HYPOTHALAMIC–PITUITARY ALTERATIONS IN PATIENTS WITH NEUROSARCOIDOSIS

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ABSTRACT

Sarcoidosis is a non-caseating, granulomatous inflammatory disorder that can affect the central nervous system (CNS), including the hypothalamic–pituitary region, although rarely. The clinical manifestations of hypothalamic–pituitary neurosarcoidosis are heterogeneous and require a prompt diagnosis to ensure the most appropriate treatment. We have reviewed the cases of neurosarcoidosis affecting the hypothalamic–pituitary axis published since 2002 and compared them with the cases reported in the literature up to 2002, which were previously meta-analysed by our research group. Since 2002, 64 cases were identified in the literature: 37 cases presented with diabetes insipidus, 36 were found to have secondary amenorrhoea, 30 with hypogonadotropic hypogonadism, 17 with hyperprolactinaemia, 15 with thyroid-stimulating hormone deficiency, and 8 cases of panhypopituitarism. Uncommon manifestations included hyperphagia, sudden death, and thermodysregulation. We confirm that neurosarcoidosis affecting the hypothalamic–pituitary axis is an uncommon manifestation of sarcoidosis. Neither changes in the clinical manifestations and diagnosis nor significantly novel management options have appeared in the last decade. While it is a rare disorder, the involvement of the CNS is an indication to treat sarcoidosis and as the symptoms of CNS involvement, including hypothalamic–pituitary alterations, may precede the diagnosis of sarcoidosis, it is important to include neurosarcoidosis in the differential diagnosis of hypothalamic–pituitary axis dysfunction in order to facilitate prompt and appropriate treatment.

Keywords: Sarcoidosis, neurosarcoidosis, hypothalamus, pituitary.

INTRODUCTION

Sarcoidosis is a multisystem, non-caseating, granulomatous inflammatory disorder, the aetiology of which is not fully understood.[1] The term was first used by a Norwegian dermatologist describing skin lesions in 1899, but these lesions can affect almost any organ, including the nervous system.[2] It is most prevalent among Northern European and African-American populations, more common in females, and more than two-thirds of cases present between the ages of 25 and 45 years.[3] In Japanese and Northern European populations, there is a second peak of incidence in female patients over 50 years and extrapulmonary manifestations are more common in this subset.[3] It is typically a sporadic phenomenon, but familial links have been reported in 3.6-9.6% of cases, with the siblings of the index case at higher risk than parents.[4]

Sarcoidosis is thought to be caused by a combination of environmental factors in genetically susceptible individuals, possibly as an exaggerated response to an unknown antigen.[3] This theory is suggested by clusters of increased incidence reported in relation to an identifiable exposure, as demonstrated recently by the high incidence in emergency responders who worked in the aftermath of the World Trade Center attack in 2001.[5]

The most common clinical manifestations of sarcoidosis include persistent cough, fatigue, and incidental findings on chest radiograph, with

over 90% of cases affecting intrathoracic lymph nodes, lungs, skin, or eyes.[2] A clinically evident neurological involvement is less common, while there is evidence of central nervous system (CNS) involvement at post-mortem in up to 25% of cases who underwent autopsy.[2] Only approximately 5-10% of patients with a diagnosis of sarcoidosis will present with neurological symptoms.[6] However, neurosarcoidosis in isolation is very uncommon, making up approximately 1% of cases.[7] The CNS manifestations of sarcoidosis can range from cranial nerve palsy, which occurs in over 50% of cases, to more unusual clinical presentations such as leptomeningitis, neuropsychiatric symptoms, spinal cord disease, and neuroendocrine alterations in the form of hypothalamic–pituitary dysfunction.[7] These symptoms may precede the diagnosis of sarcoidosis in a relevant number of cases.[2] This point further highlights the importance of including neurosarcoidosis in the differential diagnosis of hypothalamic–pituitary disorders, especially if an infiltrative disease is suspected.

ENDOCRINE MANIFESTATIONS OF NEUROSARCOIDOSIS

Hypothalamic–pituitary sarcoidosis is often asymptomatic, at least in some stages of the disease, and may be incidentally discovered on dynamic endocrine testing after the detection of unexplained, abnormal hormone levels, or can present clinically in the form of endocrine dysfunction secondary to the hypothalamic and/or pituitary infiltration. Occasionally, the disease has been reported as mimicking a pituitary mass, although this is a much less common event.[8] Endocrine disturbances occur in 2-26% of neurosarcoidosis cases,[7] most commonly causing diabetes insipidus, galactorrhoea, and amenorrhoea.[7,9] Based on post-mortem findings from patients with hypothalamic–pituitary failure, it was initially thought that the sarcoid infiltration of the hypothalamus and/or the pituitary gland can lead to the partial or total destruction of the tissues.[10] However, later studies using neuroimaging and dynamic functional testing of the hypothalamic–pituitary hormonal axis showed that neurosarcoidosis-related hypopituitarism is mostly secondary to the infiltration of the hypothalamus.[9] Although rare, the hypothalamus is the endocrine gland most frequently involved in sarcoidosis.[11]

A review article published by our research group in 2002 described the endocrine effects of neurosarcoidosis in 91 reported cases from 1943-2002, which represented all published cases to date.[12] The range of age of presentation, distribution across different age intervals, and female-to-male ratio were similar between systemic sarcoidosis and neurosarcoidosis. Hypogonadotropic hypogonadism, diabetes insipidus, polydipsia, amenorrhoea, and anterior pituitary failure were the most common endocrine manifestations. Changes in thirst without evidence of diabetes insipidus and altered thermoregulation, appetite, and body weight were the hypothalamic disturbances more frequently reported.

Table 1: Reported cases of neurosarcoidosis with endocrine dysfunction from 2002 to 2014.

Clinical manifestation	Frequency, n (N=64)[1,18,19,23-44]	Incidence, % (previously reported incidence, %)[12]
Diabetes insipidus	37	57 (37.3)
Amenorrhoea	36	56% of females (58.7% of females)
Hypogonadotropic hypogonadism	30	46 (38.5)
Hyperprolactinaemia	17	27
Thyroid-stimulating hormone deficiency	15	24
Panhypopituitarism	8	13
Adrenal insufficiency	2	3 (2.2)
Sudden death	2	3
Hyperphagia	2	3 (2.2)
Thermodysregulation	1	2 (4.4)

The anterior pituitary failure can be associated with hypothalamic sarcoid lesions or, less frequently, with the direct infiltration of the pituitary gland itself by granulomatous lesions.[13] It has also been occasionally reported as a result of an intrasellar mass.[8] In this instance, biopsy and histological confirmation may be required. The hypothalamic involvement frequently presents with polyuria and polydipsia. This can occur as a result of diabetes insipidus or a disturbance in thirst control.[9] Hyperprolactinaemia is also seen relatively often in hypothalamic–pituitary sarcoidosis, occurring in up to one-third of cases and being due to the infiltration of the pituitary stalk, which leads to the loss of the dopaminergic control of prolactin secretion.[12] However, other manifestations, including hypothyroidism, adrenal insufficiency, growth hormone deficiency, impaired response to hypoglycaemia,[14] and hypothalamic features such as weight change due to disruption of the satiety centres, increased somnolence, personality changes, and thermodysregulation are rarer features of neurosarcoidosis.[9]

We have reviewed the literature since 2002 for case reports and case series of neurosarcoidosis causing endocrine dysfunction. In total, we identified 64 cases of neurosarcoidosis affecting the hypothalamic–pituitary axis, the details of which are summarised in Table 1. We reviewed the cases with reported changes in hypothalamic–pituitary function in a similar fashion to the previous work done by our group.[12] A total of 155 cases were identified by the two reviews, which used similar selection methods. Comparing the findings with the former data,[12] diabetes insipidus is still the most common endocrine manifestation of neurosarcoidosis and presents in more than half of the reported cases. Amenorrhoea, hyperprolactinaemia, and hypogonadotropic hypogonadism are commonly seen, whereas other manifestations such as thyroid or adrenal dysfunction and impaired thermoregulation are much less frequent. This pattern of involvement is consistent with smaller retrospective studies.

DIAGNOSIS

Three criteria necessary to make a diagnosis of sarcoidosis were set down in 1999 by the American Thoracic Society, European Respiratory Society, and the World Association of Sarcoidosis and other Granulomatous Disorders.[15] Firstly, the clinical and radiological manifestation; secondly, the histological evidence of non-caseating granulomata; and thirdly, the absence of other conditions that have the potential to cause granulomatous lesions. As per the proposed diagnostic algorithm, the biopsy site is determined by the most easily accessible involved area, ideally peripheral nodes or cutaneous lesion.[6] If no superficial skin lesion, peripheral node, or conjunctival deposit is present or suitable for biopsy, ultrasound-guided endobronchial or transbronchial biopsy combined with bronchoalveolar lavage are suggested.[6] In some cases, the use of fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) can help to localise occult sites amenable to biopsy, in addition to its use in assessing disease activity.[6]

Histological confirmation of the diagnosis presents a challenge in the case of neurosarcoidosis because a biopsy is not always practical or sufficiently safe. Zajicek and colleagues proposed a classification system for the diagnosis of neurosarcoidosis, dividing it into 'definite', 'probable', and 'possible'.[16] The diagnosis of neurosarcoidosis is therefore often based on the presence of supporting evidence other than histological factors, such as cerebrospinal fluid or magnetic resonance imaging (MRI) findings.[6,16] A less invasive method for establishing a probable diagnosis may be preferred and a biopsy is rarely performed in the case of neurosarcoidosis, with cerebrospinal fluid analysis, MRI, electromyography, and assessment of the hypothalamic–pituitary axis representing the preferred diagnostic investigations.[6] However, nervous system biopsy may be pursued in cases requiring a definite diagnosis and in the absence of a systemic positive biopsy result.[17] Lumbar puncture commonly reveals elevated cerebrospinal fluid protein, a mild-to-moderate lymphocytic pleocytosis, and sometimes shows the presence of oligoclonal bands. Cerebrospinal fluid angiotensin-converting enzyme (ACE) levels have a high overall specificity, although they have poor sensitivity and can be elevated during infectious and malignant processes, which limits their usefulness.[17] While the combination of these findings is suggestive of neurosarcoidosis, lumbar puncture to obtain cerebrospinal fluid for analysis is most useful for excluding infections or malignancy, rather than confirming the presence of neurosarcoidosis.[17]

Other investigations include measurement of serum ACE levels and Kveim testing. However, despite low false-positive rates, Kveim testing remains predominantly a research tool for

logistical reasons and due to risk of infection transmission.[18] Serum ACE is elevated in a relatively small proportion of neurosarcoidosis cases in the absence of systemic involvement, and is therefore of limited use for its diagnosis.[17] Indeed, serum ACE levels have been described in the literature as not accurate enough for the purpose of diagnosis or monitoring sarcoidosis activity due to poor sensitivity and specificity.[2,6] One retrospective study of 24 patients with hypothalamic–pituitary neurosarcoidosis noted a normal serum ACE level in two-thirds of cases, compared with only 27% of controls represented by sarcoidosis patients without hypothalamic–pituitary manifestation.[18] It has been reported that chest X-ray looking for the presence of bihilar lymphadenopathy in cases of suspected neurosarcoidosis has a superior diagnostic yield to the measurement of serum ACE levels.[17] In one review of 30 cases of neurosarcoidosis published in 2009, 48% of patients had abnormal chest X-ray scans at presentation, with over half presenting with the classical finding of hilar adenopathy, and the same review found no consistent biochemical changes in the patients reviewed with specific reference to serum ACE and calcium.[19] Hypercalcaemia in sarcoidosis is related to hydroxylation of 1,25-dihydroxyvitamin D_3 by sarcoidal macrophages, and can be reinforced by sunlight exposure.[2] One study of 24 sarcoidosis patients with hypothalamic–pituitary involvement noted hypercalcaemia in only 12% of cases.[18] While the follow-up for patients with sarcoidosis includes monitoring of serum calcium on a 6-monthly-to-annual basis,[6] we do not currently find any evidence to suggest a specific correlation between hypercalcaemia and neurosarcoidosis.

MRI with gadolinium is currently the most commonly employed imaging modality and is superior to computed tomography for assessing hypothalamic involvement, which is typically reported as a cystic or enhancing mass, or thickening of the infundibulum with or without basilar leptomeningeal involvement.[19] While contrast-enhanced MRI is a sensitive method of diagnosing neurosarcoidosis, it is not specific and the differential diagnosis includes tuberculosis, lymphoma, Langerhans cell histiocytosis, and metastatic deposit.[19] It is important to note that MRI of the brain can be normal, especially in patients who have already received corticosteroid treatment.[20] In one case series of neurosarcoidosis, 11% of patients had a normal MRI scan of the brain.[1] Up to 50% of patients with hypothalamic–pituitary sarcoidosis can be radiologically normal.[17] In this scenario, 18F-FDG PET may also prove useful for visualising areas of neurological involvement not seen by MRI.[21]

MANAGEMENT

The natural history of sarcoidosis is variable. About 50% of patients experience spontaneous remission within 2 years and the incidence of relapse in this population group is quite rare.[6] There have been a number of attempts to devise a scoring system to guide which patients will require treatment and for how long. However, none of these scoring systems are internationally validated to date. A correlation between radiographic stage at diagnosis and likelihood of progressing to chronic sarcoidosis has been proposed. Broadly speaking, systemic therapy is warranted in cases with a risk of permanent damage to major organs or disabling systemic symptoms, which extends to cardiac, renal, or neurological involvement, symptomatic hypercalcaemia, or ocular involvement which fails to respond to topical therapy.[6]

The involvement of the CNS is certainly an indication for commencing treatment. Corticosteroids, namely prednisone, are the first line of therapy for severe sarcoidosis of any organ system.[6,11,22] In the case of neurosarcoidosis, higher initial doses of prednisone are warranted (1 mg/kg once daily).[6,22] Occasionally, intravenous high-dose pulse methylprednisolone can be administered.[22] Corticosteroid therapy should be maintained at high dose for 6-8 weeks before slowly tapering the dose as tolerated.[17] It is generally recommended that the treatment continues for a minimum of 12 months in order to reduce the risk of relapse, although this time course varies depending on the clinical evolution,[6] and sometimes it can be difficult to wean patients with neurosarcoidosis off corticosteroids completely.[17] In these cases, or cases of relapse occurring during weaning, second-line cytotoxic or biologic agents may be considered.[17] Relapse is more common in neurosarcoidosis than in cases where sarcoid affects other sites, with reports of relapse rates of 20-50%.[7]

A case series of 54 patients with neurosarcoidosis published in 2009 reported that over two-thirds required maintenance immunosuppression.[1] Methotrexate is currently the preferred second-line option for steroid-resistant sarcoidosis, or can be used as a steroid-sparing agent.[6] Tumour necrosis

factor alpha (TNFα) plays an important role in the formation of granulomata.[2] Data from retrospective studies have suggested that TNFα antagonists, in particular infliximab, may have an increasing role in the management of neurosarcoidosis, in addition to their role in the management of steroid-refractory pulmonary sarcoidosis. Their use is limited, however, by an increased risk of infection, in particular reactivation of tuberculosis, and an increased risk of malignancy.[6] A case series published in 2007 advocated using a combination of corticosteroids with a second immunomodulatory agent in cases deemed to be at high risk of permanent disability from the initiation of therapy.[22] Unfortunately, in the majority of cases of hypothalamic–pituitary sarcoidosis, the immunosuppressive therapy does not appear to restore the compromised endocrine functions or improve diabetes insipidus,[18] and therefore hormone replacement regimes often need to be implemented. Dopamine agonists can be required for the treatment of hyperprolactinaemia.[18]

CONCLUSION

Endocrine dysfunction is a relatively rare manifestation of neurosarcoidosis, which is an uncommon clinical condition. Altogether, a total of 155 cases of neurosarcoidosis with hypothalamic–pituitary involvement have been described in the literature. Diabetes insipidus, hyperprolactinaemia, hypogonadotropic hypogonadism, and amenorrhoea represent the most frequently observed endocrine manifestations of neurosarcoidosis. For the most part, the endocrine changes occur in previously undiagnosed cases of neurosarcoidosis, which highlights the importance of the inclusion of this condition in the differential diagnosis when investigating hypothalamic–pituitary dysfunction, especially if an inflammatory and/or infiltrative disorder is suspected. Although, in the majority of cases, treating hypothalamic–pituitary neurosarcoidosis does not result in endocrine functions returning to normal, the involvement of the CNS remains an indication for treatment and, therefore, a correct and timely diagnosis should be ensured.

REFERENCES

1. Pawate S et al. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM. 2009;102:449-60.

2. Iannuzzi M et al. Sarcoidosis. N Engl J Med. 2007;357:2153-65.

3. Hillerdal G et al. Sarcoidosis: epidemiology and prognosis. A 15-year European study. Am Rev Respir Dis. 1984;130:29-32.

4. Rybicki BA et al. Familial aggregation of sarcoidosis. A case-control etiological study of sarcoidosis (ACCESS). Am J Respir Crit Care Med. 2001;164:2085-91.

5. Perlman SE et al. Short-term and medium-term health effects of 9/11. Lancet. 2011;378:925-34.

6. Valeyre D et al. Sarcoidosis. Lancet. 2014;383(9923):1155-67.

7. Hebel R et al. Overview of neurosarcoidosis: recent advances. J Neurol. 2015;262:258-67.

8. Guoth MS et al. Neurosarcoidosis presenting as hypopituitarism and a cystic pituitary mass. Am J Med Sci. 1998;315:220-4.

9. Stuart CA et al. Hypothalamic insufficiency: the cause of hypopituitarism in sarcoidosis. Ann Int Med. 1978;88: 589-94.

10. Bleisch VR, Robbin SL. Sarcoid-like granulomata of the pituitary gland; a cause of pituitary insufficiency. AMA Arch Intern Med. 1952;89:877-92.

11. Porter N et al. Endocrine and reproductive manifestations of sarcoidosis. QJM. 2003;96:553-62.

12. Murialdo G, Tamagno G. Endocrine aspects of neurosarcoidosis. J Endocrinol Invest. 2002;25:650-62.

13. Ismail F et al. Hypothalamic-pituitary sarcoidosis. A case report. S Afr Med J. 1985;67:139-42.

14. Féry F et al. Impaired counterregulation of glucose in a patient with hypothalamic sarcoidosis. N Engl J Med. 1999;340: 852-6.

15. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Resp Crit Care Med. 1999;160:736-55.

16. Zajicek JP et al. Central nervous system sarcoidosis - diagnosis and management. QJM. 1999;92:103-17.

17. Hoyle JC et al. Neurosarcoidosis: clinical review of a disorder with challenging inpatient presentations and diagnostic considerations. Neurohospitalist. 2014;4:94-101.

18. Langrand C, Bihan H. Hypothalamo-pituitary sarcoidosis: a multicentre study of 24 patients. QJM. 2012;105(10):981-95.

19. Joseph FG, Scolding NJ. Neurosarcoidosis: a study of 30 new cases. J Neurol Neurosurg Psychiatry. 2009;80(3):297-304.

20. Stjepanović MI, Vucinic VM. Radiological presentation of neurosarcoidosis. Med Pregl. 2014;67(1-2): 24-7.

21. Bolat S et al. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in the diagnosis of neurosarcoidosis. J Neurol Sci. 2009;287(1-2):257-9.

22. Scott TF et al. Aggressive therapy for neurosarcoidosis: long-term follow-up of 48 treated patients. Arch Neurol. 2007;64(5):691-6.

23. Non L et al. Neurosarcoidosis-associated central diabetes insipidus masked by adrenal insufficiency. BMJ Case Rep. 2015; doi:10.1136/bcr-2014-206390

24. Gascon-Bayarri J, Mana J. Neurosarcoidosis: report of 30 cases and literature survey. Eur J Intern Med. 2011;22:e125-32.

25. Hwang JK et al. A case of possible

neurosarcoidosis presenting as intractable headache and panhypopituitarism. Case Rep Endocrinol. 2013;2013:816236.

26. Aghajanova L et al. Infiltrative neurosarcoidosis presenting as secondary amennorhoea: case report and review of the literature. Obset Gynecol Surv. 2013;68:482-8.

27. O'Reilly MW et al. Radiological remission and recovery of thirst appreciation after infliximab therapy in adipsic diabetes insipidus secondary to neurosarcoidosis. QJM. 2013. [Epub ahead of print].

28. Tanaka K et al. Partial improvement of anterior pituitary deficiency following steroid treatment in a patient with neurosarcoidosis accompanied by diabetes insipidus. Intern Med. 2012;51:2175-9.

29. Telford M et al. The resolution of pituitary mass in neurosarcoidosis. J Ark Med Soc. 2012;108:226-8.

30. Skowasch D et al. [Diabetes insipidus due to neurosarcoidosis]. Pneumologie. 2011;65:496-7.

31. Alam T, Thomas S. Diabetes insipidus secondary to sarcoidosis presenting as caseating granuloma. BMJ Case Rep. 2011;pii:bcr0120113702.

32. Prieto Tenriero AM, Díaz Guardiola P. [Central diabetes insipidus as the first manifestation of neurosarcoidosis]. Endocrinol Nutr. 2010;57:339-41.

33. Kimball MM et al. Neurosarcoidosis presenting as an isolated intrasellar mass: case report and review of the literature. Clin Neuropath. 2010;29:156-62.

34. de Jong PH et al. [Hyponatraemia as a clinical manifestation of hypopituitarism caused by neurosarcoidosis]. Ned Tijdschr Geneeskd. 2008;152:2575-9.

35. Shimaoka Y et al. [Case of neurosarcoidosis with panhypopituitarism]. Nihon Kokyuki Gakkai Zasshi. 2008;46:814-9.

36. Jomaa R et al. Isolated neurosarcoidosis revealed by diabetes insipidus, visual loss and diplopia in a child patient: a diagnostic problem. Clin Pediatr Endocrinol. 2009;18:51-4.

37. Ogawa Y et al. Neurosarcoidosis manifesting as tremor of the extremities and severe hypopituitarism: case report. Neurol Med Chir (Tokyo). 2008;48:314-7.

38. Miyoshi T et al. An elderly patient with sarcoidosis manifesting as panhypopituitarism with central diabetes insipidus. Endocr J. 2007;54:425-30.

39. Sugiyama K et al. [A case of sarcoidosis with diabetes insipidus]. Nihon Kokyuki Gakkai Zasshi. 2007;45:105-9.

40. Vilar H et al. [Pituitary macroadenoma associated pulmonary and cutaneous sarcoidosis--a clinical case]. Acta Med Port. 2005;18:309-13.

41. Tabuena RP et al. Diabetes insipidus from neurosarcoidosis: long-term follow-up for more than eight years. Intern Med. 2004;43:960-6.

42. Akhaddar A et al. Intrasellar neurosarcoidosis with suprasellar extension. Intern Med. 2011;50:945.

43. Pillai P et al. Solitary pituitary sarcoidosis with normal endocrine function: case report. J Neurosurg. 2008;108:591-4.

44. Bihan H et al. Sarcoidosis: clinical, hormonal and magnetic resonance imaging (MRI) manifestations of hypothalamic-pituitary disease in 9 patients and review of the literature. Medicine (Baltimore). 2007;86:259-68.

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