High-Signal Periventricular Lesions in Patients with Sarcoidosis: Neurosarcoidosis or Multiple Sclerosis?

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The vast majority of periventricular abnormalities visualized with MR imaging in patients less than 50 years old represents multiple sclerosis (MS) lesions. There are many other causes of periventricular lesions, most of which can be differentiated from MS on the basis of history and physical or MR findings. Five cases of biopsy- or Kveim test-proved sarcoidosis with MR findings consistent with MS are reported. Each of these patients, diagnosed as having sarcoidosis, had symptoms identical to those seen in MS. Although these patients have not had histologic characterization of the intraparenchymal lesions seen on MR, they illustrate the difficulty of differentiating sarcoidosis with CNS involvement from MS in some patients on the basis of clinical, radiographic, electrodagnostic, or CSF testing.

This series contributes to a growing body of evidence that neurosarcoidosis probably should be included in the differential diagnosis of isolated periventricular lesions in patients less than 50 years old.

Of the tests used to confirm the clinical diagnosis of multiple sclerosis (MS), MR imaging is the most sensitive. MR findings have been reported in 85–96% of patients with MS [1–3]. The most characteristic MR findings in MS are periventricular lesions with increased signal with spin-density and T2-weighted images. The CSF is abnormal in 68–90% [2–6]. Evoked potentials are abnormal in 90% [2–4, 7] and CT is abnormal in 25–63% [2, 5, 7, 8] of patients with MS.

Although MR abnormalities of the CNS have been reported in patients with sarcoidosis, the emphasis has been on basilar or superficial cortical lesions [9]. Recent reports have alluded to the MR findings of periventricular lesions in neurosarcoidosis; these have been mostly associated with other CNS abnormalities such as hydrocephalus and less commonly found as isolated lesions [9–12]. We report five patients with clinical and biopsy- or Kveim test-proved sarcoidosis with CNS symptoms in whom isolated periventricular with occasional subcortical lesions were the only findings noted by MR. The clinical and MR findings mimic those associated with MS and illustrate the difficulty of differentiating MS and sarcoidosis in some patients.

Materials and Methods

Five patients with ophthalmologic and CNS complaints, previously diagnosed with biopsy-proved sarcoidosis, were evaluated by cranial MR. The patients were 32–50 years old. MR was performed in two of the five patients as part of a multicenter cooperative study investigating CNS disorders and granulomatous uveitis [13]. The remaining three patients subsequently came to our attention because they also had multifocal neurologic deficits consistent with MS, yet had biopsy-proved sarcoidosis. T1-, spin-density-, and T2-weighted MR techniques were used. CT examinations, performed 1 day to 10 years before MR in four of the five patients, were reported as normal.
Results

Periventricular lesions were seen on spin-density- and T2-weighted images in all five cases. Subcortical lesions were also present in cases 1 and 3. Of three patients with hypertension (cases 1, 3, and 5), only one (case 3) had subcortical lesions. The pattern of abnormality in all cases was assessed prospectively as consistent with MS. No other abnormalities were noted on MR.

Case Reports

Case 1

A 37-year-old woman was seen at age 33 with sudden loss of vision in the left eye. Steroid therapy was given for optic neuritis and her vision returned after 1 week. At age 35, a chest film obtained for the evaluation of pain and swelling in both ankles showed bilateral hilar adenopathy. Mediastinal biopsy revealed noncaseating granuloma consistent with sarcoid disease. The patient was treated with steroids. One year later she developed double vision when looking to the left. A cranial CT examination was normal. Her sedimentation rate was elevated to 32 mm/hr. One and one-half years later, the patient had numbness of the right side of the face and intermittent numbness and tingling of the arms, legs, and hands. The neurologic examination was normal. Three months later, the patient had pain followed by blurred vision of the right eye. She received a triamcinolone acetonide injection for optic neuritis of the right eye with subsequent improvement in visual acuity. The neuroophthalmologic examination revealed macro-square-wave jerks consistent with disease of the cerebellar system. A subtle right internuclear ophthalmoplegia was also present.

Because of the history of bilateral optic neuritis and internuclear ophthalmoplegia, a diagnosis of MS was considered and the patient was referred for MR examination. The MR study shown in Figure 1 demonstrates multiple focal areas of increased signal in the periventricular white matter and centrum semiovale bilaterally on spin-density- and T2-weighted images. An additional lesion was noted in the right temporal periventricular white matter. On the basis of the clinical and MR findings, the diagnosis in this patient is of both MS and sarcoidosis.

Case 2

A 43-year-old woman with a history of hypertension and asthma was seen for evaluation of fever, chills, headache, malaise, generalized arthralgia, and myalgia. No definitive diagnosis was made at initial workup.

Two months later, the patient developed right facial weakness and a "film over both eyes." Sarcoidosis was diagnosed on the basis of histopathologic findings on mediastinal biopsy, which was performed after a chest film showed bilateral hilar adenopathy. The patient had a right peripheral seventh nerve paralysis and papilledema. CSF study showed protein elevated at 97 mg/dl (normal, 15–45 mg/dl). Gamma globulin constituted 23.5% of CSF protein. Visual acuity was 20/20 in both eyes. Small, white, keratic precipitates and mild cellular reactions in the anterior chambers and vitreous of both eyes were found on slit-lamp examination. There was bilateral inferior retinal vascular sheathing. The fever and ocular inflammation responded to steroid therapy. Sarcoid ophthalmopathy with probable meningeal involvement was diagnosed. The cranial CT examination was normal. Seven years later, the patient had an MR examination for evaluation of recurrent CNS symptoms. This examination showed closely periventricular lesions (Fig. 2).

Case 3

A 35-year-old woman with hypertension, weight loss, myalgia, fever, pain, numbness, and weakness of the right arm and left lower extremity had a mediastinal biopsy diagnostic of sarcoidosis. One year later, a biopsy of scalp nodules was also consistent with sarcoidosis. Subsequently, the patient had pain and numbness of the right arm and shortly afterward in the right leg, which gradually resolved. MR examination revealed multiple areas of increased signal on spin-density- and T2-weighted images in the subcortical and periventricular white matter (Fig. 3). Two years later, the patient had photophobia in the right eye. Cranial CT examination and CSF immunoglobulins were normal.

Case 4

A 24-year-old woman with fatigue was found to have bilateral hilar adenopathy and pulmonary infiltrates on chest film. A cervical lymph-node biopsy confirmed the presence of sarcoidosis, which was
treated with steroids. The disease was quiescent except during pregnancies 5 and 7 years later, during which she had recurrence of the infiltrates.

Bilateral uveitis was first noted 7 years after her original presentation. Her visual acuity was 20/20 in both eyes. Granulomatous-appearing keratic precipitates and an anterior chamber cellular reaction were noted on slit-lamp examination. Subsequently, the patient had recurrent bouts of granulomatous iridocyclitis involving both eyes that were responsive to topical corticosteroid drops. Eight years after her original presentation, MR examination revealed several periventricular lesions (Fig. 4).

Case 5

A 46-year-old woman had been diagnosed as having MS 14 years earlier, which was manifested by ascending numbness of the lower extremities and was treated with intrathecal steroids. She also had a 5-year history of hypertension and a previous diagnosis of sarcoidosis, made at age 20 by the finding of hilar adenopathy on chest radiography and a positive Kveim test. During the course of her illness, she had experienced peripheral numbness and tingling sensations, intermittent gait ataxia, and fatigue. She also experienced a right retrobulbar neuritis and associated central scotoma, and color desaturation in the left eye. A recent evaluation indicated a mild decrease in pinprick sensation over the torso to T7 and left lateral thigh, abnormal visual-evoked potential on the right, and an otherwise normal neurologic examination. MR examination showed multiple periventricular abnormalities characteristic of MS (Fig. 5). Family history revealed MS in one cousin and sarcoidosis in another.

Discussion

Cranial MR frequently demonstrates periventricular lesions that show increased signal intensity on spin-density- and T2-weighted images and occasionally show decreased signal intensity on T1-weighted images. In the vast majority of patients under the age of 50 years, these abnormalities represent MS lesions. However, these areas of abnormal signal in the periventricular region are not specific for MS and have also been observed in Sjögren syndrome [14], systemic lupus erythematosus, multifocal leukoencephalopathy, AIDS, encephalitis, other brain infections [15], changes after radiation treatment of the brain, subependymal tumor [16], hydrocephalus [17], pseudotumor cerebri [18], vitamin B12 deficiency [3], lymphomatoid granulomatosis (Smith AS, unpublished data), multiple cerebral infarcts (usually in patients over 50 years of age) [19, 20], andBinswanger disease.

In our series, five patients with biopsy- or Kveim test-proven sarcoidosis had periventricular lesions on MR and multifocal neurologic disease. None of our patients as studied by MR had the more common intracranial abnormalities of sarcoidosis, that is, granulomatous involvement of the leptomeninges; superficial parenchymal invasions; and, less frequently, deep parenchymal lesions and rare spinal cord involvement [21–23]. Periventricular lesions have been noted within other series of neurosarcoidosis [9–12, 24], but it should be emphasized that this can be an exclusive CNS finding and therefore is difficult to distinguish from MS.

Although the cause of these periventricular lesions in sarcoidosis remains uncertain, several possibilities exist. The lesions may be attributed to a true vasculitis, which, although rare, has been documented in neurosarcoidosis. Vasculitis has been demonstrated to be a granulomatous perivasculare infiltration around arteries and veins [22, 25]. Infiltration of the leptomeningeal disease through Virchow-Robin spaces is the suspected mechanism of the arteritis termed meningovascular sarcoidosis [26, 27]. The latter can result in “subclinical” infarcts and transient ischemic attacks. In addition, nongranulomatous inflammatory changes, which could result in periventricular lesions, are frequently seen in perivascular spaces in neurosarcoidosis [27]. A less likely explanation is that the periventricular lesions result from a progressive multifocal leukoencephalopathy; seven such cases have been reported [28]. Three of the five patients reported in our study had hypertension, which may lead to premature vascular deterioration and potentially manifest as white-matter lesions on MR. In our experience, white-matter lesions are not common under

Fig. 2.—Case 2: 50-year-old hypertensive woman with systemic sarcoidosis, sarcoid ophthalmpathy, cranial-nerve palsies, and abnormal CEE studies. MR images, 2000/20 (TR/TE), show closely periventricular lesions at lower (A) and higher (B) ventricular levels.
the age of 50, even in hypertensive patients. However, when present, subcortical rather than periventricular lesions are the predominant pattern in hypertensive individuals. Therefore, the cause of the periventricular lesions in our cases may be attributed to the following possibilities: (1) the presence of MS in patients who have sarcoidosis also, (2) intracranial manifestations of sarcoidosis resulting in symptoms similar to demyelinating disease, or (3) a subtype of demyelinating disease related to sarcoid.

MS and neurosarcoidosis can be difficult to differentiate clinically, since they share an undulant course and diverse neurologic findings. Among the shared symptoms of MS and sarcoidosis are optic-nerve abnormalities, visual disturbances, gait ataxia, and incoordination. Although CNS sarcoid is clinically present in only 1–5% of patients with systemic disease, clinically silent CNS sarcoidosis has been described in 66% of patients with known systemic sarcoidosis [29, 30]. CNS symptoms can be the presenting complaint of the systemic disease [26, 31], and the rare occurrence of CNS sarcoidosis without systemic manifestations has been documented [27, 32]. The diagnosis of sarcoidosis is especially difficult in those patients whose only manifestations are
in the CNS; estimations of misdiagnosis range from 33% to 64% [29] to 80% [30]. In patients with CNS sarcoid, Wiedeholt and Siekert [31] found that 28 patients had CNS symptoms and their systemic disease was found secondarily. Symptoms and signs include diabetes insipidus, seizures, cranial-nerve involvement, corticospinal tract signs, cerebellar deficits, and myopathy. Delaney [26] described 23 patients with CNS sarcoid who had a wide range of CNS symptoms, 15 of whom had neurologic dysfunction as the presenting complaint; in seven of the 15 the neurologic deficit was the only symptom. Both MS and sarcoidosis may produce elevated spinal fluid protein, immunoglobulin G/albumin ratios, and oligoclonal bands [33].

The problem of distinguishing MS from sarcoidosis is especially difficult in those patients with ocular disease. Both MS and sarcoidosis may present with ocular findings that are characterized by an exacerbating and remitting course. The most frequent ocular manifestation of sarcoidosis is uveitis [34]. Often, this ocular inflammation is confined to the anterior segment of the eye and is designated iridocyclitis. While less common, anterior segment inflammation has been associated with MS [35].

Retinal perivasculitis, characterized clinically by perivascular sheathing and often involving the peripheral retinal vasculature, has been reported in sarcoidosis [36] and MS [37]. Retrolubar optic neuropathy occurs in both MS [38] and sarcoidosis [39, 40], although it is much more common in MS.

Sjogren syndrome with CNS involvement can also be clinically and radiologically difficult to differentiate from MS. CNS involvement occurs in 5–20% [41, 42] of patients with this disease. The multifocal neurologic findings related to brain and spinal cord involvement—evoked responses, CSF profiles, presence of optic neuritis—may be indistinguishable from those of MS [42]. Although the mean age of presentation with CNS abnormalities is higher in Sjogren disease (38 years) than in MS, the overlap becomes significant since Sjogren syndrome is the most common rheumatologic disease [43]. MR studies in these patients have revealed periventricular lesions indistinguishable from those in MS [15].

In the series of Rudick et al. [44] of 10 patients with an incorrect diagnosis of MS, two of the patients had lesions that would be expected to give abnormal periventricular signal, Moya Moya, andBinswanger diseases.

In some cases it is not possible to differentiate the cause of periventricular lesions with MR. Age is an important criterion in differentiating the cause of these lesions. With increasing age, over 50 years old, multifibract dementia, B2 deficiency,Binswanger disease, and “aging of the brain” become more likely as the cause of these lesions, while MS and Sjogren disease become less likely. The history and clinical and MR findings can help differentiate Moya Moya, hydrocephalus, postradiation changes, subependymal tumor, pseudotumor cerebri, encephalitis, progressive multifocal leukoencephalopathy, AIDS, and other brain infections from Sjogren disease and MS in almost all cases.

In conclusion, our series and that of Miller et al. [12] indicate that patients with sarcoidosis may have bright periventricular lesions on spin-density- and T2-weighted images, without the classic peripheral granulomas of the brain, but with an MR appearance very similar to that of MS. Furthermore, it is sometimes difficult or impossible to differentiate sarcoid with CNS involvement from MS on the basis of clinical, CSF, and MR findings, as illustrated by our five patients with sarcoidosis. Histopathologic correlation was lacking in our series. However, histopathologic evidence that periventricular lesions can be present in cerebral biopsy-proved neurosarcoidosis was noted in one patient in the series of Miller et al. Autopsy examination may be the only way to exclude the possibility of coexisting sarcoid and MS.

REFERENCES


