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Neurosarcoidosis: Clinical Characteristics and Management

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Abstract

Sarcoidosis is a poly-visceral disease characterized by the presence of epithelioid and gigantocellular granulomas without caseous necrosis. The clinical manifestations of sarcoidosis are varied. Neurological involvement is reported in 5 to 10% of cases. We conducted a descriptive, retrospective study of 65 patients with sarcoidosis including 38 patients with Neurosarcoidosis and followed in the departments of internal medicine and neurology at the Military Hospital of Tunis. Clinical, paraclinical, genetic, evolutionary data, and therapeutic modalities of patients with Neurosarcoidosis were explored through statistical analyzes. The mean age was 46.68. The mediastino-pulmonary involvement is the most frequent (72.3%), followed by neurological involvement (58.5%), cutaneous involvement (50.8%) and ophthalmological involvement (40%). For neurosarcoidosis, central nervous system involvement was noted in 33 patients (86.8%), the peripheral nervous system was affected in 13.1% of cases, cranial nerve involvement was found in 26.3 % of cases. MRI was pathological in 15 cases. Genetic analysis showed a high frequency of the HLA DRB1 * 1501 allele (38%), DD genotype (30%) and D allele (54%) of the ECA gene. Treatment with corticosteroids was most often used 73.85%. The evolution was favorable in 17 cases (26.15%), and stable in 63% of cases. There is no significant difference between the group of patients with neurological impairment and no neurological involvement for the different parameters studied. The neurological involvement during sarcoidosis is severe and extremely varied. It is necessary to compare the clinical, radiological, biological and evolutionary data to

evoke the diagnosis. The prognosis depends essentially on the diagnosis delay.

Keywords: Neurosarcoidosis; Clinical Manifestation; MRI; HLA; Sarcoidosis; Treatment

Introduction

Sarcoidosis is a multi-systemic granulomatosis of unknown cause characterized by the presence of epithelioid and gigantocellular granulomas without caseous necrosis [1,2]. It results from a diffuse chronic inflammatory response whose exact mechanism is still unknown [3]. Sarcoidosis is characterized by a clinical polymorphism, related to polyvisceral lesions, the most important of which are the mediastino-pulmonary localizations. Neurological manifestations of sarcoidosis are rare, estimated at around 5 to 10% that can affect any part of the central or peripheral nervous system. Neurological disorders are particular because they are often revealing of the disease and may be the only manifestation of sarcoidosis [4,5]. The etiology of sarcoidosis remains unknown. In line with the most recent studies, not only environmental factors, but also genetic factors are involved. We therefore try in this study to determine features of neurosarcoidosis and compare clinical, para-clinical and evolutive features in patients with or without neurological manifestations. We then try to study genetic aspects in those patients.

Materials and Methods

We conducted a descriptive and retrospective single-center study of 65 patients with sarcoidosis, followed in the internal medicine and neurology departments at the Military Hospital of Tunis over a period of 20 years from 1997 to 2017. The Initial data were collected on a data sheet from selected files according to the inclusion criteria of the study. We included all patients with confirmed diagnosis of sarcoidosis who were hospitalized in our department during the study period. And all patients with clinical features suggestive of sarcoidosis associated with radiological and biological manifestations, and confirmed by biopsy with a non-caseating granuloma. For patients with an inaugural neurological involvement, cases with definite, probable and possible neurosarcoidosis have been included according to revised Zajicek criteria [4,5]. We excluded all patients in whom the combination of sarcoidosis with another granulomatosis has not been eliminated and all patients explored on an outpatient basis or from other hospitals. We collected epidemiological, clinical, paraclinical, therapeutic and evolutionary data using an individual file and then we compared data of patients with and without neurological manifestations. Genetic study concerned only patients who accepted to participate in the genetic study. DNA extraction was performed from whole blood. HLA class II typing and gene mutation testing of the ACE gene was done by amplification of the target sequence of the DNA by a polymerase chain reaction (PCR) followed by gel electrophoresis of agarose and then visualization of the DNA bands under UV.

Statistical Analysis

Data analysis was performed using SPSS (Statistical Package for Social Sciences) software, version 24. Results were expressed as average ± standard deviation (m ± SD) or median (inter-quartile range) for continuous variables and as frequencies for qualitative variables. The comparison of the age averages was performed using the Student's test with a significance threshold selected $p < 0.05$. The comparison of the frequencies was carried out by means of the chi^2 test with a threshold of significance retained $p < 0.05$.

Results

Our study concerned 65 patients followed in the Neurology and Internal Medicine departments of the Military Hospital of Tunis. Twenty seven patients met the inclusion criteria for sarcoidosis without neurologic localization and 38 patients for neurosarcoidosis. The mean age of onset of the neurosarcoidosis is at 46.66 ± 9.6 years. A female predominance was noted. Among the 38 patients, we found 28 women (73.7%) for 10 men (26.3%). The average annual number was about 3 cases / year. The disease was asymptomatic in 27.7% of the cases. General signs such as fever, asthenia and weight loss were found in 10 patients (15.3%). Respiratory manifestations were inaugural in 13 patients (20%). Neurological signs revealed the disease in 9 patients (14%). Thirty-eight patients met the inclusion criteria for Neurosarcoidosis. According to Zajicek's criteria, the diagnosis of neurosarcoidosis was certain in 2 cases, probable in 18 cases and possible in 18 cases. Neurological disorders were observed clinically in 58.5% of the studied population. Clinical attacks were multiple and diffuse. Central neurological involvement was observed in 33 patients (86.8%). The peripheral nervous system was affected in 5 patients (13.1%). Cranial nerve involvement was found in 10 patients (26.3%), and 10 patients had at least 2 types of impairment. Functional signs revealing the disease are reported in the Table 1.

Functional signs	Number of patients
Headache	8 (3 patients with intracranial hypertension)
Seizures	Focal motor seizures: 3 patients Generalized Seizures: 1 patient
Ataxia	4 patients
Sensitivo-motor disorders	Paresthesia: 5 patients A motor deficit of the 4 limbs: 2 patients A motor deficit of the lower limbs: 6 patients A hemicorporeal deficit: 2 patients.
Oculomotor and visual disorders	A decrease in visual acuity: 7 patients. A binocular diplopia: 5 patients. A ptosis: 1 patient.
Psycho-cognitive disorders	A major cognitive impairment: 2 patients. Psychiatric disorders: 3 patients.
Vesico-sphincteric disorders	1 patient.
Swallowing disorders	Dysphagia: 3 patients.

Table 1: Functional signs of neurosarcoidosis

Neurological examination showed pyramidal syndrome: Spastic paraparesis (2 patients), paraplegia (one case), hemiparesis (one patient) and hemiplegia (one case). Cerebellar syndrome was static and kinetic in 1 case. Meningeal syndrome was found in 1 case. Claude Bernard Horner syndrome was observed in one case. Pseudo bulbar syndrome was found in one case. In peripheral neurogenic syndrome, five patients presented peripheral neurogenic damage affecting the 4 limbs in one patient and the inferior limbs in 4 patients. Isolated injury to the cranial nerves was found in 10 patients: impairment of olfactory nerves(2 cases), impairment of the optic nerves (7 cases), oculomotor involvement (III in 1 case, IV in 1 case, and VI in 3 cases), impairment of V (2 cases), impairment of VII (9 cases), impairment of VIII (2 cases), IX and X involvement (1 patient).

Imaging: All patients with neurological involvement were explored by magnetic resonance imaging (MRI) cerebral and medullary imaging. Meningeal infiltration was found in 5 patients. Leptomeningeal thickening was nodular in one patient. One patient had diffuse intracranial leptomeningeal contrast enhancement associated with cervical epidural thickening. The hypothalamic-pituitary axis was affected in 3 patients: the pituitary stalk appeared in hyper T2 signal and FLAIR with heterogeneous enhancement in one patient. Pituitary hypertrophy was noted in one patient. The hypothalamus was T1 and T2 isosignal with intense contrast enhancement in one patient. Abnomality of the optic nerve signal was recorded in 3 patients: the optic nerve was T2 hypersignal and FLAIR. Contrast enhancement was noted in one patient. Thickening of the orbital fat associated with the abnormality of the optic nerve signal was noted in one patient. Increased intra-cavernous tissue infiltration after gadolinium injection was noted in one patient. A pseudo-tumor mass-effect lesion including left temporal cystitis was identified in one patient. Hyper signals T2 and FLAIR of the white matter tentatively were identified in 5 patients. These abnormalities predominated in the periventricular regions in all patients. Two patients had cervical spinal cord injuries.

Lumbar puncture (LP) was performed in 29 patients and showed: Lymphocytic meningitis with normoproteinorachy and normoglycorachia in 7 cases. A lymphocytic meningitis with hyperproteinorachia and normoglycorachia was found in 6 cases. A lymphocytic meningitis with hyperproteinorachia and hypoglycorachia was found in 1 case. Hyperproteinorachia without pleiocytosis was found in 1 case. In 14 patients, LP was normal. The conversion enzyme assay in the cerebral spinal fluid (CSF) was performed in 7 patients: It was increased in 3 cases. Protein immunoelectrophoresis in CSF was performed in 8 patients. It had shown IgG oligoclonal peak and intrathecal IgG synthesis in 7 cases. It was normal in 1 case.

Electromyogram (EMG) was performed in the presence of signs of peripheral damage in 8 of our patients. Polyradiculoneuropathy was found in one case. An axonal sensitivomotor polyneuropathy of the 4 limbs was noted in one case. Two patients had multiradicular involvement of the lower limbs.

Visual evoked potentials (PEVs) measurement was performed in 8 patients for axonal or mixed demyelinating disease. Optic nerve involvement was found in 7 cases. The mechanism was axonal in 3 cases, demyelinating in 3 cases and mixed in 1 case.

Comparative study: We compared each parameter studied as well as the clinical locations between the group with a neurological impairment and the group without neurological involvement presented in table 2. The average annual number was about 3 cases / year for the group with neurological impairment vs. 2 cases / year for the group without neurological involvement (p = 0.47). The epidemiological parameters do not differ significantly between the group of patients with neurological involvement and the group with no neurological involvement p> 0.05. There is a statistically significant difference between the group with neurological impairment and the group with no neurological involvement for some locations (ophtalmological, cutaneous, renal, articular..). There is a statistically significant difference that favors the group of patients with neurosarcoidosis only for ophthalmologic impairment. The different complementary examinations were reported for both study groups. The results of the genetic analysis for HLA typing and genotyping of the ACE gene have been reported and there is no significant binding of a particular genotype or allele to one of the two groups. Therapeutic modalities of patients were noted for both groups.

Parameters		Neurosaroidosis (N=38) (58.5%)	Without neurological manifestations (N=27) (41.5%)	P
Sociodemographic characteristics				
Age (years)		46.66±9.6	46.7±13.1	0.98
Gender	Male	10 (26.3)	6 (22.2)	0.71
	Female	28 (73.7)	21 (77.8)	
Environemental exposure	Yes	23 (60.5)	14 (51.9)	0.49
	No	15 (39.5)	13 (48.1)	
Habitation location	North	18 (47.4)	19 (70.4)	0.12
	Centre	11 (28.9)	6 (22.2)	
	South	9 (23.7)	2 (7.4)	
Season	Winter	16 (42.1)	10 (37)	0.69
	Spring	7 (18.4)	4 (14.8)	
	Summer	9 (23.7)	10 (37)	
	Autumn	6 (15.8)	3 (11.2)	
Tobacco use	Yes	11 (28.9)	4 (14.8)	0.18
	No	27 (71.1)	23 (85.2)	
Localizations				
Pulmonary		20 (52.63)	27 (100)	-
Cardiac		-	2 (3)	-
Ophtalmological		19 (50)	7 (25.92)	**0.048**
Cutaneous		15 (39.47)	18 (66.66)	0.030
Lymphadenopathies		6 (15.79)	14 (51.85)	**0.001**
Renal		2 (5.26)	8 (29.62)	**0.007**
Hepatic		6 (15.79)	4 (14.81)	0.91
Spleen		4 (10.53)	5 (18.51)	0.36
Articular		2 (5.26)	15 (55.55)	**$<10^{-3}$**
Bone involvement		1 (2.63)	1 (3.7)	0.8
ORL		2 (5.26)	3 (11.11)	0.38

Genetic involvement				
HLA typing	HLA- DRB1*1501	13 (43.33)	6 (30)	0.34
	HLA- DRB1*0301	9 (30)	5 (25)	0.69
	HLA- DRB1*1106	6 (20)	3 (15)	0.94
	HLA- DRB1*0401	3 (10)	5 (25)	0.3
ECA genotyping	II	6 (20)	5 (25)	0.67
	ID	15 (50)	9 (45)	0.72
	DD	9 (30)	6 (30)	0.99
Alleles	I	27	19	0.8
	D	33	21	0.8
Therapeutic management				
Corticosteroids		34 (89.47)	14 (51.85)	-
Immunosuppressive treatment		4 (10.53)	2 (7.4%)	-
Antimalarial treatment		--	6 (22.22)	-
Without treatment		--	5 (18.52)	-
Evolution				
Improvement		12 (31.58)	5 (18.52)	0.24
Relapses		-	2 (7.4)	-
Incomplete follow up		-	2 (7.4)	-
Death		2 (5.26)	1 (3.7)	0.63

Table 2: Comparative study of patients with and without neurological manifestations during sarcoidosis

Discussion

Sarcoidosis occurs in any organ, for this, its clinical presentation is highly variable, including nonspecific symptoms of general nature and symptoms related to organs affected by the disease [6]. The discovery of the disease is fortuitous in more than one third of cases when performing a chest X-ray in an asymptomatic patient. In two-thirds of cases patients are symptomatic. Since sarcoidosis is more than 80% intrathoracic, its most common symptoms are dry cough, dyspnea, and chest pain. It can also be observed during specific extra-thoracic clinical manifestations (ophthalmological, cutaneous, and neurological). More rarely the disease is revealed by a report of an alteration of the general state or during the exploration of a hypercalcemia [7]. In our study, the circumstances of discovery varied between general signs 15.3%, bronchopulmonary signs 20%, neurological signs 14%. The manifestations of sarcoidosis may be diffuse or at one point in time only an organ; they combine in an extreme diversity. Extra-thoracic locations are frequent, some are benign, but can be of considerable help in diagnosis, such as peripheral lymphadenopathy or cutaneous manifestations [8]. Other rarer ones may involve an organ prognosis (ophthalmological, neurological or renal localizations) or even the vital prognosis (cardiac involvement).

Neurological locations of sarcoidosis are rare (5 to 40% depending on criteria, clinical or autopsic) and can affect any part of the central or peripheral nervous system. They are often indicative of the disease and may be the only localization of sarcoidosis [5].

In the literature, neurological disorders have been reported at different frequencies. In an American study conducted by Baughman et al. 2001, including 736 patients, neurological involvement was found in 4.6% [9]. In a European meta-analysis involving 5263 patients with sarcoidosis, Fritz et al. 2016 found neurological involvement in 52% of these patients [4]. A study conducted in Amsterdam reported a frequency of 71% [8]. In our series, neurological involvement was found in 58.5% of our patients. Although all parts of the nervous system can be affected, some attacks are more common [5,10]. Meningeal attacks may be symptomatic in 8 to 64% of cases of neurosarcoidosis, while it is present at autopsy in 100% of cases. The infiltration of leptomeninges is generally asymptomatic or paucisymptomatic [11]. In our series 6 patients had meningeal involvement. Parenchymal lesions are up to 5 to 15% of cases, these manifestations are multiple and depend on the location of the lesions. This is secondary to the granulomatous process in the leptomeninges, periventricular region, parenchymatous and perivascular regions which explain the polymorphism of clinical manifestations [5]. Seizures are noted in 5 to 10% of the cases, revealing the affection in 10% of the cases and are generally generalized [10]. Pseudo-tumoral forms are asymptomatic in 75% of the cases, rare and most often supratentorial, and can be single or multiple [10]. Psychic disorders: Sometimes revealing the neurosarcoidosis, the clinical pictures are very variable with euphoric state, memory disorders and cognitive decline [10]. Neuro-endocrine manifestations are noted in 3 to 26% of cases of neurosarcoidosis. They are secondary to infiltration of the leptomeninges, hypothalamus and pituitary gland. Hypogonadism and diabetes insipidus are the most common. Hyperprolactinemia, panhypopituitarism, sleep disorders, hypothermia have also been reported [12,13]. In our series 5 patients had hypothalamic-pituitary axis involvement.

The incidence of peripheral neuropathies during neurosarcoidosis is estimated at 15%. All types of lesions have been described: single or multiple mononeuropathies, sensitivomotor polyneuropathies or Guillain-Barré syndrome [4,5,10]. It is usually subacute or chronic axonal neuropathy with no particular character [5,10]. In our series a polyradiculoneuropathy was found in one case. An axonal sensitivomotor polyneuropathy of the 4 limbs was noted in one case. Two patients had multiradicular involvement of the lower limbs.

The involvement of one or more cranial nerves is noted in 24% to 73% of cases of neurosarcoidosis [14]. The involvement of the cranial nerves is often multiple, recurrent or alternating [15]. The most frequently affected cranial nerves are the optic, trigeminal and facial nerves, followed by the cochleobuccal nerves and oculomotricity [16]. In our series, the involvement of the facial nerve is the most frequent (24%), followed by the optic nerve (18%), which is also the case in most series.

Regarding imaging during neurosarcoidosis, MRI is the best non-invasive examination to support the diagnosis of neurosarcoidosis. Cerebromedullary MRI with gadolinium injection is the gold standard method for diagnosis and to guide the therapy of neurosarcoidosis. Classical nodular or diffuse meningeal thickening (40%), periventricular and white matter lesions (40%) or multiple infra or supra-tentorial or medullary lesions (35%) are usually observed [5,17].

Lumbar puncture is very often abnormal (in 53 to 81% of cases) in neurosarcoidosis, but none of the abnormalities encountered is specific [18]. A pleocytosis, sometimes exceeding 200 nucleated cells / mm3, is present in 42-55% of cases. It is usually lymphocytic meningitis [19]. An increase in the CD4 / CD8 ratio has been reported. A hyperprotéionorachie is described in 61% of the cases on average, seldom higher than 2,5 g / L [18,19]. The elevation of angiotensin-converting enzyme in CSF is reported in 33 to 58% of cases according to the series and would be correlated, for some, to the evolution of neurological signs [17,18,20].

For the treatment of Neurosarcoidosis, systemic corticosteroids (CSS) are considered first-line therapy. The initial oral prednisone dose depends on the severity of the attack for mild to moderate disease. A treatment with methylprednisolone 1g / day for 3 to 5 days is most often proposed in severe forms [21]. In our series, 34 neurologically impaired patients were treated with corticosteroids, 4 patients with immunosuppressive therapy.

The neurological locations of sarcoidosis are serious: two thirds of patients have clinical, motor, sensory, sphincteric or cognitive sequelae. Some sites are particularly serious and have increased morbidity: spinal cord injury and the peripheral nervous system. On the other hand, the presence of isolated meningeal involvement is a factor of good prognosis. The attacks of the cranial nerves relapse willingly [5].

Regarding the comparison between the group with a neurological impairment and the group without neurological involvement, in our series, only ophthalmological involvement was found with a higher frequency in the neurosarcoidosis group ($p < 0.05$). The other parameters studied as well as the genetic analysis show

no significant difference between the two groups (p> 0.05). To our knowledge, only one publication compared a group of 13 patients with neurosarcoidosis. Six of them had isolated neurosarcoidosis and eight had neurosarcoidosis associated with other manifestations. No significant differences were found between the two groups for age, MRI, CSF analysis and disease progression, however bone marrow involvement in patients with isolated neurosarcoidosis is more common than in the other group [22].

Financial interests

The authors declare they have no financial interests

Conflict of interest

The authors declare that they have no confict of interest.

Author contributions

All authors contributed to the study conception and design

Ethics approval

Approval was obtained from the ethics committee

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