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Title	Clinical features of spinal cord sarcoidosis : analysis of 17 neurosarcoidosis patients
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Citation	Journal of Neurology, 258(12), 2163-2167 https://doi.org/10.1007/s00415-011-6080-3
Issue Date	2011-12
Doc URL	http://hdl.handle.net/2115/50771
Rights	The original publication is available at www.springerlink.com
Type	article (author version)
File Information	JoN258-12_2163-2167.pdf

Original Communication

Title:

Clinical Features of Spinal Cord Sarcoidosis: Analysis of 17 Neurosarcoidosis Patients

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Running head:

Spinal cord sarcoidosis

Word counts:

Abstract: 158 words

Text: 1180 words

Abstract

The diagnosis of neurosarcoidosis is often difficult; the imaging signs of spinal cord sarcoidosis sometimes mimic those of cervical spondylotic myelopathy, which is common in elderly persons. We examined the characteristics of spinal cord sarcoidosis in Japanese patients with neurosarcoidosis. This case series identified patients with neurosarcoidosis at 4 general hospitals and 1 university hospital from April 1998 to September 2010. All diagnoses were based on the diagnostic criteria proposed by Zajicek et al. Seventeen patients (9 men and 8 women) were involved: 6 patients with spinal cord lesions accompanied by cervical spondylosis; 5, with cerebral lesions; 3, with cranial nerve lesions; 2, with meningitis; and 1, with nerve root lesions. Patients with spinal cord sarcoidosis had a higher onset age, longer duration from onset to diagnosis, reduced leukocytosis in the cerebrospinal fluid (CSF), and lower angiotensin-converting enzyme (ACE) levels in the CSF. The results of this study indicate that diagnosis of spinal cord sarcoidosis requires careful evaluation.

Introduction

Neurosarcoidosis is a rare manifestation that occurs in 5% of systemic sarcoidosis patients; it is characterized by multisystem non-caseous granulomatous disease of an unknown etiology [1]. Neurosarcoidosis lesions mainly involve the optic and cranial nerves and the spinal cord [2]. The diagnosis of neurosarcoidosis is often difficult in clinical practice and requires magnetic resonance imaging (MRI) to detect the abnormalities and the evidence of systemic sarcoidosis [2, 3]. Spinal cord sarcoidosis exhibits intramedullary high-intensity signals on T2-weighted images (T2WI) and enhancements on gadolinium (Gd) DTPA-enhanced T1 weighted images (Gd-T1WI) [4, 5]; however, these signs also resemble cervical myelopathy with spondylosis [6]. Although cervical spondylotic myelopathy, which is common in elderly persons, sometimes mimics spinal cord sarcoidosis, a similar operative treatment is not effective for spinal cord sarcoidosis with cervical spondylosis [7]. Therefore, the diagnosis of spinal sarcoidosis is important for effective treatment. Systemic sarcoidosis shows racial differences in its incidence and clinical manifestations [8]. Case reports and case series on spinal cord sarcoidosis have been reported in western countries and Japan [5, 9]; however, the characteristics of spinal cord sarcoidosis have not been sufficiently investigated compared to other neurosarcoidosis lesions.

The purpose of this study was to identify the characteristics of spinal cord sarcoidosis that differentiate it from other neurosarcoidosis lesions in the Japanese population by reviewing consecutive patients in our

hospital.

Methods

This study enrolled patients diagnosed with neurosarcoidosis at the neurology departments of 4 general hospitals (Asahikawa Red Cross Hospital, Hakodate Municipal Hospital, Sapporo Municipal Hospital, and Obihiro Kosei General Hospital) and 1 university hospital (Hokkaido University Hospital) from April 1998 to September 2010. The diagnosis of neurosarcoidosis was based on the diagnostic criteria proposed by Zajicek et al. [2] and the response to steroid treatment. We retrospectively reviewed medical records, and collected data on the course of neurosarcoidosis, diagnostic imaging, laboratory findings, and treatment regimens as well as their results. We compared patients with spinal cord sarcoidosis with patients with other forms of neurosarcoidosis. Age at onset, duration from the onset of neurological symptoms to the diagnosis of neurosarcoidosis, serum angiotensin-converting enzyme (ACE) levels, and cerebrospinal fluid (CSF) findings were compared using Mann-Whitney U test. We also compared laboratory findings before and after treatment to evaluate the usefulness of each item for disease activity. We excluded patients who did not have sufficient evidence of neurosarcoidosis, such as hemifacial palsy without abnormal findings in diagnostic imaging. The Institutional Review Board of Hokkaido University Hospital approved this study.

Results

The demographics of the 17 patients are summarized in Table 1. Cases 3, 8, and 17 were previously

described as case reports by one of the authors of the present study [10-12]. There were 6 patients with

spinal cord lesions; 5, with cerebral lesions; 3, with cranial nerve lesions; 2, with meningitis; and 1, with

nerve root lesions. All spinal cord sarcoidoses occurred in the cervical cord, and they were accompanied

by cervical spondylosis. Three of the spinal cord sarcoidosis patients underwent

2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) examinations [13], and all

of them displayed abnormal uptake in the spinal cord lesion. Methotrexate was additionally administered

during the initial corticosteroid treatment for cases 1, 2, and 7.

A comparison between patients with spinal cord sarcoidosis and those with other forms of

neurosarcoidosis revealed significant differences in onset age, duration from onset to diagnosis,

leukocytes in CSF, and ACE levels in CSF. The onset age in spinal cord sarcoidosis (mean ± SD: 61.0 ±

10.5 years) was higher than in other forms of neurosarcoidosis (mean ± SD: 38.1 ± 18.5 years). Duration

from onset to diagnosis in spinal cord sarcoidosis (mean ± SD: 31.8 ± 36.4 months) was longer than other

neurosarcoidoses (mean ± SD: 7.3 ± 15.0 months). Patients with spinal cord sarcoidosis had lower

leukocyte and ACE levels in CSF than patients with other forms of neurosarcoidosis (Figure 1).

Alterations in the ACE levels after treatment for neurosarcoidosis are shown in Figure 2. Serum ACE

levels decreased in spinal cord sarcoidosis and other forms of neurosarcoidosis after treatment with

6

corticosteroids. The reduction in ACE levels in CSF was less obvious than that in serum.

Discussion

We identified some characteristics of spinal cord sarcoidosis from our case series. First, spinal cord sarcoidosis tended to occur in elderly patients and required a longer duration to develop from onset to diagnosis. Second, leukocytes and ACE levels were not elevated in CSF of spinal cord sarcoidosis patients. Third, serum ACE levels reflected the disease activity after treatment.

A national survey on sarcoidosis in Japan revealed the incidence rate to be 1.01 per 100,000 individuals, with 7.2% of these cases displaying neurological complications [14]. The incidence rate exhibited a bimodal distribution that consisted of young men and middle-aged to older women. In our cases, spinal cord sarcoidosis was mainly associated with the elderly. Conversely, cerebral lesions in neurosarcoidosis were mainly associated with younger men. A longer duration between onset and diagnosis in spinal cord sarcoidosis may be associated with the elderly patients and cervical spondylosis complications, because cervical myelopathy mimicked the clinical symptoms of spinal cord sarcoidosis. Laboratory findings are essential for the diagnosis of neurosarcoidosis; however, spinal cord sarcoidosis resulted in less frequent abnormal findings in CSF than other forms of neurosarcoidosis in our study. Varron et al. reported that 4 of 7 cases of spinal cord sarcoidosis had normal or near-normal cell counts, and 6 of them had normal ACE levels in CSF [5]. Cohen-Aubart et al. also reported that 8 of 28 cases of spinal cord sarcoidosis had

normal cell counts and more than 50% patients had normal ACE levels in CSF [15]. These characteristics

indicate that careful evaluation for spinal cord sarcoidosis is required for patients with systemic

sarcoidosis and cervical spondylosis.

FDG-PET is becoming an additional diagnostic tool for different forms of neurosarcoidosis, including

spinal cord sarcoidosis [9, 16]. We recently reported the usefulness of FDG-PET for the differentiation of

spinal cord sarcoidosis from cervical spondylotic myelopathy [13].

Spinal cord sarcoidosis is one of the steroid-refractory lesions among neurosarcoidoses and often

requires additional immunosuppressant therapy [17]. Methotrexate may be useful to maintain optimal

disease suppression [3]. Therefore, indicators that represent the disease activity of spinal cord sarcoidosis

are necessary for reasonable treatment. Oksanen et al. reported the usefulness of ACE levels in CSF

measured by an inhibitor binding assay to evaluate the disease activity of neurosarcoidosis [18]; however,

colorimetry was used in the present case, while investigation by Varron et al. demonstrated that spinal

cord sarcoidosis patients did not exhibit sufficient changes in the CSF-ACE levels to serve as an indicator.

Although the methods used to measure ACE levels were different in each study, the symptoms caused by

spinal cord lesions are still reliable indicators of spinal cord sarcoidosis. At the very least, on the basis of

our findings, we propose that serum ACE levels may reflect the disease activity of neurosarcoidosis as a

part of systemic sarcoidosis.

In conclusion, a review of Japanese patients with neurosarcoidosis found that spinal cord

9

sarcoidosis is frequent in elderly patients with neurosarcoidosis and evinces fewer CSF abnormalities than

other forms of neurosarcoidosis.

Tables

Table 1. Patient demographics

Case	Onset age[a]	Sex	Duration[b] (months)	Neurological lesion	Systemic lesion[c]	Serum ACE[d] (U/L)	Histology[e]	Diagnosis of neurosarcoidosis	Exacerbation during initial treatment	Comments
1	42	M	104	Spinal cord	M	24.4	M	Probable	Yes	MTX
2	61	F	6	Spinal cord	O, M	18.0	N.D.	Probable	No	MTX
3	61	M	27	Spinal cord	M	27.9	M	Probable	No	
4	76	F	24	Spinal cord	O, M	19.5	M	Probable	Yes	
5	63	F	6	Spinal cord	O, M, T	15.3	N.D.	Probable	Yes	
6	67	M	23	Spinal cord	O, M	23.0	M	Probable	No	
7	27	M	1	Cerebrum	O, A	23.9	A	Probable	No	MTX
8	26	M	51	Cerebrum	M	17.5	L	Probable	No	
9	28	M	1	Cerebrum	M	32.6	L	Probable	No	
10	25	M	7	Cerebrum	M	15.7	C	Definite	No	
11	33	M	1	Cerebrum	O	12.8	N.D.	Probable	No	
12	33	F	0	Cranial nerves	O, M, S	23.6	S	Probable	No	
13	57	F	3	Cranial nerves	M	14.4	M	Probable	No	
14	25	F	0	Cranial nerves	O, M, S	N.D.	S	Probable	No	
15	24	M	1	Meningitis	O, M	18.8	L	Probable	Yes	
16	70	F	13	Meningitis	O, S	15.0	S	Probable	No	

| 17 | 71 | F | 2 | Nerve roots | M, S | 33.6 | Lung | Probable | No |

[a]Onset of neurological symptoms

[b]Duration between onset and diagnosis

[c]M: Mediastinal adenopathy; O: Orbit, S: Skin lesion, T: Thyroid nodule, A: Axillary adenopathy

[d]ACE: Angiotensin converting enzyme; Normal range: 8.3–21.5 U/L

[e]The site of positive histology with sarcoidosis; M: Mediastinal adenopathy, A: Axillary adenopathy, L: Lung, C: Cerebrum, S: Skin lesion

MTX: Methotrexate was additionally administered during the initial corticosteroid treatment.

Key: M, male; F, female

N.D.: Not done

Figure Legends

Fig. 1 Distribution of laboratory findings at diagnosis for leukocytes in CSF (A), protein in CSF (B),

glucose in CSF (C), and ACE in CSF (D)

Key: CSF, cerebrospinal fluid; ACE, angiotensin-converting enzyme

Fig. 2 Comparison of laboratory findings before and after treatment for serum angiotensin-converting

enzyme (ACE) (A) and ACE in cerebrospinal fluid (CSF) (B)

Key: ACE, angiotensin-converting enzyme

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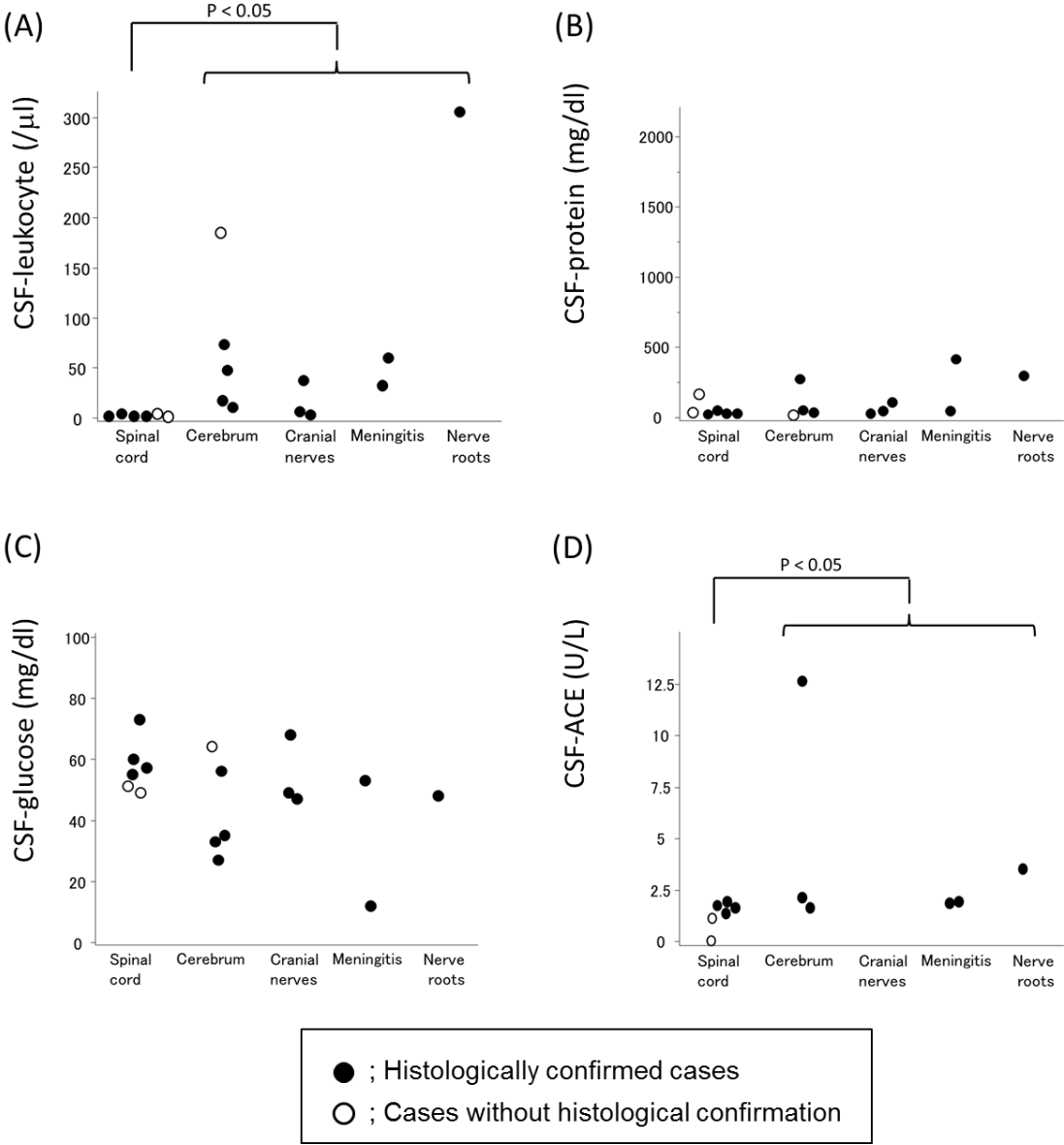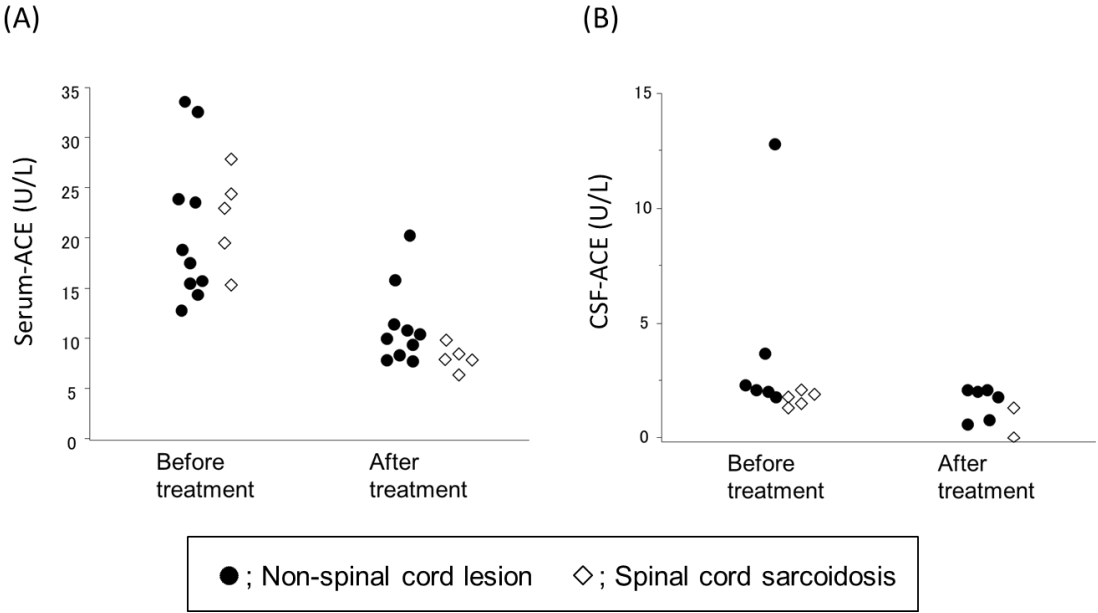
Fig. 1

Fig. 2