Neurosarcoidosis presenting with persistent vomiting

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ABSTRACT

يصيب مرض الساركوئيد أعضاء مختلفة من الجسم، وبالرغم من أن المرض يصيب الرئتين أكثر من غيرها من أعضاء الجسم إلا أن الكبد، و الجلد والغدد اللمفاوية والجهاز العصبي تصاب أيضاً بالمرض. تسمى إصابة الجهاز العصبي بساركوئيد الجهاز العصبي و أعراض المرض فى هذه الحالة تعتمد على أي جزء من الجهاز العصبي أصيب بالمرض. فى بعض الأحيان توجد مشكلة أو صعوبة فى تشخيص و معرفة المرض حيث يعتمد التشخيص على علم الأنسجة فى فحص العينة من المصاب. و للرنين المغناطيسي دور كبير فى اكتشاف إصابة المخ و النخاع الشوكي بالمرض كما أن فحص سائل النخاع الشوكي مهم جداً فى تحديد إصابة الجهاز العصبي CNS بالمرض. نعرض تقرير حالة مريض يبلغ من العمر 39 عام هندي الأصل ظهرت أعراض المرض لمدة 2 عام و أثبتت الفحوصات وجود خمول فى الغدة النخامية و مرض الساركوئيد فى المخ.

Sarcoidosis is a multi-system granulomatous disease of unknown etiology. It mainly affects the lungs more than other organs, but liver, skin, lymph nodes, and nervous system can be involved. The last is referred to as neurosarcoidosis with a wide range of clinical manifestations depending on the area of the nervous system involved. The differential diagnosis is wide, and the diagnosis, which is based on the histopathology, is sometimes difficult to confirm. Magnetic resonance imaging is the imaging modality of choice for establishing CNS involvement along with the clinical presentation. Cerebrospinal fluid analysis is indicative of the disease activity. We report a 39-year-old man of Indian origin who presented with persistent vomiting for over 2 years due to hypopituitarism and active neurosarcoidosis.

Neurosciences 2010; Vol. 15 (2): 117-121

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Received 2nd May 2009. Accepted 15th December 2009.

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Sarcoidosis is a multi-system disorder, which mainly involves the lungs. In its extra-thoracic forms it may involve the liver (50-80%), spleen (40-80%), eye (20-50%), extrathoracic lymph nodes (30%), skin (25%), nervous system (10%), heart (5%), kidney, muscle, and bone.[1] Although the etiology remains unknown, the documented ethnicity, histocompatibility associations, and familial case reports suggest an underlying genetic predisposition. Environmental and occupational exposures are also reported to be associated with sarcoidosis.[2] It is a rare disease and affects all races and ages, but is more common between 20-40 years of age. Sarcoidosis has a prevalence of 10-50 per 100,000 depending on the location, although in certain racial groups such as West Africans it can be substantially higher.[3] The symptoms caused by the disease depend on the organ or the system involved, and the presence of multiple non-caseating epithelioid granuloma is the pathological hallmark of sarcoidosis. Involvement of the CNS is referred to as neurosarcoidosis, which can affect different parts, and the clinical manifestations depend on the area of the nervous system involved. It may affect the brain and cranial nerves, meninges, spinal cord, and peripheral nerves. The overall frequency of neurologic involvement is reported between 5-10%.[4,5] We report a patient in whom the nervous system is affected after his pulmonary sarcoidosis was confirmed and the patient presented with persistent vomiting over 2 years, initially from pituitary hypofunction and then hydrocephalus. This particular case highlights dissimilarities in neurosarcoidosis and represents different issues related to clinical manifestations and treatment of this multi-system disorder.

Case Report. A 39-year-old man of Indian origin with no significant past medical history presented with persistent vomiting. He did not smoke and consumed alcohol socially. Initial investigations including gastroscopy did not reveal any cause. He later presented with tiredness, fatigue, and weight loss. At the time, he was found to have normocytic normochromic anemia and a high erythrocyte sedimentation rate. A summary of his full blood count and other blood tests are detailed in **Table 1**. Chest radiograph and high

Table 1 - Microcytic micro chromic anemia, lymphopenia, and raised ESR are seen in the patient's blood tests. These findings are consistent with sarcoidosis.

Blood tests	Results	Normal range
Hemoglobin	10.3 g/dl	12.5-16.5 g/dl
MCV	78.9 fl	80-100 fl
MCH	25.6 pg	26-33 pg
White cell count	6.9 x 10^9/l	4.0-11 x 10^9/l
Platelets	243 x 10^9/l	150-450 x 10^9/l
Neutrophils	5.4 x 10^9/l	2.5-7.5 x 10^9/l
Lymphocytes	0.9 x 10^9/l	1.5-4.5 x 10^9/l
Monocytes	0.4 x 10^9/l	0.2-0.8 x 10^9/l
Eosinophils	0.2 x 10^9/l	0.0-0.4 x 10^9/l
Basophils	0.0 x 10^9/l	0.0-0.1 x 10^9/l
ESR	38 mm/hr	1-12 mm/hr
C-Reactive protein	2 mg/l	1-6 mg/l
ACE	129 U/l	12-68 U/l
Calcium	2.09 mmol/l	2.00-2.65 mmol/l
Corrected calcium	2.27 mmol/l	

MCV - mean corpuscular volume, MCH - mean corpuscular hemoglobin, ESR - erythrocyte sedimentation rate, ACE - angiotensin converting enzyme

Table 2 - Patient's blood tests showing evidence of hypogonadism and hypothyroidism all secondary to anterior hypopituitarism.

Blood tests	Results	Normal range
TSH	0.01 mU/l	0.27-4.20 mU/l
Free T4	33.1 pmol/l	12.0-22.0 pmol/l
FSH	1.4 U/l	1.7-12.4 U/l (in male)
LH	0.6 U/l	1.7-8.6 U/l (in male)
Testosterone	<0.1 nmol/l	9.9-27.8 nmol/l (in male)
Growth Hormone	1.1 mIU/l	0.0-5.5 mIU/l
ACTH	10.9 ng/l	<46 ng/l
Cortisol	20 nmol/l (baseline)	>450 nmol/l
Cortisol- 30 minutes post synacthen injection	269 nmol/l	>450 nmol/l
Cortisol- 60 minutes post synacthen injection	334 nmol/l	>450 nmol/l
Prolactin	289 mU/L	98-456 mU/L

TSH - thyroid stimulating hormone, FSH - follicle stimulating hormone, LH - luteinizing hormone, ACTH - adrenocorticotropic hormone

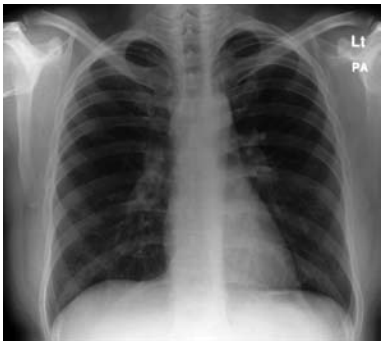

Figure 1 - Chest radiograph showing hilar shadow.

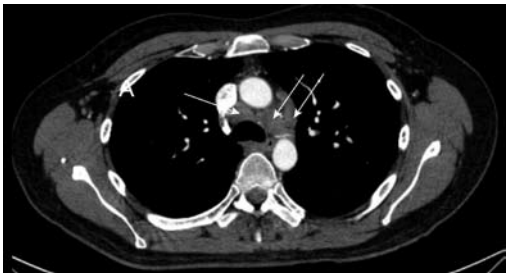

Figure 2 - Chest CT confirming mediastinal lymphadenopathies (arrows).

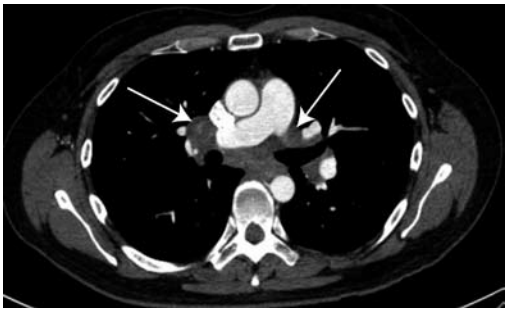

Figure 3 - Chest CT showing multiple hilar lymphadenopathies (arrows).

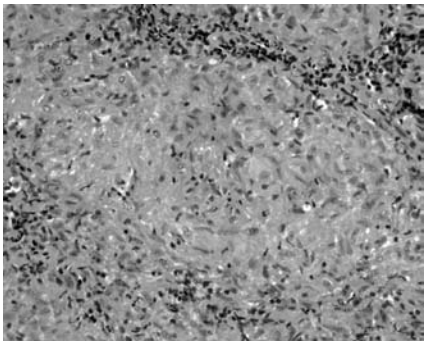

Figure 4 - Histopathology of lymph nodes shows noncaseating granuloma surrounded by epithelioid cells and inflammatory infiltrates, consisting of multinucleated giant cells, macrophages and lymphocytes, which are consistent with sarcoidosis (high power).

resolution CT scan of the chest revealed mediastinal and bilateral hilar lymphadenopathy (**Figures 1-3**). The histopathology following the biopsy of mediastinal lymph node, confirmed the diagnosis of sarcoidosis (**Figure 4**). In addition to persistent vomiting, he noticed cold intolerance, constipation, joint aches, and a husky voice. Endocrine tests confirmed hypothyroidism, hypogonadism, and hypoadrenalism secondary to anterior hypopituitarism (**Table 2**). He was commenced on hydrocortisone, thyroxine, and androgen replacement. A few months later, he developed headache and confusion. Neurological assessment revealed blurred disc margins and generalized hypo-reflexia; and he was somewhat slow in general, and confused. The MRI scan of his brain showed a normal pituitary gland, but confirmed the presence of hydrocephalus with fourth ventricular outflow obstruction (**Figure 5**). A lumbar puncture (LP) was performed and showed a CSF opening pressure

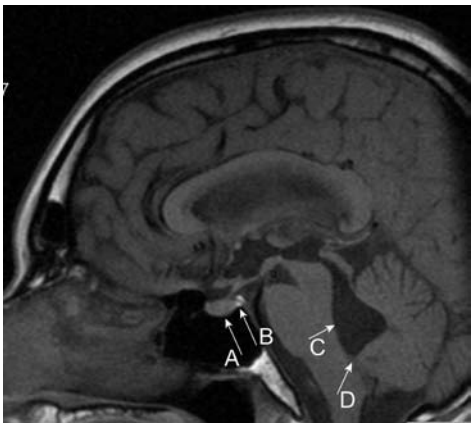

Figure 5 - Brain T1 weighted MRI shows normal anterior and posterior pituitary gland (arrow A and B) and the pituitary stalk. However, dilated fourth ventricle (arrow C) and ventricular outflow obstruction (arrow D) are evident in these images.

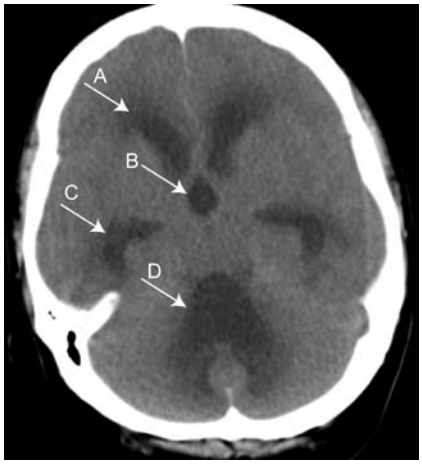

Figure 6 - Brain CT shows hydrocephalus evident by dilated horns (A), third ventricle (B), temporal horns (C) and fourth ventricles (D).

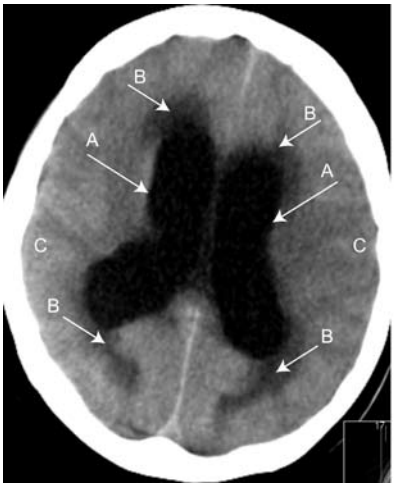

Figure 7 - Brain CT shows hydrocephalus evident by dilated ventricles (A), trans-ependymal edema (B), and sulcal effacement (C) confirming hydrocephalus.

Table 3 - The results of CSF analysis on 2 occasions compared with serum sample.

Analysis	First LP	Repeat LP	Normal range
CSF opening pressure	17 cmH_2O	36 cmH_2O	10 -22 cmH_2O
CSF protein	1.86 g/l	0.72 g/l	0.10-0.40 g/l
CSF white cell count	4.0 x 10^9/l	0.0 x 10^9	<5 x 10^9
CSF glucose	1.9 mmol/l	2.7 mmol/l	2.0-6.0 mmol/l †
Plasma glucose	6.1 mmol/l	6.3 mmol/l	2.0-6.0 mmol/l
CSF gram stain	Negative	Negative	
CSF culture	No growth	No growth	
CSF AFB	No AFB seen	No AFB seen	
CSF TB culture	No growth after 6 weeks		
CSF and serum electrophoresis	Oligoclonal bands in CSF only	Oligoclonal bands in CSF only	

LP - lumbar puncture, CSF - cerebrospinal fluid, AFB - acid fast bacillus, TB - tuberculosis, †as a general rule, CSF glucose is approximately two thirds of the serum glucose at a time

of 17 cmH_2O, glucose 1.9 mmol/l, compared with 6.1 mmol/l serum glucose, and protein 1.86 g/l, no white cells were seen (**Table 3**). He was then started on prednisolone 60 mg/day. Initial response to steroids was good. However, his symptoms recurred once steroids were tapered down to replacement doses. Repeat CT scan showed worsening hydrocephalus (**Figures 6 &** 7) and a repeat LP showed CSF pressure of 36 cmH_2O, CSF protein of 0.72 g/l, CSF white cell count of 4 x 10^9, CSF glucose of 2.7 mmol/l, compared with 6.3 mmol/l serum glucose (**Table 3**). The neurosurgeons were involved and a ventriculoperitoneal shunt was inserted. His symptoms improved after shunt insertion. On the follow up visit a few months after the shunt, he had no symptoms of vomiting, confusion or neurological signs whilst on replacement dose of steroids and standard hormone replacement therapy for hypopituitarism.

Discussion. The neurological manifestations of sarcoidosis depend on the area involved, and patients may present with a wide range of symptoms. The differential diagnosis of neurosarcoidosis is wide, and sometimes it is difficult to confirm the diagnosis. The clinical presentations of neurosarcoidosis include: cranial neuropathies, meningitis, cerebral sarcoid lesion, spinal cord disease, peripheral neuropathies and myopathies, hydrocephalus, and psychiatric manifestations. Intracranial sarcoidosis has a predilection for the basal leptomeninges commonly affecting the cranial nerves; cranial nerve involvement is the most common single symptom in approximately 50-75% of patients with neurosarcoidosis.[6] Cranial neuropathy, being unilateral in 69% and bilateral in 31% of cases with CNS involvement, may be caused by increased intracranial pressure, nerve granulomas or, most commonly, by

granulomatous basal meningitis. Facial palsy, which is of a lower motor neurone type and usually bilateral, and optic neuritis are the most common cranial neuropathies.[6] Meningeal involvement, occurring in 24%,[4] can manifest as leptomeningeal thickening, which may present with acute or chronic meningitis; headache is the prominent feature in these patients with or without neck stiffness. Cerebral sarcoidosis may occur in 3-26% with, or without meningeal involvement.[3] The clinical features of the cerebral granulomata are similar to those of any space-occupying intracranial mass. The brain stem and cerebellum may also be affected. The involvement of the hypothalamus and/or the pituitary gland by granulomata is a rare condition of acquired hypothalamic dysfunction and hypopituitarism. It may cause the symptoms of polydipsia, polyuria, diabetes insipidus, hypothalamic hypothyroidism, changes in appetite, somnolence, impaired temperature regulation, obesity, impotence, changes in menstrual period, galactorrhea and/or amenorrhea.[5] Involvement of the spinal cord is rare. Cord compression and myelitis are the main presenting features; rarely cauda equina symptoms occur. Peripheral nerve involvement, occurring in 24% of the patients, can include mononeuropathy, mononeuropathy multiplex or polyneuropathy in various forms of sensory and/or motor neuropathies.[7] Skeletal muscle disease, involved in 8%, is more commonly asymptomatic.[7] If epileptic seizures occur, a more severe progressive or relapsing clinical course is expected. Seizures most likely reflect the presence of an underlying intracranial mass lesion, vasculopathy, or hydrocephalus.[3] Hydrocephalus occurs in 6-17% of patients with neurosarcoidosis.[1,8] The non-communicating or obstructing type is known as the etiology of hydrocephalus due to fourth ventricular outflow obstruction, granulomatous lesions compressing the aqueduct, or granulomatous meningitis resulting in reduced absorption of CSF. Alternatively, infiltration of granuloma to the ependyma and choroid plexus may alter CSF dynamics resulting in the overproduction of CSF.[8,9] Hydrocephalus can present with lethargy, nausea, vomiting (sometimes explosive), blurred or double vision, amnesia, and cognitive difficulties.

Despite relatively straightforward diagnosis in patients with multi-system involvement and late presentation of typical neurological features, no neuro-diagnostic tests alone are pathognomonic for neurosarcoidosis. Hence, the confirmation of the disease can be challenging and sometimes it is a diagnosis of exclusion and response to a trial of treatment. A CT scan and MRI of the brain and spine are essential in assessment of CNS involvement, with MRI now the modality of choice due to the superiority of the images. In 65% of patients, there are changes on the MRI scan of the CNS, but without the evidence of the pathogen, these findings remain non-confirmatory and supportive only.[10] The MRI manifestations of the disease are non-specific, as neurosarcoidosis can affect any portion of the CNS. Non-enhancing periventricular white matter lesions and meningeal enhancement are the more common abnormalities.[10] Magnetic resonance imaging can be used to show subclinical disease and the response of pathologic lesions to treatment, but a normal MRI does not exclude the presence of neurosarcoidosis, especially in those with cranial neuropathies only or receiving corticosteroid treatment. Apart from blood tests, the laboratory investigation of neurosarcoidosis includes CSF analysis, which is normal in 30% of cases. They may otherwise reflect a non-specific pattern with high protein level (>0.5 g/L), lymphocyte pleocytosis (>5 cells/μL); one fifth have a low CSF glucose level.[11] It may demonstrate high levels of angiotensin converting enzyme, lysozyme and beta-2 microglobulin in the CSF; high immunoglobulin G, immunoglobulin index, and oligoclonal bands have been reported in the CSF.[11] Frequently, demonstration of sarcoidosis becomes possible only with tracing the systemic infiltration of the disease and obtaining pathological evidence from the organ tissue biopsy such as lymph nodes, lung, skin, liver, or conjunctiva following clinical and radiological assessments. Brain biopsy may be required to establish the diagnosis in individuals with isolated brain involvement.

Neurosarcoidosis has no known cure, and treatment alleviates symptoms that are severe or progressive. The disease can follow a monophasic, relapsing, or chronic course.[5] Although corticosteroids remain the mainstay of treatment, other immunosuppressive and immunomodulatory agents can be used in the multi-modality therapy of sarcoidosis.[12] Although spontaneous remission has been observed, long-term therapy often is required. In cases of exacerbation, intravenous pulsed methylprednisolone followed by oral taper may be necessary. Relapses may respond poorly, however, requiring chronic steroid therapy.[5] In cases of pituitary dysfunction, hormone replacement therapy is required. In a patient with symptomatic hydrocephalus, a ventricular drain can be lifesaving. Due to the wide range of clinical picture, types of neurosarcoidosis, combination of systemic and nervous system involvement as well as variety of treatment methods, clinical management and treatment strategies for hydrocephalus cannot be easily formulated from review of the literature. The possible options include: early shunting at the diagnosis of hydrocephalus, steroid therapy with shunting if the ventricles fail to show reduction in size radiologically, or the patient fails to improve clinically, and medical therapy without a shunt using very high doses of corticosteroids for a prolonged period.

In conclusion, our case represents dissimilarities in neurosarcoidosis and another example of issues related to treatment of these cases. This patient had evidence

of epithelioid granuloma in the lymph nodes; he later presented with pituitary hypofunction followed by hydrocephalus. In this case, we think that infiltration of sarcoidosis in the brain causing hypopituitarism and obstructing hydrocephalus might have caused the vomiting. This is why all investigations by the gastroenterologists were normal whilst the patient suffered from vomiting for over 2 years. His persistent vomiting marginally improved once steroids initiated for treatment of hypopituitarism and hydrocephalus, but recurred more severely with steroid reduction dose. Whether his persistent vomiting was purely related to the infiltration of sarcoidosis in the pituitary gland, or an additional mild hydrocephalus at the earlier stage of the disease exacerbated the central cause of vomiting, remains unclear. Although his symptoms improved with steroids, his vomiting did not resolve completely until his treatment was combined with the shunt insertion.

Acknowledgment. *We acknowledge the help of Dr. Hilten Mehta, Consultant Neuroradiologist at the University Hospitals Coventry and Warwickshire, who kindly reviewed all the radiology images. We also acknowledge the help from Dr. David Rowlands, Consultant Histopathologist in New Cross Hospital. Thanks to Jason McAllister, Geographic Designer, and Simon Glazebrook from the Medical Illustration Department.*

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