An Unusual Presentation of Neurosarcoidosis in an 11-Year-Old Boy

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Sarcoidosis is a chronic, multisystem, granulomatous disease which typically develops between the ages of 20 and 40 years[1]. Neurosarcoidosis occurs in only 5-15% of adults with sarcoidosis, and is seldom reported in children[2-5]. Of the cases described in the literature, children were found more likely to present with seizures, and less commonly space-occupying lesions[6]. The tumefactive brain lesions are difficult to distinguish from the tumefactive demyelinating lesions of multiple sclerosis, from brain neoplasms, acute disseminated encephalo-myelitis (ADEM), or from parasitic foci[7,8]. We report the clinical and radiographic features of an 11-year-old boy with biopsy-proven neurosarcoidosis in order to highlight key features that distinguish neurosarcoidosis from tumefactive demyelination.

Case report

A previously healthy 11-year-old male presented in status epilepticus. The seizure started with an altered level of awareness and focal twitching of the right side of his face. The ictus lasted 45 minutes and responded to intravenous administration of lorazepam and phenytoin.

Investigations revealed a peripheral white blood cell count of 28.2 (4.5-13 $X10^9$/L), and normal hemoglobin and platelets. Electrolytes, glucose, renal and liver function, and coagulation parameters were normal. A toxicology screen was negative. Bacterial, viral, and fungal cultures were negative in blood. Cerebrospinal fluid (CSF) analyses revealed 20 X 10^6/L leucocytes (90% lymphocytes), normal glucose and protein, no malignant cells, and negative bacterial and viral cultures. Polymerase chain reactivity for Herpes viruses was negative. Oligoclonal banding was detected, but as serum electrophoresis was not performed, this finding could not be evaluated. Serum anti-nuclear factor was negative.

Computerized tomography of the head showed a focal, non-enhancing mass of the left frontal lobe with no evidence of mass effect or hydrocephalus. As shown in Figure 1, magnetic resonance imaging (MRI) demonstrated a region of increased T2/FLAIR signal involving the white matter of the left frontal lobe with leptomeningeal enhancement after gadolinium contrast administration. Magnetic resonance spectroscopy (MRS) demonstrated a lactate peak with normal choline and N-acetylaspartate. A second MRI obtained one week later showed improvement, with normalization of mass spectroscopy.

Following recovery from the post-ictal period, the child was noted to have a normal neurological and general physical examination, including normal cognition and no focal deficits. Given the normal examination, and repeat MRI showing improvement in the lesion appearance, brain biopsy was deferred. Phenytoin was weaned and carbamazepine was substituted as the primary anti-epileptic drug prior to discharge from hospital in stable condition.

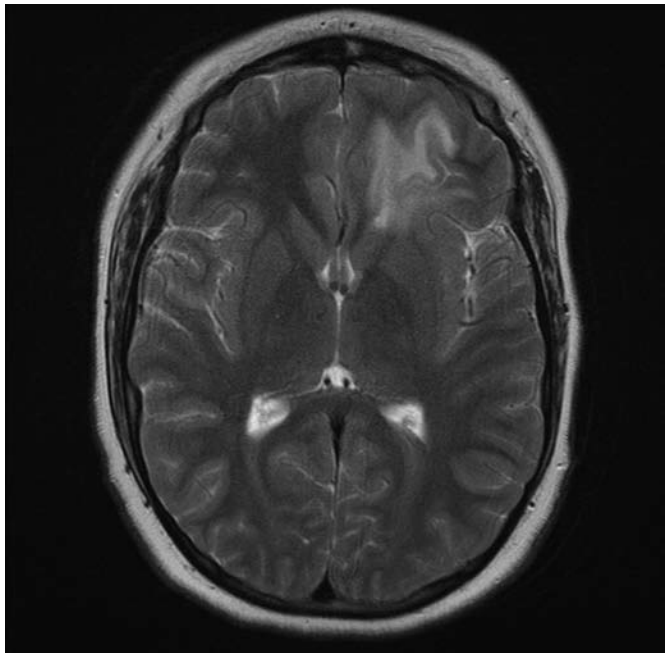

Figure 1: *MR image of the head showing high T2/FLAIR signal involving the inferior left frontal lobe, predominantly within the white matter.*

The boy's past medical history was unremarkable. He was a good student with appropriate social skills. Family history was unremarkable. There was no history of recent travel.

The patient was enrolled in the Prospective Study of the Clinical Epidemiology, Pathobiology and Neuroimaging Features of Canadian Children with Clinically Isolated Demyelinating Syndromes[9], which required regular follow-up

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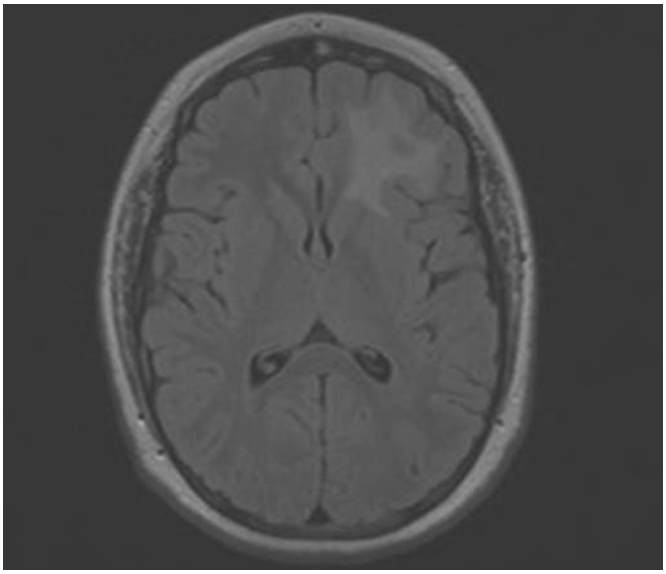

Figure 2: *MR image of the head showing re-occurrence of extensive periventricular and subcortical white matter T2 signal abnormality within the inferior left frontal lobe.*

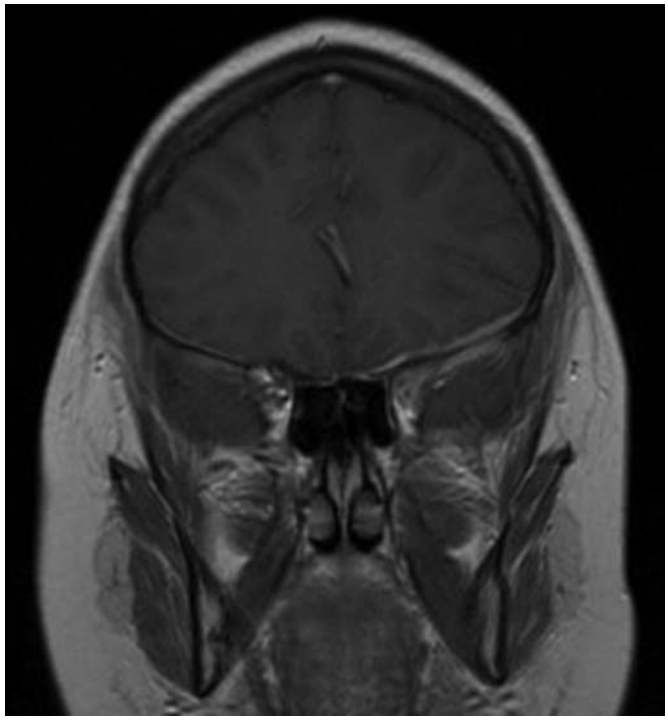

Figure 3: *MR image of the head showing complete resolution of parenchymal signal abnormality within the left frontal lobe, with a new dural thickening and enhancement involving the inferior left frontal skull base. There is also a proptotic left globe, with new left orbital enhancing inflammatory change, in continuity with the intracranial left frontal dural disease.*

MRI scans. At three and seven months of follow-up, MRI scans were normal. He complained intermittently of headaches and was started on propranolol. The MRI scan at twelve months showed re-occurrence of the left frontal white matter lesion without clinical symptoms (Figure 2). At his 15-month visit the MRI lesion had again resolved.

Seventeen months after his initial presentation, the patient complained of worsening headaches. He had insidiously developed left ptosis with diplopia on extreme leftward gaze. An MRI done at this time showed continued resolution of frontal lobe abnormalities, but a new dural thickening and enhancement of the inferior left frontal skull base and left orbit (Figure 3). The ptosis resolved, but he subsequently developed an inflamed conjunctival nodule in the left eye (Figure 4). A conjunctival biopsy revealed non-necrotizing granulomatous inflammation and macrophage infiltration, consistent with the diagnosis of sarcoidosis (Figure 5). A second attempt at a CSF sample was unsuccessful. Serum angiotensin converting enzyme (ACE) was normal and a chest radiograph did not show any granulomatous lesions.

The patient was started on systemic and topical ophthalmic steroids which led to resolution of his eye findings. There has been no further clinical symptomatology. A recent MRI scan, performed twenty months from initial presentation, showed resolved meningeal enhancement.

Discussion

Sarcoidosis is a multisystem granulomatous disease of unknown etiology without an inciting organism identified. Diagnosis requires biopsy confirmation of noncaseating granulomatous inflammation, and histological evidence of epithelioid differentiation of macrophages in the center of noncaseating non-infectious lesions with surrounding lymphocytes[10]. Meningeal and conjunctival biopsies, the latter often performed blindly, are the most common means of confirming a histological diagnosis[11].

Involvement of the central nervous system occurs in only 5-15% of cases[3,4]. Isolated neurosarcoidosis is rare: Spencer et al[12] found 10-17% of patients had isolated CNS involvement, while others detected systemic sarcoidosis in more than 95% of cases of sarcoidosis initially presenting with neurological symptoms[10]. Manifestations of neurosarcoidosis include cranial nerve palsies, meningeal involvement, brain lesions, seizures, hypothalamic and endocrine dysfunction, and peripheral neuropathy[13]. Unlike adults, who characteristically present with a seventh cranial nerve palsy, prepubertal children are more likely to present with seizures and are perhaps more likely to have a space-occupying lesion[6]. Twenty nine cases of childhood neurosarcoidosis have been reported, with 38% (11/29) presenting with seizures and 24% (7/29) with mass lesions or focal edema on imaging. Of the seven that presented with mass lesions or focal edema on imaging, three patients presented with seizures[6]. Neurosarcoidosis may remit spontaneously[7].

Tumefactive demyelinating lesions occur as large solitary mass lesions or as large focal areas of demyelination of white matter surrounded by ring enhancement, with little mass effect[14]. These demyelinating plaques may occur in patients presenting with the first attack of multiple sclerosis, in children or adults

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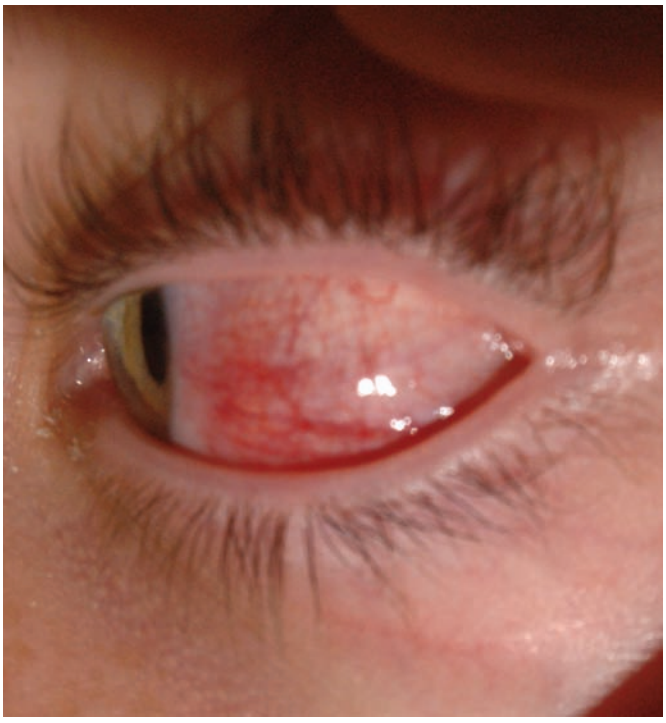

Figure 4: *Clinical photograph of patient showing area of inflammation in left conjunctiva.*

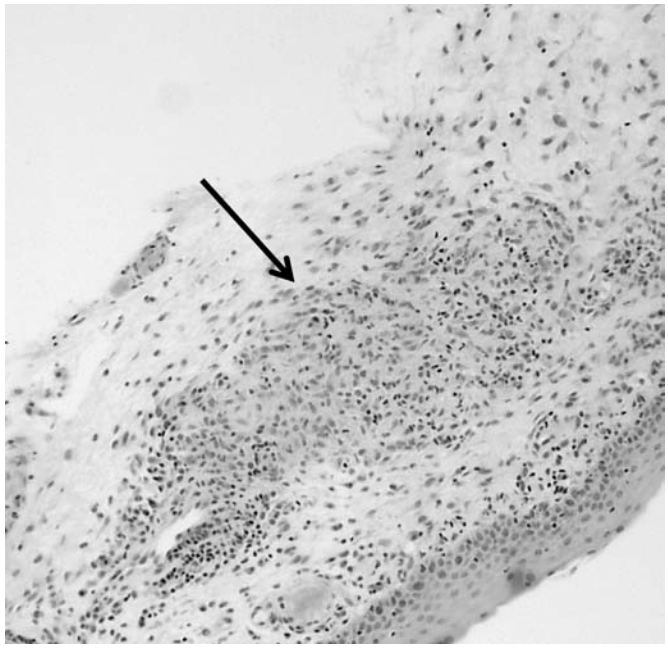

Figure 5: *Conjunctival biopsy of the left eye showing a non-necrotizing granuloma in the substantia propria (black arrow). The histiocytes do not show the characteristic nuclear changes of Langerhans type histiocytes. Vasculitic changes are not seen. Stains for acid fat bacilli and fungal organisms were negative (not shown).*

with acute disseminated encephalomyelitis, and have recently been documented in patients with neuromyelitis optica[15]. Tumefactive demyelinating lesions must be distinguished from brain neoplasms, parasitic foci, or granulomatous diseases[8]. Neuroimaging features that favour demyelination on CT scan include the tumefactive demyelinating lesion appearing as a plaque surrounded by an area of decreased attenuation precontrast, with a patchy rim of enhancement after contrast. Magnetic resonance imaging features that favour demyelination include lesion hyperintensity, occasionally with a heterogeneous appearance, and associated with other demyelinating lesions, particularly if these lesions are located in the periventricular white matter[16]. While demyelinating lesions may enhance on T2-weighted MRI, meningeal enhancement is not a feature of demyelination[17]. On MRS, acute demyelinating plaques are similar to low grade gliomas, with a reduction in *N*-acetylaspartate, an increase in choline, and a variable increase in lipid and an elevation of the lactate peak. These features are consistent with neuronal loss, axonal membrane breakdown, and possibly ischemia secondary to acute inflammation[18]. In contrast, MRI features of neurosarcoidosis include diffuse leptomeningeal thickening and enhancement, focal dural or brain parenchymal enhancement with or without mass effect, periventricular radial vascular enhancement, and enhancement, enlargement, or atrophy of cranial nerves or the pituitary stalk[11]. The brain lesions themselves are often difficult to distinguish from the tumefactive demyelinating lesions of Multiple sclerosis[7].

Laboratory studies consistent with neurosarcoidosis include an elevated spinal fluid protein and a mild pleocytosis with a predominant lymphocytosis[3]. However, CSF abnormalities are not specific to neurosarcoidosis and in more than a third of cases, patients have normal CSF[2]. Eighty percent of children have elevated serum ACE levels during active sarcoid, however normal ACE levels do not exclude the diagnosis of sarcoidosis, especially in the absence of pulmonary disease[1]. In a retrospective review of the Mayo Clinic record system, oligoclonal banding was present in the spinal fluid of 18% of patients[11].

In the present case, the CT scan appearance of vasogenic edema suggested a primary brain neoplasm; contrast injection did not show definite pathologically enhancing mass or peripheral enhancement, which made this diagnosis less likely. Initial T2-weighted MRI studies showed a focal high signal in the left frontal lobe with leptomeningeal enhancement. The MRI findings were initially suggestive of an infective process, but there was no laboratory evidence to support infection. The rapid spontaneous reduction in the size of the lesion also argued against infection or tumour, and thus demyelination was considered more probable. Enrolment in the pediatric clinical demyelinating disease study involved regular clinical and radiological studies[9]. This led to the discovery of clinically asymptomatic imaging changes. When clinical evidence of ptosis and diplopia occurred, MRI revealed orbital disease and dural enhancement, prompting consideration of granulomatous processes such as eosinophilic granuloma or sarcoidosis.

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As there have been no controlled studies of the efficacy of treatment for neurosarcoidosis, oral corticosteroids, 40-80mg/day remain the standard of care[3]. Anecdotal support exists for the use of azathioprine, methotrexate, cyclosporine, cyclophosphamide, hydroxychloroquine, tacrolimus, and mycophenolate mofetil[19]. More recently, tumour necrosis factor (TNF-alpha) blockers, including thalidomide, infliximab and etanercept have also been tried[11]. Neurosurgical decompression is an option for large mass lesions or hydrocephalus[5].

Conclusion

We highlight the clinical and radiographical features of neurosarcoidosis, a very rare disease in childhood, by describing the case of an 11-year-old boy who presented in status epilepticus with a presumed demyelinating lesion of the left frontal lobe. The lesion resolved spontaneously but then recurred without correlation of clinical symptoms. With the development of ocular findings 17 months after his initial presentation, a conjunctival biopsy confirmed the diagnosis of sarcoidosis. This unusual case demonstrates that neurosarcoidosis should be included on the differential of tumefactive demyelinating lesions.

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References

1. Kone-Paut I, Portas M, Wechssler B, Girard N, Raybaud C. The pitfall of silent neurosarcoidosis. Pediatr Neurol. 1999;20:215-8.
2. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, et al. Central nervous system sarcoidosis-diagnosis and management. Q J Med. 1999;92:103-17.
3. Hoitsma E, Faber CG, Drent M, Sharma OP. Neurosarcoidosis: a clinical dilemma. Lancet Neurol. 2004;3(7):397-407.
4. Gullapalli D, Phillips LH II. Neurological manifestations of sarcoidosis. Neurol Clin. 2002;20:59-83.
5. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med. 1997;336:1224-34.
6. Bauman RJ, RobertsonWC Jr. Neurosarcoid presents differently in children than in adults. Pediatrics. 2003;112:e480-6.
7. Hahn JS, Pohl D, Rensel M, Rao S. Differential diagnosis and evaluation in pediatric multiple sclerosis. Neurol. 1997;68(16): S13-22.
8. McAdam LC, Blaser SI, Banwell BL. Pediatric tumefactive demyelination: case series and review of the literature. Pediatr Neurol. 2002;26:18-25.
9. Ghassemi R, Antel SB, Naravan S, Franci SJ, Bar-Or A, Sadovnick AD, et al. Canadian pediatric demyelinating disease. Lesion distribution in children with clinically isolated syndromes. Ann Neurol. 2008 Mar;63(3):401-5.
10. Nowak DA, Widenka DC. Neurosarcoidosis: a review of its intracranial manifestations. J Neurol. 2001;248:363-72.
11. Aksamit A. Continuum, neurologic manifestations of systemic disease. AAN. Feb 2008;14(1):181-96.
12. Spencer TS, Campellone JV, Maldonado I, Huang N, Usmani Q, Reginato AJ. Clinical and magnetic resonance imaging manifestations of neurosarcoidosis. Semin Arthritis Rheum. 2005;34(4):649-61.
13. Stern BJ. Neurological complications of sarcoidosis. Curr Opin Neurol. 2005;17(3):311-6.
14. Given CA, Stevens BS, Lee, C. The MRI appearance of tumefactive demyelinating lesions. AJR Am J Roentgenol. 2004;182(1): 195-9.
15. Pittock S, Lennon V, Krecke K, Wingerchuk D, Lucchinetti C, Weinshenker B. Brain abnormalities in neuromyelitis optica. Arch Neurol. 2006;63(3):390-6.
16. Barkovich JA. Intracranial, orbital, and neck masses of childhood. In: Pediatric Neuroimaging. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 513.
17. Banwell B, Shroff M, Ness JM, Jefery D, Schwid S, Weinstock-Guttman G. International Pediatric MS Study Group. MRI features of pediatric multiple sclerosis. Neurology. 2007;17;68 (16 Suppl 2):S46-53.
18. Puri V, Chaudhry N, Gulati P, Tatke M, Singh D. Recurrent demyelination in a child. J Clin Neurosci. 2005;12(4):495-500.
19. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological neurosarcoidosis. Arch Intern Med. 1997;157(16):1864-8.