Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

ANNEE 2020

N°

NEUROSARCOIDOSIS: AN OBSERVATIONAL STUDY OF 44 PATIENTS
NEUROSARCOÏDOSE : ETUDE OBSERVATIONNELLE A PROPOS DE 44 PATIENTS

THESE

Présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 11 septembre 2020

pour obtenir le grade de Docteur en Médecine

par AUVENS Clément

Né le 19/09/1990

À Bourges (18)

Université de Bourgogne

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Monsieur le Professeur SÈVE Pascal

SERMENT D'HIPPOCRATE

"Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque."

Remerciements

Au président du jury et directeur de thèse, Monsieur le Professeur Bernard BONNOTTE :

Vous me faites l'honneur de présider mon jury de thèse. Je vous remercie pour votre confiance, votre implication et votre aide dans la réalisation de ce travail. Je mesure la chance d'avoir reçu une telle qualité d'enseignement et de formation durant ces années d'internat. A moi maintenant d'être à la hauteur de l'excellente réputation de la médecine interne Dijonnaise. Soyez assuré de ma sincère reconnaissance et de mon plus profond respect.

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À ma mère, merci d'avoir été et d'être encore infailliblement présente pour moi dans les bons comme dans les moins bon moments de nos vies. Tu as toujours privilégié le bonheur de Victor et moi avant tout le reste. Je ne serais pas ici aujourd'hui sans ton soutien et sans ton éducation. Je t'aime.

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LISTE DES ABREVIATIONS

18-FDG: 18-Fluorodeoxyglucose

ACE: Angiotensin-Converting Enzyme

ADA: Adalimumab

ANA: Antinuclear Antibodies

AQP4: Aquaporin 4

AZA: Azathioprine

CNS: Central Nervous System

CS: Corticosteroids

CSF: Cerebrospinal Fluid

CYC: Cyclophosphamide

EDSS: Expanded Disability Status Scale

EMG/NCS: Electromyography/Nerve conduction study

FLAIR: Fluid Attenuated Inversion Recovery

HCQ: Hydroxychloroquine

IFX: Infliximab

IV: Intravenous

IL-2: Interleukin 2

IL-6: Interleukin 6

IL-10: Interleukin 10

MMF: Mycophenolate Mofetil

MOG: Myelin Oligodendrocyte Glycoprotein

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

MTX: Methotrexate

NS: Neurosarcoidosis

NCCG: Neurosarcoidosis Consortium Consensus Group

OR: Odds Ratio

PET/CT: Positron Emission Tomography/Computerised Tomography

PMSI: Medical Information System Program

PNS: Peripheral Nervous System

RTX: Rituximab

SD: Standard Deviation

SIADH: Syndrome of inappropriate Antidiuretic Hormone Secretion

TNFα: Tumor Necrosis Factor Alpha

INTRODUCTION

La sarcoïdose est une granulomatose multisystémique ubiquitaire d'étiologie inconnue. Le diagnostic repose sur l'existence d'arguments cliniques, biologiques et d'imagerie compatibles, associés à la mise en évidence d'un granulome épithélioïde sans nécrose caséeuse en anatomopathologie et à l'exclusion des diagnostics différentiels. Son incidence à travers le monde est estimée entre 1 et 40 pour 100 000 personnes par an, variable selon les études, avec une incidence plus élevée chez les populations africaines, afro-américaines, d'Europe du Nord et chez les femmes (sexe ratio environ 1,2 à 1,5/1) [1–5]. La sarcoïdose peut survenir à tout âge, mais surtout chez les jeunes adultes âgés de 20 à 45 ans [1]. Bien que la physiopathologie de la sarcoïdose n'ait pas été entièrement élucidée, divers facteurs environnementaux, génétiques et infectieux ont été décrits dans l'implication cette maladie inflammatoire [2,6]. Tous les organes peuvent être affectés, mais plus fréquemment les poumons, les ganglions lymphatiques médiastinaux, la peau, les yeux, le foie et la rate.

Les autres atteintes sont relativement rares, comme la neurosarcoïdose (NS) avec une prévalence rapportée de 5% à 20%. L'atteinte neurologique est le mode de révélation de la maladie chez 50 à 70% des patients atteints de NS [7-12]. L'apparition peut être insidieuse et les patients présentent fréquemment des symptômes non spécifiques tels que des céphalées, une asthénie ou de la fièvre. Les manifestations neurologiques sont multiples et hétérogènes, par conséquent leur fréquence est sous-estimée. En effet, les études autopsiques suggèrent que 10 à 15% de patients supplémentaires atteints de sarcoïdose présentaient une NS sans manifestations cliniques neurologiques rapportées au cours de leur vie [13].

Malgré la publication récente d'une définition et de critères diagnostiques consensuels par le Neurosarcoidosis Consortium Consensus Group (remplaçant les critères suggérés en 1999), qui permet la standardisation des études sur la NS, les essais randomisés prospectifs de phase III manquent [14,15]. Aucune recommandation sur la prise en charge thérapeutique n'a été établie jusqu'à présent, bien que des algorithmes et des stratégies thérapeutiques empiriques aient été proposés, sur la base de données recueillies sur des séries de cas et des études rétrospectives de faibles effectifs [10,16–23]. La corticothérapie est considérée comme le pilier du traitement de la NS, mais les agents immunosuppresseurs et les biothérapies tiennent une place de choix dans la stratégie d'épargne cortisonique en cas de NS sévère et/ou réfractaire.

L'objectif principal de notre étude était de décrire de façon exhaustive les caractéristiques de 44 patients atteints de NS, d'évaluer l'efficacité et la sécurité des traitements utilisés, mais également d'identifier des facteurs pronostiques de la réponse thérapeutique.

ARTICLE

Neurosarcoidosis: an observational study of 44 patients

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Abstract

Introduction Neurosarcoidosis (NS) diagnosis remains challenging regarding the heterogenicity of the symptoms, the neurological features and the imaging presentations. The objective of the study was to describe patient characteristics and imaging results, to assess treatments and to identify prognostic factors of therapeutic response.

Methods All the patients of Dijon and Chalon-sur-Saone hospitals (Burgundy, France) diagnosed with NS, as defined by the Neurosarcoidosis Consortium Consensus Group criteria, from 1995 to 2019, were included in an observational retrospective study.

Results 738 patients diagnosed with sarcoidosis were identified, among whom 44 NS patients were included (6%). Mean follow-up time was 5.8 years. The onset of the disease was at a mean age of 47.6 ± 14.4 years. Symptoms were heterogeneous and nonspecific. Central nervous system involvement (64%) was more frequent than peripheral involvement (20%). The majority of the patients (88%) presented an abnormal brain MRI, and the spinal cord MRI was abnormal in half of them. PET/CT was underused, performed in only 25 patients (57%), leading to diagnosis confirmation in only 36% of cases. Corticosteroids were used in the majority of patients with frequent relapses. Methotrexate appeared to be the most effective immunosuppressive agent with a remission rate of 76.5%. Concerning severe or refractory NS, infliximab appeared to be more effective than cyclophosphamide with a better remission rate (76.9% vs 37.5%, p = 0.164). No treatment response predictive factors were significantly brought to light.

Conclusion NS is heterogeneous. Some tools are underused in diagnosis work-up, such as PET/CT imaging. More extensive prospective trials are needed to identify prognostic factors and to establish therapeutic guidelines.

Introduction

Sarcoidosis is a ubiquitous multisystemic granulomatous disease of unknown aetiology. The diagnosis requires compatible clinical and biological findings, imaging pathologic features, the pathological hallmark of non-caseating granulomas and exclusion of other diseases. The worldwide estimated incidence rate of sarcoidosis is variable, depending on the study, ranging from about 1 to 40 per 100,000 persons per year, with greater incidence in African, Afro-American, Northern European populations and women (gender ratio about 1.2–1.5/1) [1–5]. Sarcoidosis can occur at any age, but mostly in young adults between 20 to 45 years old [1]. Although the pathogenesis of sarcoidosis has not been fully elucidated, various environmental, genetic and infectious factors have been described to be involved in this inflammatory disease [2,6]. All the organs can be affected, most frequently lung, mediastinal lymph nodes, skin, eyes, liver and spleen.

Other involvements are relatively uncommon, such as neurosarcoidosis (NS) with a reported prevalence from 5% to 20%. NS is the first revealing sign of the disease in 50–70% of the NS patients [7–12]. Onset can be insidious and patients frequently present nonspecific symptoms such as headache, fatigue, and fever. Other neurological manifestations are multiple and heterogenous, therefore, their frequency is underestimated. Indeed, autopsy studies suggest an additional 10 to 15% of patients with sarcoidosis presented NS without neurological clinical manifestations reported during their life [13].

Despite the recently published definition and consensus diagnostic criteria for NS from the Neurosarcoidosis Consortium Consensus Group (replacing criteria suggested in 1999), which allows the standardisation of NS studies, prospective randomised phase III trials are still missing [14,15]. No therapeutic guidelines have been established so far, though therapeutic algorithms and empirical treatment strategies have been proposed, based on data collected on case report series and retrospective studies with few patients [10,16–23]. Corticosteroids (CS) are considered as the mainstay of NS treatment, but immunosuppressive and biological agents hold a choice place in therapeutic use for steroid-sparing in severe and refractory NS.

The main objective of our study was to extensively describe the characteristics of 44 NS patients in order to assess treatment efficacy and security, and also identify prognostic factors of therapeutic response.

Methods

Patients and study design

We conducted an observational retrospective multicentre study from 1995 to 2019 at Dijon university hospital and Chalon-sur-Saone hospital, in Burgundy (France). All the patients with a diagnosis of sarcoidosis from the PMSI network, a French medical information system program, were analysed. Only patients diagnosed with NS, as defined by the Neurosarcoidosis Consortium Consensus Group (NCCG) criteria [14] were included. Clinical presentation and diagnostic evaluation suggested NS, as defined by magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) and/or electromyography (EMG)/nerve conduction study (NCS) histological findings were noted. Patients were classified using the NCCG criteria [14]. The diagnosis of NS was defined as "definite" if nervous system pathology consistent with NS was found; as "probable" if extraneurological pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis was found; as "possible" for all the other patients with a strong clinical suspicion of NS but without pathologic confirmation of granulomatous disease. A complete medical history was obtained for each patient from their medical records. Data regarding epidemiological characteristics, clinical features associated with the disease, ancillary tests performed (sample and imaging), treatment and outcome were recorded. For imaging data, brain and spinal cord MRI were considered abnormal by neuroradiologists if they observed gadolinium enhancement, T2-weighted or FLAIR hyperintensities of an abnormal number, size and suitable localisation. 18-fluorodeoxyglucose-positron emission tomography/computerised tomography (18-FDG-PET/CT) was assessed by nuclear medicine specialist, especially abnormal increased 18-FDG uptake of the central nervous system (CNS) or other organs have been searched when this exam was performed for the diagnosis or monitoring strategy. Regarding treatment data, we described the agents used and treatment line efficacy if received at least 3 months, and security.

Outcome measurement

Treatment failure was defined as worsening or absence of improvement of symptoms and signs despite sufficient posology and a minimum treatment duration of 3 months for each agent used, as assessed by the clinician. Relapse was defined as the occurrence of any new symptom and/or sign, and/or new MRI feature during or after treatment, as assessed by the clinician or the neuroradiologist. Remission was defined as an improvement of symptoms and/or signs, with or

without sequelae, during or after treatment, as assessed by the clinician. Recovery was defined by remission at least for 36 months without treatment and disease. Treatments were given either alone or in association.

Statistical analysis

Statistical analyses were performed using R platform from open source. Data were presented as mean and standard deviation (SD) for continuous variables. Categorical variables presented with counts and percentages were compared using the Fisher's test or the $\chi 2$ Pearson's chi-squared test, especially superiority comparison test for treatments response. Multivariable binary stepward logistic regression with logit and probit models were used to evaluate predictors of treatment response. P values <0.05 were considered to be statistically significant.

Results

Demographic data

Using the PMSI, a total of 738 patients diagnosed sarcoidosis were studied, among whom 44 patients with NS were identified. The neurological manifestation prevalence was 6% in our study. The mean follow-up time was 5.8 years (SD = 5.1). The patients' demographic characteristics are presented in Table 1, Figure 1 and 2. We observed a female predominance with female to male ratio 1.3/1. The onset of the disease was at a mean age of 47.6 years (SD = 14.4). The diagnosis was definite for only 3 patients (7%), probable for 25 patients (57%) and possible for 16 patients (36%). For 64% of patients, neurological involvement was the primary presentation of the disease, and appeared with a mean delay of 14 months (SD = 37) for the other patients. There were only 2 patients with an associated autoimmune disease, such as ulcerative colitis and Hashimoto's thyroiditis.

Clinical features

A majority of patients (73%) had extra neurological involvement at the time of diagnosis of NS. Lymph nodes, lungs and eyes were the most affected organs, as reported in Table 2, Figure 3. Symptoms were heterogeneous and nonspecific (Table 3, Figure 4). CNS involvement was found in 64% of patients and peripheral nervous system (PNS) one in 20% of patients (Table 3, Figure 5). The most commonly reported NS features were meningeal (n = 24, 55%), intraparenchymal brain (n = 19, 43%), affected cranial nerves (n = 17, 39%) or spinal cord (n = 12, 27%). PNS manifestations were axonal neuropathy (n = 6, 14%) and multiradicular involvement (n = 5, 11%). Muscular involvement was rare (n = 2, 5%).

Ancillary tests

Serum and CSF analysis are described in Table 4. Serum angiotensin-converting enzyme (ACE) was elevated in 20 of 41 patients tested (49%). CSF ACE was elevated in 5 of 12 patients (42%). Only 1 patient out these 5, had an increase in serum ACE, and there was no significant association between CSF and serum ACE levels (p = 0.899). More than two-thirds of patients had an increase in antinuclear antibodies (ANA) in serum, without specificity, mainly with heterogenous or fine speckled fluorescence patterns. Two cases of syndrome of inappropriate antidiuretic hormone secretion (SIADH) were identified. Therefore, 47% of patients had a lymphopenia and 27% presented a hypergammaglobulinemia. Hypercalcemia was reported in

only 6 of 43 patients (14%). There was no case of positive anti-AQP4 or anti-MOG antibodies, including patients with possible diagnosis, spinal cord or optic nerve involvement. CSF analysis emphasised lymphocytic meningitis in 20 of 34 patients (59%), hypoglycorrhachia in 4 of 31 patients (13%), elevated protein level in 16 of 33 patients (48%), intrathecal IgG synthesis (index over 0.7) in 7 of 30 patients (23%) and there were no case of elevated IL-6/IL-10.

Concerning imaging characteristics, the majority of the patients (88%) presented abnormal brain MRI, as reported in Table 5. The most common findings concerned supratentorial white matter (50%), leptomingeal (33%), cranial nerves (25%) and hypothalamo–pituitary (18%) localisations. About half of the available spinal cord MRI were abnormal, including 75% of longitudinally extensive transverse myelitis, defined by 3 or more metameric level lesions. Five patients had conus medullaris involvement. All patients with abnormal spinal cord MRI had abnormal brain MRI. Overall, contrast enhancement was reported for 77% of patients who presented abnormal MRI.

Interestingly, 18-FDG-PET/CT was performed in 25 patients (57%), always for diagnosis strategy, and highlighted an increased uptake in CNS in 7 of these 25 patients (28%), including 7 of 23 patients (30%) with CNS involvement. Eight PET/CT exams guided lymph node (usually mediastinal lymph node) biopsy to confirm sarcoidosis diagnosis (probable NS). One exam confirmed the absence of extra neurological involvement and guided stereotactic neurological biopsy to confirm NS diagnosis (definite NS). Therefore, 9 of PET/CT exams (36%) led to diagnosis confirmation. Two PET/CT exams revealed unknown associated bone involvement. The majority of the 18-FDG-PET/CT was realised before treatment introduction, especially in patients who had not 18-FDG CNS hypermetabolism except in 2 patients treated by corticosteroids (CS). The female to male ratio and mean age onset were higher in the patients with increased 18-FDG CNS uptake with the predominance of possible diagnosis (57%). The extra neurological involvement rate was lower in patients with increased 18-FDG CNS uptake (29%) than in the absence of 18-FDG CNS uptake (83%). About the 25 patients who had whole body 18-FDG-PET/CT, 15 patients (60%) presented extra neurological increased 18-FDG uptake. In the order of decreasing frequency, the most common hypermetabolic organs were mediastinal lymph nodes (48%), other lymph nodes (33%) and lungs (20%). Patients with increased 18-FDG CNS uptake had a lower frequency of extra neurologic uptake (29%) than patients without CNS uptake (72%). Patients with increased 18-FDG CNS uptake had more intraparenchymal brain involvements than other patients (especially supratentorial white matter 71%, hypothalamo–pituitary 48%, brainstem 43%, peduncles cerebellum 29%). They also had more spinal cord (71%) and PNS (57%) involvements but less meningeal (43%) and cranial

nerve (0%) involvements than other patients. Concerning patients with increased 18-FDG CNS uptake who underwent spinal cord MRI, 83% had abnormal spinal cord MRI including 100% of longitudinally extensive transverse myelitis. All the 9 patients with longitudinally extensive transverse myelitis of the study had 18-FDG-PET/CT, including 5 patients (56%) with increased uptake of the spinal cord. All increased 18-FDG CNS uptake lesions corresponded to contrast enhancement MRI lesions.

Serum ACE was less frequently elevated in patients with increased 18-FDG CNS uptake than without 18-FDG CNS uptake (2 of 7 patients = 29% versus 10 of 18 patients = 56%). No patient presented hypergammaglobulinemia in the increased 18-FDG CNS uptake group. However, more frequently elevated CSF protein and intrathecal IgG synthesis rates were reported in patients with increased 18-FDG uptake than other patients, indeed highest inflammatory CSF (respectively 71% and 43%, versus 48% and 23%).

Treatment

All the drugs, their therapeutic line and their outcome are resumed in Table 6. Intravenous CS were used in 24 patients (57%), generally as a bolus in first-line treatment for 83% of these patients, and led to remission for 9 (39.1%), relapse for 11 (47.8%) and failure for 3 (13%) patients. Orally CS were used in 40 (91%) patients, mainly isolated as first-line treatment, or in association from the second line. The first-line therapy as monotherapy response evaluation was calculated for all the patients except for 9 patients who directly received a therapeutic association as first-line therapy: corticosteroid associated with azathioprine (n = 2), methotrexate (n = 5), cyclophosphamide (n = 1), infliximab (n = 1). Remission was obtained for 19 patients (48.7%), including 2 with sequelae, 14 patients (35.9%) relapsed and 6 patients (15.4%) did not respond at all. Azathioprine (AZA) was used in 5 patients (12%), equally as first-line and second-line therapy. Treatment response evaluation was available for only 3 patients with an absence of remission observed. Two patients experienced a relapse and one a failure. Methotrexate (MTX) was used in 19 (44%) patients, mainly as second-line therapy for 58% of these patients which led to remission for 13 patients (76.5%), including 2 with sequelae, relapse for 4 patients (23.5%). There was no reported failure. Mycophenolate mofetil (MMF) was used in 3 patients (7%), as second-line therapy for 1 patient and as third-line for 2 patients which led to relapse for 2 patients and failure for 1 patient. No remission was obtained. Hydroxychloroquine (HCQ) was used in 3 patients (7%) but started for concomitant cutaneous involvement in 2 cases. A third patient was treated as the second line and experienced a failure. Cyclophosphamide (CYC) was used in 8 (18%) patients, mainly as second-line therapy for 88% of these patients which led to remission for 3 patients (37.5%), relapse for 4 (50%) including 1

inobservance and failure for 1 patient. Concerning anti-TNFα biological agents, infliximab (IFX) was the most used with 13 patients(30%), mainly as second-line treatment for 62% of these patients which led to remission in 10 patients (76.9%), including 2 with sequalae, relapse for 2 patients (15.4%) and failure for 1 patient (7.7%). Adalimumab (ADA) was used for only 1 patient as fourth-line treatment, who experienced relapse caused by treatment immunisation confirmed by anti-adalimumab antibodies >160ng/mL. Concerning usual immunosuppressive agents, MTX appeared to be the most effective with a better remission rate (76.5%) than AZA or MMF (0%). Concerning severe or refractory forms, IFX appeared to be most effective compared to CYC with a better remission rate (76.9% versus 37.5% respectively) without significant difference (OR 5.06, 95% IC 0.58–57.51, p = 0.164) at Fisher's test nor Pearson's chi-squared test (X-squared 1.81, p = 0.179).

Treatment response predictive factors

Therapeutic response prognostic factors were studied. Regarding the most effective drugs, demographic, clinical, biological and imaging factors were evaluated. Neither remission predictive factors for MTX and IFX, failure predictive factors for CS, nor failure or relapse predictive factors for MTX were statistically significant brought to light as reported in Table 7. In regard to our results, increased 18-FDG CNS uptake do not seem to be a treatment response prognosis factor for similar presentation patients (e.g., extensive myelitis). The majority of our patients required successfully anti-TNFα agents in severe or refractory forms to usual immunosuppressive agents.

Side effects and long-term outcomes

Recovery was obtained in 5 of 37 patients (13.5%). Only 1 patient, a woman older than 70 years, died during the study out of 41 patients (2%), secondary to pulmonary embolism. Severe adverse events globally affected 10 of 42 patients (24%), including cytopenia (*n* = 5, 12% with 4 lymphopenia), severe infection (*n* = 3, 7% with 3 pneumocystis pneumonias and 1 staphylococcus pneumonia) and hematologic malignancies (*n* = 2, 5% with 1 mantle cell lymphoma unrelated to treatment and 1 cutaneous T-cell lymphoma attributed to MTX). No case of solid cancer was reported. Concerning anti-TNFα agents, only one case of ADA immunisation was noted, needing a switch for IFX. However, no case of demyelinating disease caused by anti-TNFα agents and no case of injection-site reaction was noted. Few cases of treatment discontinuation for side effects were reported. Intravenous CS were interrupted for 1 patient (4%) due to worsening diabetes. Orally CS were stopped for 2 patients (5%) due to psychiatric disease and fracture osteoporosis. AZA was stopped for 1 patient (25%) due to

pneumocystis pneumonia. MTX was discontinued for 2 patients (11%) due to cytolytic hepatitis and cutaneous lymphoma. IFX was discontinued for 1 patient (8%) due to alopecia areata.

Discussion

Demographic and clinical outcomes

Diagnosis of NS remains challenging, particularly in the case of forms with CNS involvement whose only neurological symptoms point to other inflammatory diseases such as multiple sclerosis (MS), neuromyelitis optica, neuropsychiatric systemic lupus erythematosus, neuro-Behçet's disease and infectious or neoplastic diseases. Heterogeneous and nonspecific symptoms can mislead diagnosis, especially in the absence of symptoms of extra-neurological sarcoidosis. Indeed, headaches, fatigue or cognitive/psychiatric disorders have been observed in almost half of our population. Our demographic and clinical data, including symptoms and neurological features, were broadly comparable to data reported in other series and reviews with meta-analyses [4,11,12,15,19,24–36]. However, the NS prevalence is probably underestimated in our study as in previous ones given the inclusion of patients from tertiary care centres only, misdiagnosis (e.g., isolated facial nerve involvement considered as Bell's palsy) and general alteration without other symptoms in the context of meningeal damage. The rate of extraneurological involvement rate was lower than the percentages reported in the literature, 73 and 80–90% respectively, and was lower in the Caucasian group than in the other ethnic groups in our study, 64% and 100%, respectively. NS is usually the first sarcoidosis presentation and occurs at onset in more than half of the cases (64% in our study) or within the first three years (14 months in our study) [24].

The meningeal involvement may cause focal nodular improvement that may mimic common basal skull tumours that are not reported in our patients [26]. Meningeal impairment caused headaches in 50% of our patients and was complicated by hydrocephalus in 4 patients requiring 2 ventriculoperitoneal shunts. Cerebrovascular events were rare in our study, including a CNS vasculitis-like manifestation. However, no ischemic stroke was reported. In terms of neurological features, optic nerve involvement is well-known with a prevalence of 20% in previous studies [24]. We emphasised the unilateral nature for all 6 patients in our study. Two patients had compatible clinical involvement without MRI findings. On the contrary, one asymptomatic patient had MRI contrast enhancement. For 5 of the 6 patients, there was an associated spinal cord involvement, including 4 patients with longitudinally extensive transverse myelitis and 1 patient with increased in spinal cord absorption by FDG-PET scan. Anti-AQP4 and anti-MOG antibodies were tested for only 3 of these 6 patients and were negative, excluding Devic's neuromyelitis optica disease, anti-MOG antibodies associated

syndrome or NS associated with anti-MOG antibodies. All of these 6 patients had other CNS involvements and pathologic confirmation of granulomatous disease.

Spinal cord involvement reveals the disease in 60–70% of cases. Age is generally less than 40 at onset of the disease, and young age at diagnosis has been described as a relapse factor in previous studies [37]. The mean age was 42 years in this study with a delayed diagnosis for a 67 year-old-woman. The cervical and thoracic areas are the most affected in the literature, 7 out of 12 patients in this study. We noticed several patients with conus medullaris impairment (5 patients, including 1 cauda equina syndrome), less described in previous studies. In general, one-third of patients had a relapse, another third had sequelae [37–41]. There was no case of isolated myelitis in this study. All patients presented other manifestations, mainly intraparenchymal lesions of the brain, meninges and optic nerve . One patient presented an associated hypothalamo–pituitary damage. Six patients achieved remission with IFX (first-line therapy for 1 patient and relapse/failure with usual immunosuppressive agents for others), including 1 with sequelae. One patient achieved remission and 1 patient presented an asymptomatic radiologic relapse with CYC. Two patients achieved remission with MTX, including one with sequelae. One patient whose diagnosis was delayed had spinal cord atrophy with no response to CS. One patient was lost to follow-up.

Meningeal involvement which may cause focal nodular enhancement that can simulate common cranial base tumours otherwise has not been reported in these patients [26]. Meningeal impairments caused a headache in 50% of these patients and were complicated by hydrocephalus in 4 patients requiring 2 successfully ventriculoperitoneal shunt surgeries. Cerebrovascular events were rare in this study, including 1 CNS vasculitis-like manifestation. However, no ischemic stroke was reported [42]. PNS involvements are heterogenous and probably underestimated but systematic EMG achievements seem unreasonable [43]. Overall, the majority of relapse are generally at the same neuroanatomic location, as described before [44].

Biology

Use of CSF ACE is discussed in the literature. CSF ACE activity is described as significantly higher for NS patients than control patients, depending on cut-off value [45]. However, CSF ACE level utility is limited in view of poor sensitivity (24 to 55%) and variable specificity (67 to 95%) according to some articles [46–48]. Indeed, the level can be elevated in numerous conditions such as multiple sclerosis, brain tumour, and degenerative diseases [19]. Two large studies found only 33 to 50% patients with elevated CSF ACE levels presenting NS, while 5%

to 7% NS patients had normal CSF ACE levels [45,49]. In our study, 3 patients had pathologic sarcoidosis confirmation, and only 1 patient had extra neurological involvement out of 5 patients with increased CSF ACE level. There was no significant association between CSF and serum increased ACE. Actually, CSF ACE level, especially for low serum ACE patients and neurological isolated forms, seems to be an additional but no sufficient argument for NS diagnosis.

Some widely used biological markers provide guidance for NS diagnosis and rule out differential conditions. Indeed, patients with sarcoidosis were more likely to have serum hypergammaglobulinemia (27% of our patients), as well as CSF higher protein content (48% of our patients) and white blood cell count (59% of our patients) than patients with multiple sclerosis or neuromyelitis optica [40]. Others biological markers showed their utility but were not sufficiently used in our study. For example, CSF CD4/CD8 ratio is increased in NS compared to idiopathic intracranial hypertension, multiple sclerosis and other inflammatory disorders explained by increased activated CD4+ T cells [50,51]. An increased CSF IL-6 concentration and IL-6/IL-10 ratio are associated with active NS [50,52,53]. Serum IL-2 receptor levels has been reported for monitoring NS [10]. S100B is a promising biomarker, a calcium-binding protein found in glial cells which can leak into CSF and systemic circulation in case of neuronal injury. S100B levels are significantly more elevated for NS patients compared to healthy controls [54].

Imaging

MRI is the gold standard to evaluate CNS involvement in NS despite the reported high sensitivity but low specificity [55–59]. Longitudinally-extensive T2-hyperintense spinal cord lesions (≥3 vertebral segments) are associated with neuromyelitis optical spectrum disorders but occur with other disorders, including spinal cord sarcoidosis. Dorsal subpial enhancement on MRI spine accompanied by central cord/canal enhancement during the axial post-gadolinium sequences may reveal “trident sign”, not reported in our study, but previously shown to be strongly suggestive of spinal cord sarcoidosis and avoiding misdiagnosis [60–62]. MRI imaging not always allowed to determine a diagnosis.

18F-FDG-PET/CT is a non-invasive imaging technique that can be crucial in the NS diagnosis, offering an early metabolic window, showing abnormalities linked to neuroinflammation in the absence of infiltrative lesions detected by MRI, especially on the spinal cord and helping avoid unnecessary invasive procedures for difficult cases [24,63–69]. It appears to be accurate and contributes to very tiny regions evaluation, also extrapulmonary involvement, establishing a

pre-therapeutic map and monitoring treatment response [66,70]. However, the exact role is not well established and still unclear in the diagnostic work-up. This study highlights that PET/CT exam is underused, and was realised for only half of our patients (57%). NS CNS lesions identified on MRI showed 18-FDG-PET/CT avidity in 30% of patients. In our patients, more than a third of PET/CT exams guided to biopsy leading diagnosis confirmation. It is interesting to note that all patients with increased 18-FDG uptake of the spinal cord in our study had longitudinally extensive myelitis (≥3 metameric levels).

Treatment

CS were mostly the first-line therapeutic agent; 1 mg of prednisone/kg/day, and up to 1000 mg of intravenous methylprednisolone for acute severe forms. We reported several relapses during CS tapering, meaning CS dependence. This treatment was associated with immunosuppressive agents if cases of failure/resistance or dependence over 10 mg/day, or immediately for severe forms (including optic nerve involvement) as previously suggested [7]. Fibrosis sequelae may be the consequences of delayed diagnosis and therapeutic, inducing refractory forms (2 patients with spinal cord atrophy presented paraparesis).

Several immunosuppressive agents substantiated their efficacy in NS treatment. Indeed, AZA, MTX and MMF were used successfully in several series/case reports. Data suggests that MMF is effective in CNS sarcoidosis but not in sarcoid myopathy, with a CS sparing effect and a better tolerance profile than other immunosuppressive agents [71]. To our knowledge, only one comparative retrospective multicenter study found that MTX significantly increased the survival time without relapse compared to MMF. This study provided class IV evidence that MTX is superior to MMF, reducing relapse risk [72]. In our study, MTX appeared to be the most effective immunosuppressive agent, with better remission rates than AZA or MMF, respectively, but few patients were treated and study design was not suitable for treatment comparison. Ciclosporin A was not used.

Short-course CYC appears to be a reasonable steroid-sparing treatment option for patients with corticosteroid-refractory NS [73]. This agent is mainly recommended as a second- or third-line treatment, for severe or refractory forms patients [24]. TNF-α antagonists efficacy has been reported in the literature for pulmonary and extrapulmonary sarcoidosis treatment [74]. IFX appears to be efficacious for refractory and severe NS with 70 to 90% favourable imaging and clinical treatment responses [75–81]. However, relapses usually occur during follow-up, especially with treatment discontinuation (up to 50%) [44]. In our study, IFX was always associated with CS. Four patients were treated with IFX without immunosuppressive agent

associated, including the only patient presenting treatment failure. Eight patients had an association with MTX et 1 with MMF. Two patients presented relapse because of discontinuation or every 8 weeks maintenance treatment spacing, demonstrating the suspensive nature of this agent. Concerning ADA (n = 1), we observed immunisation probably secondary to MTX discontinuation (stopped for hepatic cytolysis). It seems necessary to continue associated immunosuppressive treatment to avoid this complication. Etanercept was not used in our study. With regard to third-line treatments that are usually used for severe or immunosuppressive agents refractory forms, no comparative study assessing CYC versus anti-TNFα exists yet. In our study, IFX appeared to be most effective than CYC with identical safety and better remission rate but without significant difference, probably attributable to lack of power. Some of our patients without histologic confirmation (possible diagnosis), had received CYC rather than anti-TNFα when a demyelinating attack like multiple sclerosis was not formally excluded, practitioners fearing anti-TNFα utilisation. In literature, several CNS demyelination reported cases to evoke the possibility of a causal association with anti-TNF-α agents. Whether the demyelinating events were the result of latent demyelinating predisposition, or novel demyelinating event (MS or MS-like syndrome) directly caused by anti-TNFα agents, or were a coincidental coexistence of 2 disorders, still remains controversial. Systematic long-term follow-up could help distinguish which patients would safely benefit from TNF-α blockers. Avoid anti-TNFα is advised for patients with familial history of occurrence of demyelinating lesions. Although brain MRI imaging before starting anti-TNFα is not recommended, it might reveal silent demyelinating disease [82,83]. However, no case of the demyelinating disease was noted during anti-TNFα therapy in our patients. Rituximab (RTX) was not used in our study despite good tolerance and extended remission in a few patients nonresponsive to established treatment regimens [84]. It could be an interesting treatment for refractory diseases and requires further studies.

Prognostic factors

Some poor prognostic factors were reported in previous studies, such as CNS involvement, especially spinal cord and hypothalamo–pituitary involvements, and hydrocephalus, with higher relapse risk [85]. In this study, CNS involvement at onset was associated with a less favourable disease course compared to PNS involvement. The NS onset form, acute or progressive, was not associated with treatment response [25,28]. Older age, PNS involvement, higher baseline EDSS score were associated with higher mortality and encephalic involvement was associated with shorter neurologic relapse-free survival in another study [86]. Laboratory findings, including CSF and blood, were not predictor factors of refractory NS in first study

[28]. More recently, an increased CSF IL-6 and IL-6/IL-10 ratio are associated with active NS, higher NS relapse and progression risk. [50,52,53]. Furthermore, elevated CSF protein was described as a relapse factor and hypoglycorrhachia associated with poor treatment response in myelitis forms [37]. A lower relapse risk was induced by cyclophosphamide, methotrexate and infliximab treatments [86].

The treatment response predictive factors have been poorly studied to our knowledge. In our study, we didn't find significant predictive factors for the most used treatments. This result can be explained by missing data and the lack of power of this study. Relapse predictive factors for orally CS treatment was not assessed because most of the cases were explained by the CS decrease (CS dependence >10 mg/day). IFX predictive failure factors were not statistically assessed because only one patient presented a failure. In the same way, IFX relapse predictive factors were not assessed because the 2 relapses followed discontinuation or spacing. The mortality rate among NS patients remains 5% versus 2% in our study [24].

Limitations

Our study had many limitations. First, the study was observational and retrospective. Second, the disease being rare, the small sample size led to a lack of power. Then, the design of the study was not suitable for performing treatment superiority comparison tests, accounting for a questionable statistical value.

Conclusion

NS diagnosis remains challenging regarding heterogeneous symptoms, neurological features and imaging presentations. The 18-FDG-PET/CT is an underused non-invasive imaging technique, completing MRI features, can help avoid unnecessary invasive procedures and leading to diagnosis pathology confirmation in more than third of cases. An increased 18-FDG CNS uptake is frequent in NS, can highlight early lesions not detected by gold standard techniques. Better use of well-known and promising biomarkers can also facilitate diagnosis work-up. Previously suggested treatment strategy algorithms compensate lack of prospective randomised trials. Based on the results of the current study, MTX and anti-TNFα appear to be the most effective agents for second- and third-line therapies respectively, in case of refractory/severe forms. Significant treatment response predictive factors could allow adapted therapy decisions for each patient and require further, larger studies.

CONCLUSIONS

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THESE SOUTENUE PAR Mr AUVENS Clément

CONCLUSIONS

Le diagnostic de neurosarcoïdose (NS) est un véritable défi étant donné l'hétérogénéité de ses symptômes, de ses atteintes et de sa présentation en imagerie. L'objectif de l'étude était de décrire les caractéristiques des patients et les résultats d'imagerie, d'évaluer les traitements et d'identifier les facteurs pronostiques de la réponse thérapeutique. 738 patients avec un diagnostic de sarcoïdose ont été identifiés, parmi lesquels 44 patients présentant une NS ont été inclus (6%). La durée moyenne du suivi était de 5,8 ans. L'âge moyen à l'apparition de la maladie était de 47,6 ± 14,4 ans. Les symptômes étaient hétérogènes et non spécifiques. L'atteinte du système nerveux central (64%) était plus fréquente que l'atteinte périphérique (20%). La majorité des patients (88%) présentaient une imagerie par résonance magnétique (IRM) cérébrale anormale et l'IRM médullaire était anormale chez la moitié d'entre eux. La tomographie par émission de positons au 18-fluorodésoxyglucose couplée au scanner (TEP-scanner au 18-FDG) était une technique d'imagerie non invasive sous-utilisée, complétant les données de l'IRM et conduisant à la confirmation diagnostique anatomopathologique dans plus d'un tiers des cas. Des algorithmes de prise en charge thérapeutique précédemment suggérés compensent le manque d'essais prospectifs randomisés. Sur la base des résultats de cette étude, la corticothérapie a été utilisée chez la majorité des patients avec cependant des rechutes fréquentes. Le méthotrexate et les anti-TNFα semblaient être les agents les plus efficaces concernant respectivement les thérapies de deuxième et troisième ligne, en cas de formes réfractaires et/ou sévères. Aucun facteur prédictif de réponse au traitement n'a été mis en évidence de manière significative. De tels facteurs prédictifs pourraient orienter des décisions thérapeutiques adaptées pour chaque patient et nécessitent des études plus approfondies et de grande envergure.

Le Président du jury,

Pr. B. BONNOTTE

Vu et permis d'imprimer
Dijon, le 19 Aout 2020
Le Doyen

Pr. M. MAYNADIÉ

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TABLES ET FIGURES

Table 1. Demographic characteristics.

	Number of patients n = 44 (%)
Gender	
Female	25 (57)
Age at onset (years)[1]	47.6 ± 14.4
Ethnic group	
Caucasian	33 (75)
African	3 (7)
Antillean	1 (2)
Maghreb	6 (14)
Mediterranean	1 (2)
Diagnosis	
Definite	3 (7)
Probable	25 (57)
Possible	16 (36)
Occurrence	
Immediately	28 (64)
Secondarily	16 (36)
Delay of onset (months)[2]	14 ± 37
Associated autoimmune disease	2 (5)

[1] variable expressed as mean ± standard deviation.

[2] variable expressed as mean time to onset between sarcoidosis diagnosis and neurological impairment if secondarily occurrence ± standard deviation.

Table 2. Extraneurological involvement.

	Number of patients n = 44 (%)
Extra neurological involvement	32 (73)
Lung	19 (43)
Eye	13 (30)
Lymph node	26 (59)
Skin	7 (16)
Liver/spleen	7 (16)
Joint	7 (16)
Heart	4 (9)
Bone	2 (5)
Kidney	1 (2)
Otorhinolaryngeal/exocrine gland	6 (14)

Table 3. Symptoms and neurological features.

	Number of patients n = 44 (%)
Symptoms	
Motor disorders	7 (16)
Facial nerve palsy	8 (18)
Sensory disorders	21 (48)
Sphincter disorders	8 (18)
Gait disturbances	12 (27)
Headache	18 (41)
Diplopia	7 (16)
Visual loss	12 (27)
Cognitive/psychiatric disorders	13 (30)
Myalgia	3 (7)
Fatigue	20 (45)
Balance disorders	8 (18)
Hearing loss	3 (7)
Seizures	4 (9)
Consciousness disorders	1 (2)
Neurological features	
CNS	28 (64)
Intraparenchymal brain	19 (43)
Meningeal	24 (55)
Intracranial hypertension	3 (7)
Hydrocephalus	4 (9)
Hypothalamo–pituitary	8 (18)
Cranial nerve	17 (39)
II	6 (14)
III	2 (5)
VI	2 (5)
VII	11 (25)
VIII	1 (2)
Spinal cord	12 (27)
PNS	9 (20)
Multiradicular involvement	5 (11)
Demyelinating like neuropathy	1 (2)
Axonal neuropathy	6 (14)
Small fibre neuropathy	2 (5)
Muscular	2 (5)

CNS, central nervous system; PNS, peripheral nervous system.

Table 4. Serum and CSF analysis.

	Number of patients (%)
Serum analysis	
Elevated ACE[1]	20/41 (49)
ANA ≥1/80	24/34 (71)
Lymphopenia[2]	20/43 (47)
Hypergammaglobulinemia[3]	11/41 (27)
Hypercalcemia[4]	6/43 (14)
SIADH	1/42 (2)
Anti-AQP4	0/9 (0)
Anti-MOG	0/7 (0)
CSF analysis	
Elevated ACE[5]	5/12 (42)
Lymphocytic meningitis[6]	20/34 (59)
Hypoglycorrhachia[7]	4/31 (13)
Elevated protein[8]	16/33 (48)
Intrathecal IgG synthesis index > 0,7	7/30 (23)
IL-6/IL-10 >1	0/2 (0)

CSF, cerebrospinal fluid; ACE, angiotensin converting enzyme; ANA, antinuclear antibodies; SIADH, syndrome of inappropriate antidiuretic hormone secretion; AQP4, anti-aquaporin 4 antibodies; MOG, anti-myelin oligodendrocyte glycoprotein antibodies.

[1] ACE >70 UI/L

[2] Lymphopenia <1 G/L

[3] Serum protein electrophoresis

[4] Calcemia >2.60 mmol/L albumin corrected

[5] ACE >0.25 UI/L

[6] Cells >5/mm^3

[7] Glycorrhachia/glycemia <0.6

[8] Protein >0.60 g/L

Table 5. Imaging involvement.

	Number of patients (%)
Abnormal brain MRI	35/40 (88)
Supratentorial white matter	20/40 (50)
Brainstem	5/40 (13)
Basal ganglia	4/40 (10)
Peduncles cerebellum	3/40 (8)
Cranial nerve	10/40 (25)
II	4/40 (10)
III	3/40 (8)
V	1/40 (3)
VII	5/40 (13)
VIII	1/40 (3)
Floor of the 4th ventricle	2/40 (5)
Hypothalamo–pituitary	9/40 (23)
Leptomingeal involvement	13/40 (33)
Trapped ventricle	4/40 (10)
Vascular-like	3/40 (8)
Abnormal spinal cord MRI	12/22 (55)
≥3 Metameric levels	9/12 (75)
Trident sign	0/40 (0)
Conus medullaris	5/22 (23)
Contrast enhancement	27/35 (77)
Increased **18-FDG** uptake of CNS	7/25 (28)

MRI, magnetic resonance imaging; 18-FDG, 18-fluorodeoxyglucose.

Table 6. Treatments and outcome.

Agents	Number of patients (%)										
	Total	1st line	2nd line	3rd line	4th line	5th line	**Failure**	**Relapse**	**Remission**		
									with sequelae	*no sequelae*	*Total*
IV corticosteroids	24/42 (57)	20/24 (83)	7/24 (29)	1/24 (4)	-	1/24 (4)	3/23 (13)	11/23 (47.8)	7	2	9/23 (39.1)
Oral corticosteroids	40/44 (91)	38/40 (95)	19/40 (48)	5/40 (13)	1/40 (3)	1/40 (3)	6/39 (15.4)	14/39 (35.9)	17	2	19/39 (48.7)
Azathioprine	5/43 (12)	2/5 (40)	2/5 (40)	1/5 (20)	-	-	1/3 (33.3)	2/3 (66.6)	0	0	0/3 (0)
Methotrexate	19/43 (44)	5/19 (26)	11/19 (58)	4/19 (21)	1/19 (5)	-	0/17 (0)	4/17 (23.5)	11	2	13/17 (76.5)
Mycophenolate mofetil	3/43 (7)	-	1/3 (33)	2/3 (67)	-	-	1/3 (33.3)	2/3 (66.6)	0	0	0/3 (0)
Hydroxychloroquine	3/43 (7)	-	1/1 (100)	-	-	-	1/1 (100)	0/1 (0)	0	0	0/1 (0)
Cyclophosphamide	8/44 (18)	1/8 (13)	7/8 (88)	-	-	-	1/8 (12.5)	4/8 (50)	3	0	3/8 (37.5)
Infliximab	13/43 (30)	1/13 (8)	8/13 (62)	3/13 (23)	1/13 (8)	1/13 (8)	1/13 (7.7)	2/13 (15.4)	8	2	10/13 (76.9)
Adalimumab	1/43 (2)	-	-	-	1/1 (100)	-	0/1 (0)	1/1 (100)	0	0	0/1 (0)

IV, intravenous.

Table 7. Treatment response predictive factors.

	Corticosteroids		Methotrexate		Infliximab	
	OR	*p* value	OR	*p* value	OR	*p* value
Remission predictive factors						
Age <40 years	-	-	1.50	0.841	-	-
Definite diagnosis	-	-	1.19	0.426	-	-
Extra neurological involvement	-	-	5.60	0.402	3.75	1.000
CNS involvement	-	-	-	-	2.04	0.999
Spinal cord involvement	-	-	-	-	1.61	0.999
Occurrence at onset	-	-	3.38	0.597	4.49	1.000
Hypergammaglobulinemia	-	-	8.37	0.547	2.12	1.000
Elevated serum ACE	-	-	2.96	0.614	5.06	0.999
Remission after corticosteroids	-	-	7.52	0.995	-	-
Failure or relapse predictive factors[a]						
Age> 45 years	1.57	0.999	8.84	0.999	-	-
Possible diagnostic	7.25	1.000	3.28	0.999	-	-
PNS involvement	2.99	0.999	8.87	1.000	-	-
Spinal cord involvement	1.96	0.999	1.02	0.999	-	-
Absence of elevated serum ACE	1.10	0.999	4.67	0.999	-	-
Absence of hypergammaglobulinemia	2.12	0.999	2.51	0.999	-	-
Hypoglycorrhachia	5.12	0.999	1.15	1.000	-	-
Absence of lymphocytic meningitis	3.28	0.999	3.45	0.999	-	-
Absence of CSF elevated protein	9.90	0.999	1.59	0.999	-	-
Absence of MRI contrast enhancement	2.80	0.999	2.84	0.999	-	-

OR, odds ratio; CNS, central nervous system; ACE, angiotensin converting enzyme; PNS, peripheral nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

[a] predictive factors calculation based on failure for corticosteroids and failure or relapse for methotrexate.

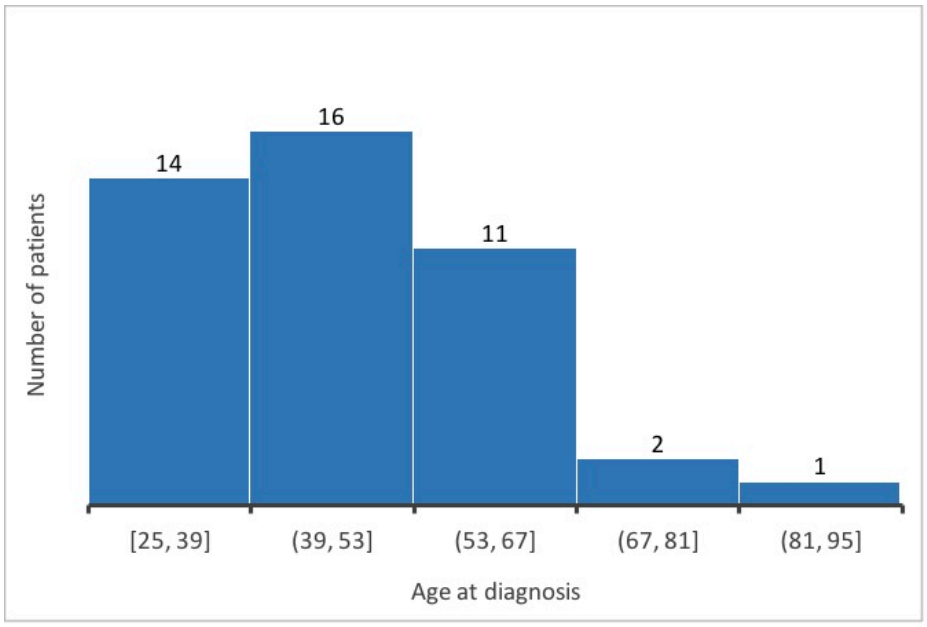

Figure 1. Age at diagnosis.

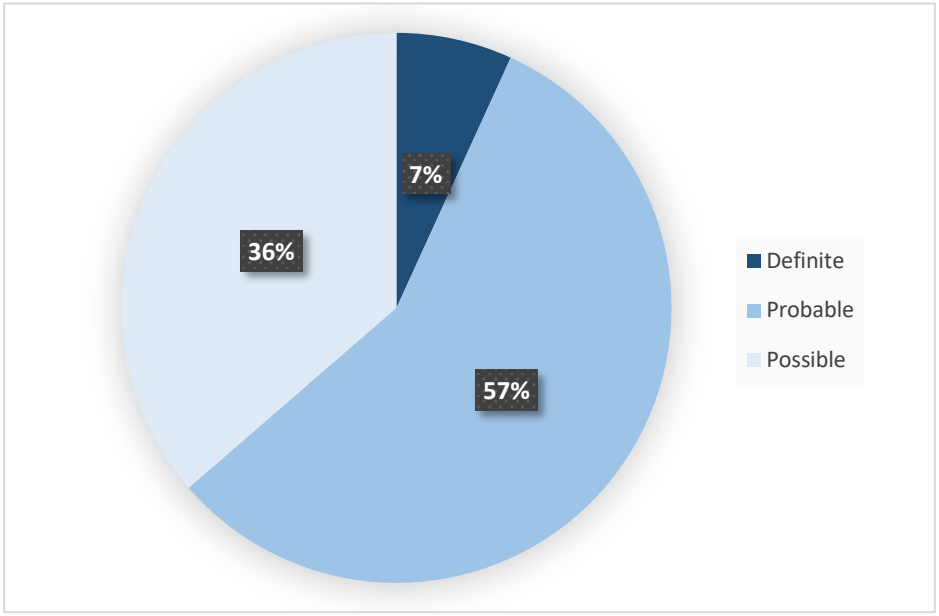

Figure 2. Diagnosis.

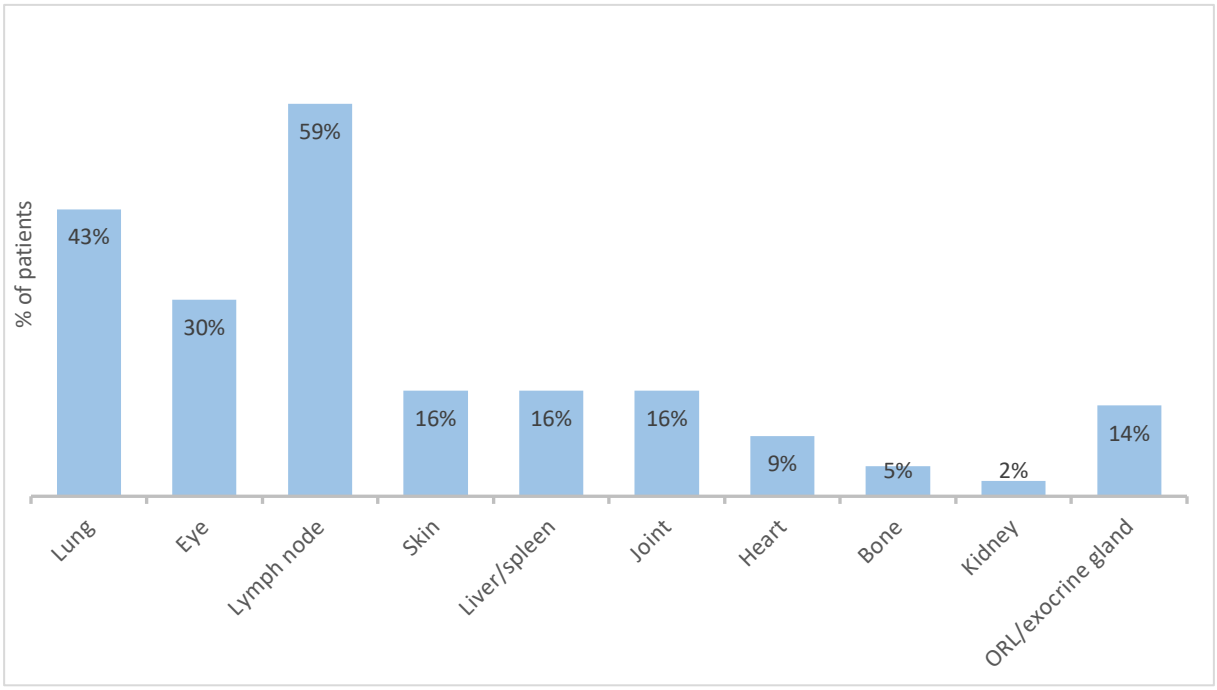

Figure 3. Extraneurological involvement.

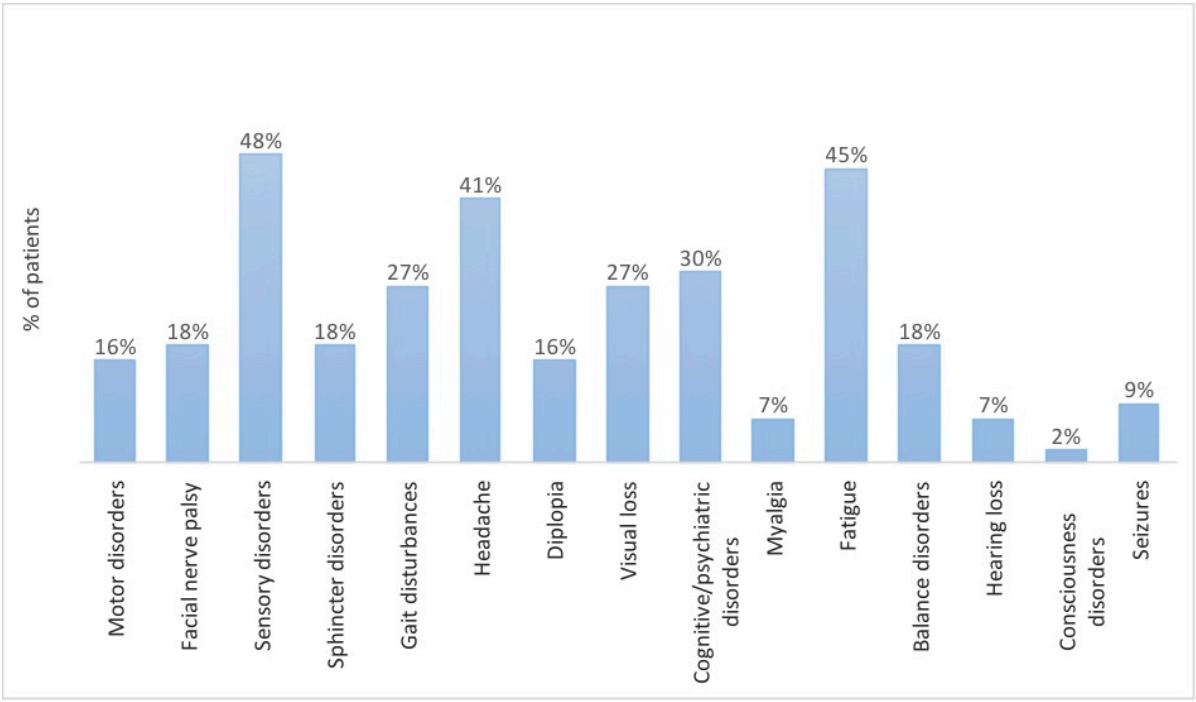

Figure 4. Symptoms.

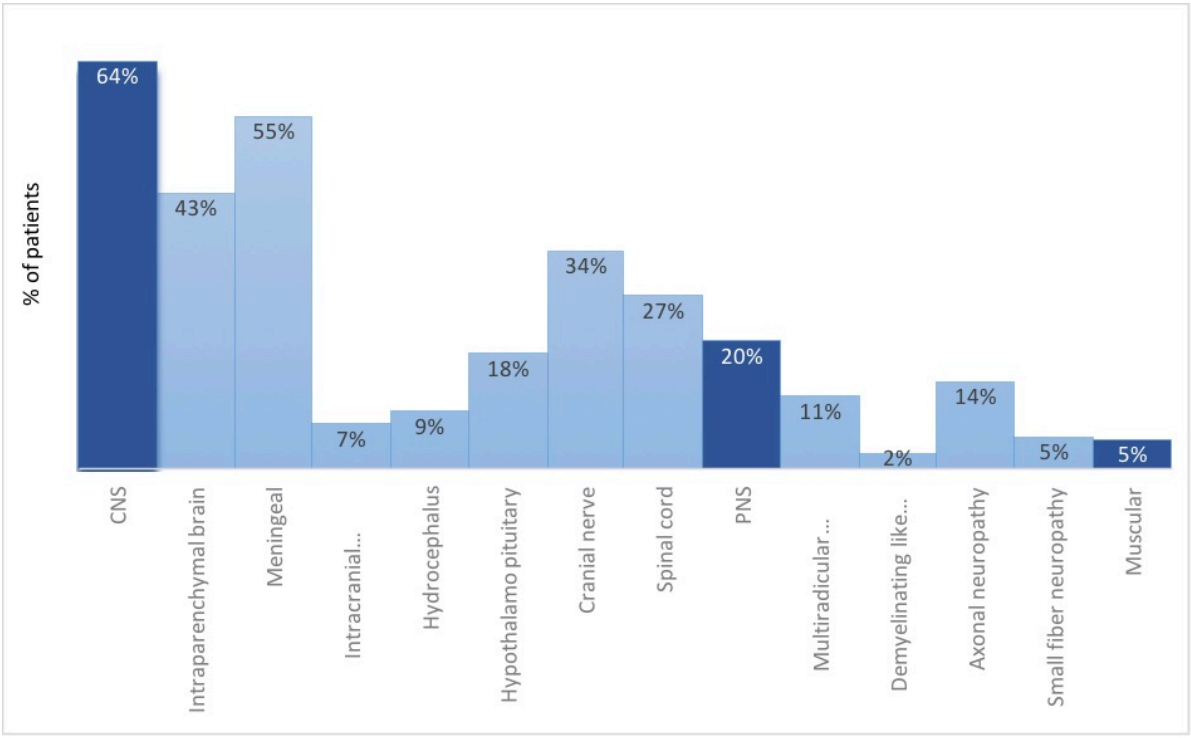

Figure 5. Neurological features.

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

TITRE DE LA THESE :

NEUROSARCOIDOSIS: AN OBSERVATIONAL STUDY OF 44 PATIENTS
NEUROSARCOÏDOSE : ETUDE OBSERVATIONNELLE A PROPOS DE 44 PATIENTS

AUTEUR : AUVENS CLEMENT

RESUME :

Introduction Le diagnostic de neurosarcoïdose (NS) reste un défi étant donné l'hétérogénéité de ses symptômes, de ses atteintes et de sa présentation en imagerie. L'objectif de l'étude était de décrire les caractéristiques des patients et les résultats d'imagerie, d'évaluer les traitements et d'identifier les facteurs pronostiques de la réponse thérapeutique.

Méthodes Tous les patients des hôpitaux de Dijon et Chalon-sur-Saône (Bourgogne, France) avec un diagnostic de NS, tel que défini par les critères du Neurosarcoidosis Consortium Consensus Group, de 1995 à 2019, ont été inclus dans une étude observationnelle rétrospective.

Résultats 738 patients avec un diagnostic de sarcoïdose ont été identifiés, parmi lesquels 44 patients présentant une NS ont été inclus (6%). La durée moyenne du suivi était de 5,8 ans. L'âge moyen à l'apparition de la maladie était de 47,6 ± 14,4 ans. Les symptômes étaient hétérogènes et non spécifiques. L'atteinte du système nerveux central (64%) était plus fréquente que l'atteinte périphérique (20%). La majorité des patients (88%) présentait une imagerie par résonance magnétique (IRM) cérébrale anormale et l'IRM médullaire était anormale chez la moitié d'entre eux. La tomographie par émission de positons au 18-fluorodésoxyglucose couplée au scanner (TEP-scanner au 18-FDG) était sous-utilisée, réalisée chez seulement 25 patients (57%), conduisant à une confirmation anatomopathologique du diagnostic dans 36% des cas. Une corticothérapie était utilisée chez la majorité des patients avec de fréquentes rechutes. Le méthotrexate semblait être l'agent immunosuppresseur le plus efficace avec un taux de rémission de 76,5%. Concernant les NS sévères et/ou réfractaires, l'infliximab apparaissait plus efficace que le cyclophosphamide avec un meilleur taux de rémission (76,9% vs 37,5%, p = 0,164). Aucun facteur prédictif de réponse au traitement n'était mis en évidence de manière significative.

Conclusion La NS est une maladie complexe et hétérogène. Certains outils sont sous-utilisés dans la stratégie diagnostique, comme le TEP-scanner au 18-FDG. Des essais prospectifs plus approfondis sont nécessaires pour identifier des facteurs pronostiques et établir des lignes thérapeutiques directrices.

MOTS-CLES : Neurosarcoïdose, TEP-scanner au 18-FDG, facteurs pronostiques, traitement