

## Parkinsonism and intractable hiccup in a patient with relapsing sarcoidosis

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### Abstract

We describe a 56-year-old man with relapsing sarcoidosis who presented with persistent hiccup responsive to steroid and clonazepam treatments. The patient also showed parkinsonism. The interval between the initial presentation and current symptoms was about 30 years. Brain MRI demonstrated foci of abnormal signal intensity in the cerebral white matter bilaterally, with decreased signal intensity on T1-weighted imaging and increased signal intensity on T2-weighted, diffusion-weighted, and FLAIR images. Gadolinium-enhanced MRI of the brain showed diffuse linear enhancement throughout the cerebral white matter with a configuration suggesting perivascular infiltration. Spinal MRI revealed spotty gadolinium-enhancing lesions from C2 to T3 segments. This case suggests that in some sarcoidosis patients intractable hiccup may be associated with high spinal cord lesions and parkinsonism with frontal white matter lesions.

### INTRODUCTION

Clinically recognizable involvement of the nervous system occurs in 3.5-9.1% of patients with sarcoidosis.<sup>1-3</sup> However, intractable hiccup is a rare symptom of sarcoidosis. Moreover, to our knowledge there have been no reports of parkinsonism associated with sarcoidosis. In this report, we describe a 56-year-old man with relapsing sarcoidosis who presented with persistent hiccup and parkinsonism, and discuss his neuroimaging findings.

### CASE REPORT

Our patient had a history of lung sarcoidosis from the age of 23 and skin sarcoidosis at the age of 26. This was proven by biopsy of lung and skin. At age 56, he started to exhibit bradykinesia. One month later, he developed intractable hiccup and myoclonus of the right lower limb, which were observed even in his sleep. Urinary incontinence and constipation were additional complaints. On neurological examination, he had a mask-like face and decreased spontaneity. His neck was stiff. Cranial nerve examination including ocular funduscopy identified no abnormalities except for a positive jaw jerk. He had moderate

bradykinesia and mild rigidity and spasticity in all four limbs with no significant asymmetry of features. Resting tremor was not seen. He had a mildly stooped posture. A short-stepped and frozen gait, absence of arm swing bilaterally, and postural instability were observed. Persistent hiccup and right leg myoclonus were observed. There were no abnormalities of muscle strength or cerebellar function. Deep tendon reflexes were normal except for decreased ankle jerk. Babinski reflex was not observed. Superficial sensation was normal, but deep sensation was moderately impaired. The results of laboratory studies including erythrocyte sedimentation rate, serum C reactive protein, IgG, IgM, IgA, IgE, soluble interleukin-2 receptor, and angiotensin converting enzyme were normal and failed to reveal evidence of diabetes mellitus, collagen disease, or infection including human immunodeficiency virus and JC virus. The CD4/CD8 ratio in the blood was also normal. Cerebrospinal fluid analysis revealed an opening pressure of 70 mmH<sub>2</sub>O, pleocytosis (27 white blood cells/ $\mu$ l, 96% mononuclear), elevation of total protein (107 mg/dl), and normal glucose. Examination of bronchoalveolar lavage fluid showed an elevated CD4/CD8 ratio (6.54). Motor and sensory nerve conduction

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studies and short-latency somatosensory evoked potentials were normal. Chest radiography and gallium scintigraphy revealed no abnormalities. Chest CT scan revealed post-inflammatory changes predominantly distributed in the upper and middle lung fields with slight mediastinal lymphadenopathy. Brain MRI showed low signal intensity of the periventricular and deep white matter bilaterally on T1-weighted imaging, with high signal intensity on fluid-attenuated inversion recovery (FLAIR), T2-weighted, and diffusion-weighted sequences. Gadolinium-enhanced MRI demonstrated diffuse areas of linear enhancement suggestive of perivascular infiltration (Figure 1). SPECT, using  $^{99m}\text{Tc}$ -ECD revealed hypoperfusion of the frontal lobes bilaterally and right temporal lobe (Figure 2). Spinal MRI revealed spotty gadolinium-enhanced lesions from C2 to T3 (Figure 3). Upon treatment with methylprednisolone pulse therapy (1000 mg/day for 3 days) and clonazepam (3 mg/day), the patient's hiccup and myoclonus disappeared within one day. Parkinsonism and urinary incontinence improved only slightly but persisted with L-dopa treatment (300 mg/day).

## DISCUSSION

We have presented a case of a patient with a history of lung and skin sarcoidosis who presented

neurological symptoms as the manifestation of disease relapse. Gadolinium-enhanced MRI showed lesions that ran along the perivascular space, a finding compatible with spread of sarcoidosis through the Virchow-Robin space.<sup>4,5</sup> Our case has three notable features as follows: 1) long-standing hiccup; 2) parkinsonism; and 3) a very long remission period between initial presentation and subsequent relapse with neurological features.

There is a neuronal network coordinating the hiccup reflex within the medulla.<sup>6</sup> The afferent portion of the hiccup reflex arc comprises the glossopharyngeal, phrenic and vagus nerves and the sympathetic chain arising from thoracic spinal cord segments. The efferent portion of the hiccup reflex arc comprises the phrenic and vagus nerves, and motor neurons to the anterior scalene and external intercostal muscles.<sup>7,8</sup> A study of 220 cases of intractable hiccup revealed that the most common etiology was diaphragmatic hernia and only one patient had sarcoidosis.<sup>9</sup> There have been only two detailed case reports describing sarcoidosis with long-standing hiccup.<sup>10,11</sup> Details of these previously described cases and the present case are given in Table 1. All three affected individuals were male and exhibited good outcome with respect to hiccup with corticosteroid treatment. In Kondo's case,

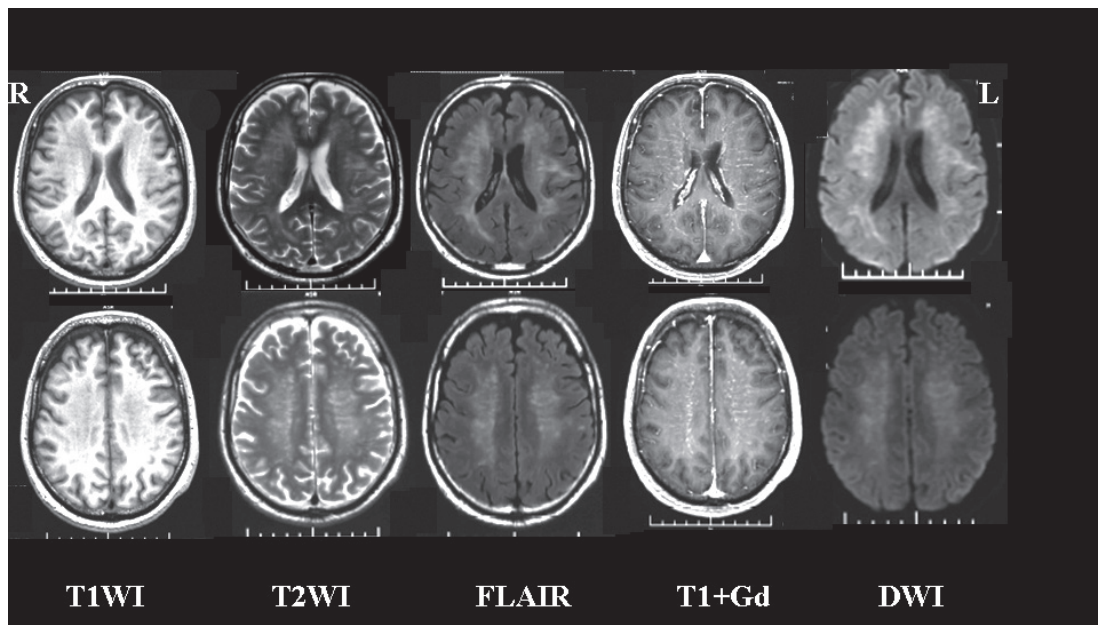


Figure 1. Axial T1-weighted MRI demonstrates decreased signal intensity in the periventricular and deep white matter. T2, FLAIR, and diffusion-weighted MRI demonstrate abnormally increased signal intensity in the periventricular and deep white matter. Gadolinium-enhanced axial MRI demonstrates diffuse areas of enhancement.

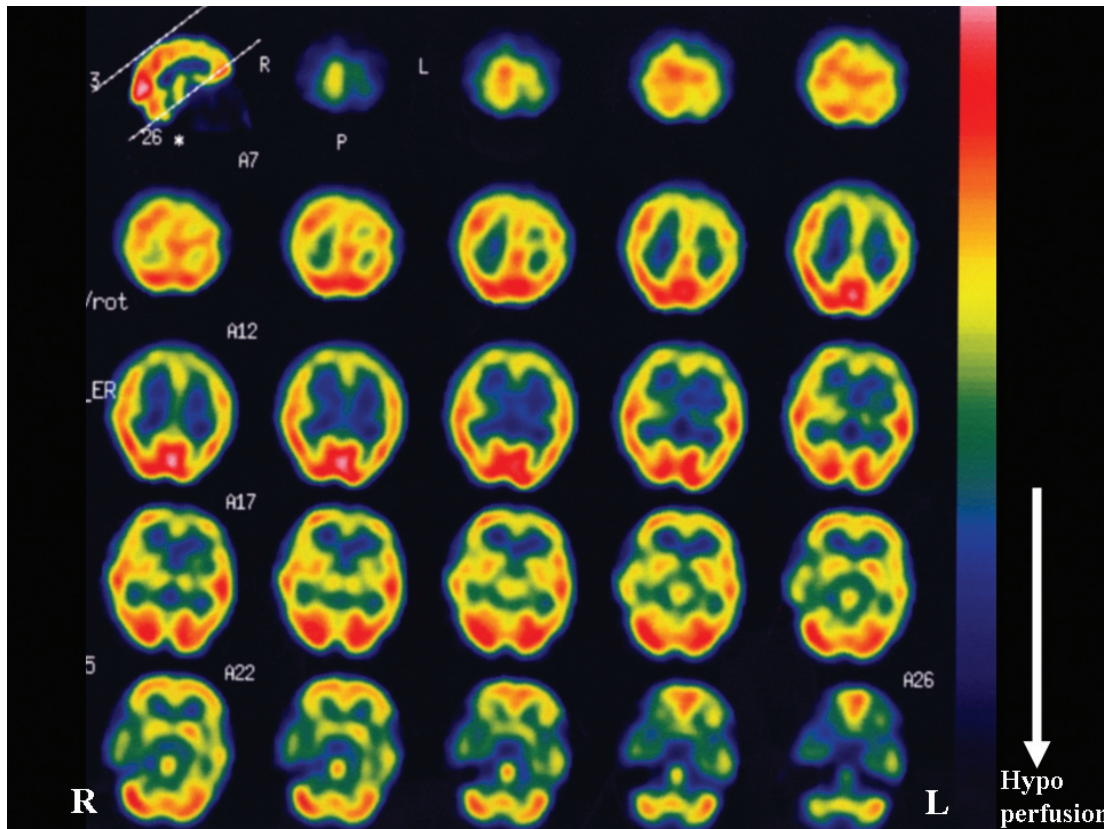


Figure 2. SPECT using  $^{99m}\text{Tc}$ -ECD shows hypoperfusion of the frontal lobes bilaterally and right temporal lobe. Green~Blue indicates hypoperfusion.



Figure 3. Midline sagittal spinal MRI with gadolinium shows areas of spotty enhancement in the C2 to T3 segments (arrowhead).

**Table 1 Case reports of sarcoidosis patients with intractable hiccups**

| Year | Author                       | Age | Sex | Brain MRI                                                                                | Spinal MRI                                | Treatment                  | Outcome |
|------|------------------------------|-----|-----|------------------------------------------------------------------------------------------|-------------------------------------------|----------------------------|---------|
| 1989 | Kondo et al. <sup>10</sup>   | 67  | M   | normal                                                                                   | not done                                  | prednisolone               | good    |
| 1991 | Conolly et al. <sup>11</sup> | 26  | M   | nodular meningeal enhancement (basilar) bilateral enlarged, enhancing 5th cranial nerves | nodular meningeal enhancement (C2-C7)     | prednisone                 | good    |
| 2010 | Our case                     | 56  | M   | abnormal signal in the periventricular and deep white matter, bilaterally                | intramedullary spotty enhancement (C2-T3) | steroid pulse + clonazepam | good    |

brain MRI was normal but spinal MRI was not performed. In the other two cases, MRI showed gadolinium-enhanced lesions in the region of the cervical spinal cord. Although, in general, intractable hiccup due to lesions in the cervical or thoracic spinal cord is rare<sup>9</sup>, the mechanism of hiccup in some sarcoidosis patients could be dysfunction of the afferent or efferent portion of the hiccup reflex arc located in the cervical segments of the spinal cord.

To our knowledge, this is the first case of neurosarcoidosis presenting with parkinsonism. In this case, the parkinsonism was mainly characterized by gait disturbance, similar to vascular parkinsonism. Vascular parkinsonism might be related to frontal white matter lesions.<sup>12</sup> Our patient showed diffuse cerebral white matter lesions on brain MRI with SPECT evidence of hypoperfusion of the frontal lobes bilaterally. Therefore, in our case, we propose that his parkinsonism is likely to be explained by the bilateral frontal lobe lesions.

There are some cases with recurrence of sarcoidosis following complete remission and a prolonged period of inactivity.<sup>13,14</sup> The longest recorded disease-free interval without treatment is 209 months (17 years).<sup>13</sup> In our patient, the disease-free interval without treatment was about 30 years. This suggests that we may need to follow patients with sarcoidosis for a prolonged period even during complete remission.

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