximately 5% of cases and is not unusual as a first presentation (31.4%) [1–3]. The diagnosis of this condition may be difficult because the cause is unknown, the presentation varies considerably, the diagnosis is based on pathological criteria, and it is difficult to define organ involvement in this disease [4].

The aim of this study is to determine the frequency of Neurosarcoidosis in our setting, and to analyze the clinical–radiological findings in this condition and the evolution of 30 Neurosarcoidosis patients. In addition, a related literature review is provided.

2. Methods and patients

Between 1974 and 2005, 445 patients were diagnosed with suspected or proven sarcoidosis in our hospital. All patients underwent a protocolled diagnostic workup and follow-up. The medical records of patients with Neurosarcoidosis were reviewed, and data regarding the clinical features associated with the disease, ancillary tests performed, treatment, and outcome were recorded.

The diagnosis of sarcoidosis is supported by the following criteria [5]: a) consistent clinical and radiological features; b) histological demonstration of non-caseating granulomas comprised of multinucleated giant cells surrounded by lymphocytes in one or more tissues, with negative stains and cultures for mycobacteria and fungi, or a positive Kveim–Siltzbach test; c) exclusion of other granulomatous diseases. The diagnosis can also be established without histological confirmation if the clinical picture is consistent with Löfgren syndrome [6,7], or if there are compatible signs and symptoms and two or more of the following indirect indicators show positive findings: chest imaging, gallium scan, and serum angiotensin converting enzyme analysis.

The diagnosis of Neurosarcoidosis was established in 3 categories [5,8]:

- Definite: neurologic clinical features and results of neurodiagnostic evaluation (elevated levels of protein and/or cells in cerebrospinal fluid, presence of oligoclonal bands, Magnetic Resonance Imaging

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findings) suggestive of Neurosarcoidosis, with exclusion of alternative diagnoses, and positive nervous system biopsy.
- Probable: neurologic clinical features and neurodiagnostic evaluation suggestive of Neurosarcoidosis, with exclusion of alternative diagnoses, in patients with histologically-proven systemic sarcoidosis. Löfgren syndrome and consistent signs and symptoms and two or more positive indirect indicators (mentioned above) in patients without a positive biopsy, are considered as having probable Neurosarcoidosis [6,7].
- Possible: neurologic clinical features and neurodiagnostic evaluation consistent with Neurosarcoidosis, with exclusion of alternative diagnoses, in which the criteria for definite or probable disease are not met.

Only patients with definite and probable Neurosarcoidosis were included in this study.

The onset was defined as acute when neurologic symptoms developed over a period of less than 6 months and chronic when they evolved over more than 6 months. Neurosarcoidosis was considered acute when the duration of the disease was less than 2 years and chronic when it was greater than 2 years [8]. The Siltzbach classification was used to classify the chest radiography findings [9]. Patients with a score of ≤ 3 on the Modified Rankin Scale were considered to have no or slight–moderate sequelae and those with a score of >3 to have severe sequelae [10].

The statistical analysis was performed with a nonparametric test. The Wilcoxon rank test was used to compare quantitative variables, and the chi-square test or Fisher exact test, when appropriate, to compare proportions. Significance was set at a level of less than 0.05.

3. Results

3.1. Demographic data

Thirty patients (6.7%) were included, and 14 of them had been reported in a previous study [11]. The mean age at the onset of Neurosarcoidosis symptoms was 48.3 years (range: 23–84), and 66.7% of patients were women. Twenty-nine patients were White, and one patient was Black (from Gambia), (Table 1).

3.2. Clinical features

Seven patients received a diagnosis of definite Neurosarcoidosis, and 23 patients, probable Neurosarcoidosis (76.6%). One of the latter did not have a histological diagnosis. She is a 64-year-old woman, who presented an erythema nodosum and mediastinal lymph adenopathy on chest radiograph (stage I), computed tomography and gallium scintigraphy. She presented a right facial palsy and a III cranial nerve neuropathy simultaneously to Löfgren syndrome. Her magnetic resonance imaging and the cerebrospinal fluid study were normal and serum angiotensin converting enzyme concentrations were elevated. We did a biopsy of an abdominal scar and it did not present typical lesions of sarcoidosis. She was treated with 30 mg of prednisone and she had a good outcome.

An acute onset was documented in 24 patients (80%). In all patients except one, the neurologic clinical features were found in association with systemic features at some time over the evolution of the condition. In 18 patients (60%), nervous system signs and symptoms were an initial feature and occurred in parallel to the non-neurologic features. In 2 patients, neurologic involvement was the initial, isolated sign, preceding the extraneurologic signs by 10 and 19 months, respectively. In 1 patient, neurologic signs were the only feature of the disease. In 9 cases (30%), the neurologic signs developed after the systemic features: within the first 2 years after symptoms onset in 7 patients and at 6 and 19 years following onset, respectively, in 2 patients.

The most frequent manifestation was cranial neuropathy, occurring in 17 patients (56.6%) (Table 2). Fourteen of them (46.6%) presented peripheral facial palsy, which was bilateral (3 simultaneous and 3 consecutive) in 6 patients (20%), and associated with other cranial neuropathies in 4 patients (13.3%). The second cranial nerve affected, in descending order, was VIII (4 patients, 13.3%), followed by IX and X (3 patients, 10%). Cranial nerves III, V, VI, and XI were each affected in 2 patients, and cranial nerves II and XII in only 1 patient each. Neuropathy of cranial nerve I (also examined in our series) or IV was not observed. Twelve patients (40%) presented cranial multineuritis. One patient (3%) showed cranial neuropathy associated with Central Nervous System symptoms: peripheral facial palsy and hypothalamus-hypophyseal signs, as well as hemiparesis due to a space-occupying lesion.

Ten patients (33.3%) presented Central Nervous System involvement. Seizures were the most common manifestation, affecting 6 patients (20%), 3 of whom presented a partial crisis and 3 a generalized crisis. Space-occupying lesions were in the second position (3 cases, 10%); two were intraparenchymal lesions and one a meningeal lesion. Meningeal syndrome, diffuse encephalopathy and hydrocephalus were observed in 2 patients, whereas psychiatric signs, pure motor

Table 1
Demographic and extraneurological characteristics in previous and present series.

Author (year)	N	Male/Female	Ethnic (W/B/others)	Mean age (years) onset NS	Extraneurological manifestations
Present series	30	10/20	29/1	48.3 (r: 23–84)	97% (chest 66%, general 46%, uveitis 33%, skin 30%)
Pawate (2009)	54	14/40	NA	40.8 (r:12–66)	80%
Joseph (2008)	30	16/14	29/1/0	40 (r: 20–72)	73% (ocular 53% (uveitis23%), chest 17%, renal 7%)
Kellinghaus (2004)	13	8/16	NA	37 (SD: 11)	NA
Spencer (2004)	21	12/9	3/17/1	41 (r: 20–65)	95% (chest)
Allen (2003)	32	15/17	32/0/0	48 (r: 21–80)	100% (general 88%, respiratory symptoms 72%)
Ferriby (2000)	40	20/20	35/5[a]	41.3 (r: 17–72)	87.5% (chest 72.5%)
Zajicek (1999)	68	36/32	NA	38.9 (r: 21–64)	91% (chest, ocular)
Lower (1997)	71	24/47	28/43/0	NA	97% (chest 94%, ocular 37%, skin 30%, hepatic 13%)
Sharma (1997)	37	21/16	18/18/1	41 (r: 20–80)	95% (chest 78%, ocular 22%, skin 13% peripheral lymph nodes 11%)
Chen (1992)	15	4/11	NA	44 (r: 22–78)	NA
Chapellon (1990)	35	17/18	32/3/0	46 (r: 21–80)	83% (chest 71% ,constitutional symptoms 51%, skin 29%, peripheral lymph nodes 26%)
Oksanen (1986)	50	18/32	NA	44 (r: 10–69)	100%
Stern (1985)	33	12/21	5/28/0	33 (r: 20–63)	97% (chest 88%, ocular 55%)
Pentland (1985)	19	4/15	19/0/0	32 (r: 17–60)	84% (chest 84%, ocular 32%, peripheral lymph nodes 26%)
Delaney (1977)	23	14/8	3/20/0	36 (r: 18–66)	70% (chest 60%, ocular 22%)
Wiederholt (1965)	28	7/21	NA	41.4 (r: 12–61)	NA (chest 79%, ocular 29%, salivary 14%, skin 7%)
Colover (1948)	118	NA	NA	NA	NA (parotiditis 62%, uveitis 56%, fever 37%, skin 28%)

B: Black; W: White; r: range; SD: Standard deviation; NS: Neurosarcoidosis; NA: Not available.
[a] 5 non Caucasian.