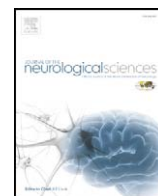




Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical and laboratory characteristics of atopic myelitis: Korean experience

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ARTICLE INFO

Article history:

Received 24 April 2009

Received in revised form 15 June 2009

Accepted 16 June 2009

Available online xxxx

Keywords:

Atopy

HyperIgEemia

Myelitis

Neuromyelitis optica

ABSTRACT

HyperIgEemia and atopy have recently been reported to be related to various neurological diseases such as Hirayama disease and idiopathic myelitis. The aims of this study are to determine frequency of atopy or hyperIgEemia in idiopathic myelitis and to characterize the clinical and laboratory profiles of atopic myelitis (AM). From January 2006 to August 2008, 29 consecutive patients with idiopathic myelitis were recruited. We compared demographic data, laboratory results and radiologic findings between patients with atopic diathesis and those without. Allergic or atopic history was found in only 4 patients (13%), but hyperIgEemia and mite antigen-specific IgE were observed in 17 (58%) and 19 (65%) of idiopathic myelitis patients, respectively. Patients with AM ($n = 14$, 48%) showed the following distinctive features: (1) younger age at onset, (2) non-acute onset and long duration of symptoms at admission, (3) predominant sensory symptoms with mild weakness, (4) low EDSS score, (5) low frequency of abnormal SEP findings, and (6) increased eosinophils in peripheral blood. Common MR findings of AM included eccentric lesions occupying more than two-thirds of spinal cord with focal peripheral enhancement on axial image. These lesions were usually extended over more than 3 to 5 vertebral segments with cord swelling. HyperIgEemia and mite antigen-specific IgE are fairly common in idiopathic myelitis patients. The AM patients show relatively homogenous clinicolaboratory and radiological features. It is noteworthy that none of these patients showed brain abnormalities suggestive of multiple sclerosis or neuromyelitis optica (NMO).

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1. Introduction

Atopy refers to enhanced IgE response to common antigens. Recently, various neurological diseases including Hopkins' syndrome [1], Hirayama disease [2,3] and idiopathic myelitis [4–7] have been found to be related to atopy such as atopic dermatitis, allergic rhinitis, or bronchial asthma. Kira et al. were first to describe 4 patients with atopic dermatitis suffering from myelitis during the exacerbation of atopic symptoms [4]. More recently, they found a substantial portion of idiopathic myelitis to be associated with hyperIgEemia as well as atopic disease [5–7]. Of interest, patients with hyperIgEemia and mite specific antibody (IgE) in the absence of known history of atopy share common clinicolaboratory features with those with known atopy [6]: young age of onset, slow progressive course and predominant sensory symptoms with mild motor weakness, and few CSF abnormalities. These findings were recently confirmed by a Japanese nation-wide survey [7]. Based on these distinct clinicolaboratory features, the term “atopic myelitis (AM)” has been proposed.

Most AM patients have been investigated in Japan, with very few cases of AM being reported in western countries [8,9]. It has been unclear whether AM was as frequent in other Asian countries as in the case of Hirayama disease and whether it was a distinct entity, different from other idiopathic myelitis disorders, multiple sclerosis or neuromyelitis optica (NMO).

2. Methods

2.1. Patients

From January 2006 to August 2008, patients with idiopathic myelitis were recruited from the prospectively enrolled Ajou Myelitis Registry. Inclusion criteria were as follows: 1) acute or non-acute myelitis confirmed by clinical findings and spine MRI 2) no previous history of other neurological diseases or symptoms. Patients with a clinical course of more than one month were included given that long duration had been frequently seen in atopic myelitis [6,7]. Exclusion criteria were as follows: 1) compressive lesion 2) collagen-vascular diseases 3) parainfectious myelitis (clinical infection with fever within one month of the onset of clinical symptoms and CSF pleocytosis (>50 mg/dl) and 4) history of previous radiation of the spinal cord.

AM is defined as idiopathic myelitis with either: 1) atopic diseases such as bronchial asthma, atopic dermatitis, and allergic rhinitis, or 2) hyperIgEemia and specific IgE to mite antigen (*Dermatophagoides*

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pteronysinus, D1 and *fabrinae*, D2), as proposed by Kira et al. [5]. Thirty-nine age and sex-matched subjects without a history of any atopic diseases were recruited as a control.

2.2. Clinical assessment

The mode of onset was defined as either acute (a maximal deficit within two weeks) or non-acute. The disability was evaluated according to Kurtzke's expanded disability status scale (EDSS) [10]. Steroid response was considered effective if improvement of more than 1 point in EDSS score was achieved.

2.3. Measurement of total and specific IgE

The level of total IgE and two common mite antigens, *D. pteronyssinus* (D1) and *fabrinae* (D2)-specific IgE were measured using the CAP system (Pharmacia) according to the manufacturer's instructions. The upper normal limit of the serum total IgE and the mite antigen-specific IgE level were 250 IU/ml and 0.35 IU/ml, respectively.

2.4. Measurement of NMO-IgG

Testing for NMO-IgG was performed by indirect immunofluorescence on a substrate of mouse cerebellum and midbrain, as previously described [11]. Readers were blind to all clinical information.

2.5. MRI

Spine MRIs were performed on all patients using the 1.5 T GE system after intravenous injection of contrast material. The MR imaging protocol for spine included the collection of T1- and T2-weighted images as well as gadolinium-enhanced T1-weighted images in the axial and sagittal planes. The MR images were reviewed for the following characteristics: cord swelling on T1-weighted sagittal images, segmental body length of the high signal on T2-weighted sagittal images, cross-sectional location, size and pattern of the high signal on T2-weighted images, and the location, extent, and pattern of contrast enhancement on T1-weighted axial and sagittal images. Lesions spanning three or more vertebral segments in length were regarded as longitudinally extensive spinal cord lesions (LESCL) [12]. Central linear high signal intensity seen above or below the diffuse lesion on T2WI was not con-

sidered as a true lesion. Brain MRI was obtained in all of 29 patients with myelitis. Brain lesions were classified as suggestive or atypical for multiple sclerosis, according to Barkhof's criteria [13].

2.6. Statistical analysis

A Mann Whitney-U test was used for comparison of continuous variables (the level of total IgE and mite antigen-specific IgE) and a Chi-square or Fisher's exact test was applied to compare frequency data. Statistical significance was set at $p < 0.05$.

3. Results

During the study period, 32 patients with non-compressive myelopathy were identified. After excluding 3 cases (SLE 1, spinal cord infarction 1, parainfectious myelitis 1), 29 patients (19 men, 10 women; mean age at onset, 45.5 years) were diagnosed with idiopathic myelitis.

Of them, four patients had known atopic disease (2 allergic rhinitis, 2 bronchial asthma). All 4 of these patients had both hyperIgEemia and mite antigen-specific antibodies; however, none of them experienced an exacerbation of atopic symptoms during the course of myelitis. Another 10 patients showed both hyperIgEemia and mite specific antibody but without a known history of atopic disease. Thus, these 14 patients were considered as AM whereas the remaining 15 patients as non-AM.

3.1. Comparison of total IgE and mite specific IgE between myelitis patients and normal control

The level of total serum IgE and two mite antigen-specific IgE in patients with myelitis and in normal control are shown in Fig. 1. HyperIgEemia was more frequent in patients with myelitis (58%) than in normal control (20%, $p = 0.005$) (Table 1). The level of total IgE was significantly higher in the myelitis group (median 324 IU/ml, range 18–2345 IU/ml) than in the control group (median 62 IU/ml, range 8–472 IU/ml) ($p < 0.005$) (Fig. 1A).

Both D1 and D2 mite antigen-specific IgE were detected in about two-thirds of myelitis cases and in about one-fifth of control subjects ($p = 0.05$ and $p = 0.001$, respectively) (Table 1). In addition, myelitis patients showed significantly higher median level of *D. pteronyssinus*

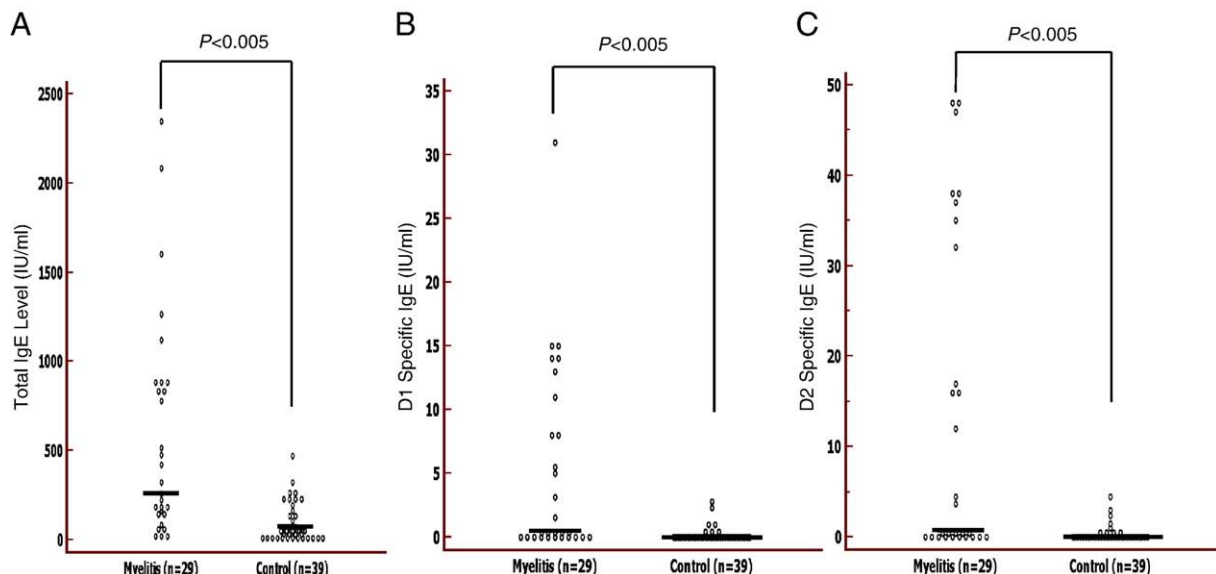


Fig. 1. Distribution of the level of total IgE (A) as well as *Dermatophagoides pteronyssinus* (D1) and *fabrinae* (D2)-specific IgE (B, C) in myelitis patients and normal control. NC = Normal control. The upper normal limit of serum total IgE and the mite antigen-specific IgE level are 250 IU/ml and 0.35 IU/ml, respectively. Horizontal bars indicate median values.

Table 1

Frequency of positivity for hyperIgEemia and mite antigen-specific IgE.

	HyperIgEemia	<i>D. pteronyssinus</i> (D1) IgE positivity	<i>D. fabrinae</i> (D2) IgE positivity
Idiopathic myelitis (n = 29)	17 (58%)*	18 (62%)*	19 (65%)*
Healthy control (n = 39)	8 (20%)	7 (17%)	9 (23%)

*p<0.05.

(0.5 IU/ml) and *fabrinae* (0.45 IU/ml)-specific IgE than normal control ($p<0.005$) (Fig. 1B and C).

3.2. Comparison of clinical features in patients with and without AM

We compared clinical and laboratory findings in patients with and without AM (Table 2). AM patients showed a male preponderance (78% vs. 53%) and were significantly younger than non-AM patients (39 years vs. 51 years; $p<0.001$). With regard to characteristics of the clinical presentation at admission, non-acute onset (92% vs. 33%) and asymmetry (78% vs. 26%) were significantly more frequent in AM patients. Among patients with non-acute onset, disease course progressed slowly in most patients. In addition, symptom duration at the presentation was significantly longer in AM patients (76 days vs. 16 days; $p<0.001$). While sensory symptoms were predominant during the entire course as well as at onset of AM, moderate to severe motor weakness was less frequent (0% vs. 66%; $p<0.001$), which resulted in lower mean EDSS scores in AM patients (2.1 vs. 5.6; $p<0.001$). There was no significant difference in the frequency of urinary or sphincter symptoms between two groups.

Pleocytosis and elevated protein levels in CSF were more common in patients with non-AM; however, the difference was statistically significant in only with regard to CSF protein (21% vs. 66%; $p<0.05$).

Table 2

Clinicolaboratory findings between patients with and without atopic myelitis (AM).

	AM (n = 14)	Non-AM (n = 15)	p value
Age of onset (years, mean $\pm$ SD)	39 $\pm$ 6.6	51 $\pm$ 8.5	<0.001
Male	11 (78%)**	8 (53%)	NS***
Known history of atopy	4 (28%)	0 (0%)	NS
Mode of onset			0.002
Acute	1 (7%)	10 (66%)	
Non-acute	13 (92%)	5 (33%)	
Clinical course			0.008
Slowly progressing/Fluctuating	12 (85%)	5 (33%)	
Monophasic	2 (14%)	10 (66%)	
Symptom duration (days, mean $\pm$ SD)	76 $\pm$ 56	16 $\pm$ 25	<0.001
Asymmetry	11 (78%)	4 (26%)	0.009
Clinical symptom			
Initial paresthesia	10 (71%)	5 (33%)	NS
Motor weakness			<0.001
Normal to mild	14 (100%)	5 (33%)	
Moderate to severe*	0 (0%)	10 (66%)	
Paresthesia/dysesthesia	12 (85%)	7 (46%)	NS
Hypesthesia	10 (71%)	13 (86%)	NS
Urinary/Sphincter symptom	6 (42%)	11 (73%)	NS
Mean EDSS at admission	2.1 $\pm$ 0.5	5.6 $\pm$ 2.1	<0.001
Eosinophil (% , mean $\pm$ SD)	5.0 $\pm$ 3.2	1.0 $\pm$ 1.18	<0.001
SEP abnormality	2 (14%)	11 (73%)	0.003
VEP abnormality	0 (0%)	0 (0%)	NS
CSF			
Increased Protein (>45 mg/dl)	3 (21%)	10 (66%)	0.025
Pleocytosis(>5 cells)	1 (7%)	4 (26%)	NS
Oligoclonal band	0 (0%)	0 (0%)	NS
Elevated IgG index	0 (0%)	2 (13%)	NS
Early steroid response	1 (7%)	3 (20%)	NS
NMO-Ab	0 (0%)	2 (13%)	NS
Recurrence	0 (0%)	4 (26%)	NS

*Moderate to severe weakness is defined as motor power below grade IV.

**Number of patients (percentage).

***Not Significant.

Table 3

Radiological findings between patients with and without atopic myelitis (AM).

	AM (n = 14)	Non-AM (n = 15)	p value
Spinal cord MRI findings			
Swelling	10 (71%)*	4 (26%)	0.027
Axial T2WI			
Eccentric large	13 (92%)	0 (0%)	<0.001
Central	1 (7%)	10 (66%)	<0.001
Holocord	0 (0%)	2 (13%)	NS**
Peripheral	0 (0%)	3 (20%)	NS
Gd-Enhancement	14 (100%)	11 (73%)	NS
Focal	13 (92%)	3/11 (27%)	<0.001
Ill-defined and patch	1 (7%)	8/11 (63%)	<0.001
MRI spine lesion length (vertebral segments; median, range)	3.5 (1–6)	4 (1–15)	NS
Longitudinally extensive spinal cord lesion (LESCL)	10 (71%)	11 (73%)	NS
Spinal cord involved			
Cervical	4 (28%)	2 (13%)	NS
Cervical to thoracic	0 (0%)	2 (13%)	NS
Thoracic	10 (71%)	5 (33%)	NS
Thoracic to lumbar	0 (0%)	5 (33%)	0.042
Cervical to lumbar	0 (0%)	1 (7%)	NS
Brain MRI findings	0 (0%)	5 (33%)	0.042
MS-like lesions	0 (0%)	2 (13%)	NS
Atypical lesions	0 (0%)	3 (20%)	NS

*Number of patients (percentage).

**Not Significant.

None of AM patients had an increased IgG index, neuromyelitis optica (NMO)-antibody, or CSF oligoclonal bands, but 4 (26%) of the 15 non-AM patients showed an elevated IgG index or NMO-Ab. Mean eosinophil percentage in peripheral blood was significantly higher in AM patients (5% vs. 1%; $p<0.001$); however, definite eosinophilia (>10% in the peripheral blood) was observed in only two AM patients.

Regarding electrophysiological studies, most non-AM patients showed abnormal somatosensory evoked potentials, but AM patients did not (73% vs. 14%; $p<0.05$). An abnormality of visual evoked potentials was absent in both groups.

3.3. Comparison of MRI findings in patients with and without AM

We compared MRI findings in patients with and without AM (Table 3). Spinal cord swelling was found in 71% (10/14) of AM patients compared to 26% (4/15) in non-AM patients ($p<0.05$). In AM patients, the thoracic cord (71%) was the most frequently affected, followed by the cervical cord (28%), while the thoracic (33%) and the thoracic to lumbar (33%) were the most commonly involved region in non-AM patients. Longitudinally extensive spinal cord lesions (LESCL) were found in the 71% (10/14) of AM and 73% (11/15) of non-AM patients at a similar frequency. Although both groups frequently showed longitudinally extensive transverse myelitis (LETM), extremely long segment involvement (e.g. mid-cervical to lower thoracic or entire thoracic cord) was present only in non-AM patients.

On axial T2WI, in AM patients, most lesions (13/14) occupied more than two-thirds of the cross-sectional area of the spinal cord and were peripherally located toward one side (eccentric large pattern), irrespective of the lesion length on sagittal image (Fig. 2A and C) except one patient who showed central gray matter-predominant lesion. By contrast, heterogeneous patterns were observed in non-AM patients; a central gray matter-predominant pattern in 66% (10/15), a focal peripheral white matter-predominant pattern in 20% (3/15) and holocord pattern in 13% (2/15). Most (9/10) of patients with a central gray matter-predominant pattern had LESCL, whereas two of three patients with a focal peripheral white matter-predominant pattern had lesions affecting less than two vertebral segments.

Nearly all AM patients (92%) had clear contrast enhancement on both axial (Fig. 2B) and sagittal T1WI (Fig. 2D). On axial T1WI, the

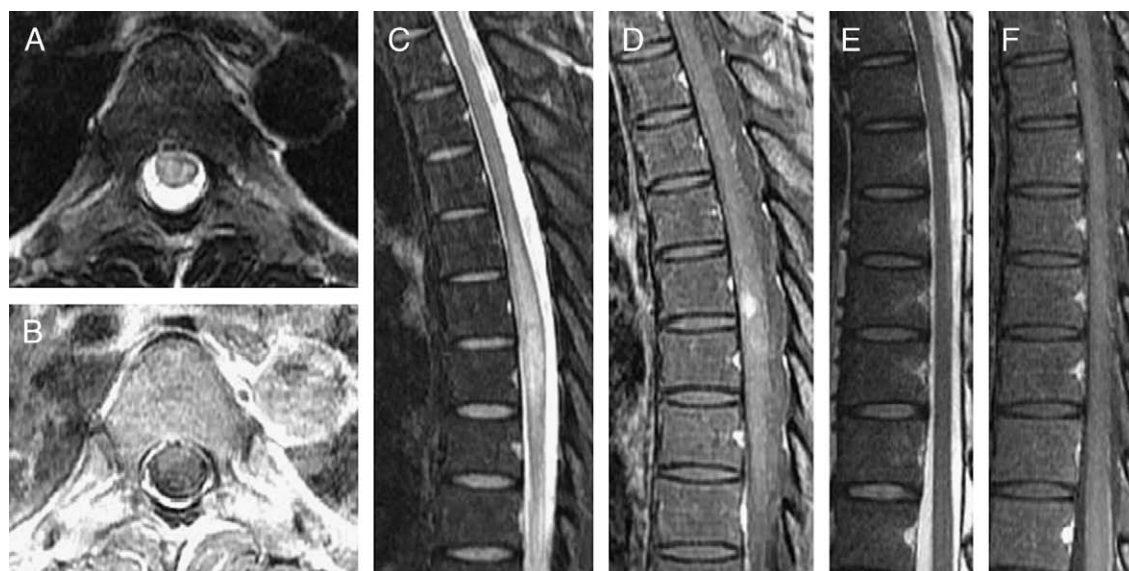


Fig. 2. Representative MRI findings of atopic myelitis (AM). A 40-year-old man with progressive left leg paresthesia lasting 3 months. The patient had no brain abnormalities or NMO-IgG in serum. (A) On axial T2WI, high signal intensity lesions were eccentric to the right but occupied more than two-thirds of the cross-sectional area of the spinal cord. (B) Only a small marginal portion of the lesion is enhanced on post-contrast axial T1WI. (C) Sagittal T2WI of the thoracic spine demonstrates high signal intensity at the T8–T11 level with cord swelling. (D) Post-contrast sagittal T1WI demonstrate focal enhancement in the middle of the lesion. Three months later, most of the lesion on the sagittal T2WI (E) and post-contrast sagittal T1WI (F) disappeared despite mild persistent symptoms.

enhancement occupied only a small portion at the margin of the lesion. By contrast, in non-AM patient, an ill-defined pattern (8/11) was the most common, followed by focal contrast enhancement pattern (3/11).

In all patients with AM, brain MRIs showed normal findings whereas 5 (33%) of non-AM patients showed brain lesions ($p < 0.05$). Of these 5 patients, 2 patients had lesions suggestive of MS and another 3 patients showed nonspecific brain lesions involving the corpus callosum, internal capsule, and subcortical white matter.

3.4. Treatment and prognosis

All patients were treated with a high-dose intravenous steroid pulse therapy except one with side effects to steroid. The steroid was ineffective in most AM and non-AM patients. The median duration of follow-up was 23.7 months in AM (range 7.1 to 31.5 months) and 14.7 months in non-AM patients (range 8.1 to 36.6 months). None of 14 AM patients experienced either subsequent myelitis or optic neuritis, although mild symptoms persisted in most patients. Of these, 7 patients (50%) had repeated spine MRIs 3 to 6 months after steroid pulse therapy. In all of them, swelling disappeared and the lesion markedly improved (Fig. 2E). Furthermore, contrast enhancement disappeared in most (6/7) patients (Fig. 2F), although one patient still had focal enhancement, albeit much reduced.

In non-AM patients, 4 (26%) of 15 patients suffered from recurrent myelitis and the relapse was severe, leading to paraplegia in three patients.

4. Discussion

Although myelitis can be caused by many factors such as viral infection, vaccination, demyelinating diseases, and collagen-vascular diseases, a substantial portion of myelitis cases turn out to be idiopathic [14]. Recently, a large percentage of idiopathic myelitis cases in Japan have been found to have hyperIgEemia and common mite antigen-specific IgE, as well as atopy [5–7]. Our study also shows that hyperIgEemia and mite antigen-specific IgE are fairly common in idiopathic myelitis while atopy is less common.

In our study, patients with AM showed the following distinctive features compared with those with non-AM patients: 1) younger age at onset, 2) a non-acute onset and long duration of symptoms, 3) a

slow progression or fluctuating disease course, 4) prominent asymmetrical sensory symptoms with mild weakness, 5) less frequent abnormal CSF and SEP findings, 6) increased peripheral eosinophils, and 7) rare recurrence. Although many features such as younger age onset, predominant sensory symptom with mild weakness, and rare CSF abnormality are similar with the findings of a Japanese nationwide survey [7], several differences exist. Firstly, in our study, there was male predominance and preferential thoracic cord involvement in AM patients. The differences could have resulted from the frequency of atopic diseases such as atopic dermatitis or bronchial asthma, which are less common in Korean AM patients. According to Kira [6], myelitis patients with known atopic diseases have a tendency to have more female predominance and cervical spine cord involvement than myelitis with only hyperIgEemia and mite antigen-specific IgE, even though clinical features are similar to each other. However, it is unclear whether the presence of atopy implies the variable underlying pathophysiology in atopic myelitis. Considering that some parasites such as *Toxocara canis* can enhance allergic manifestation to common environmental allergen [15], it is possible that such a parasitic infection may contribute to the development of atopic myelitis without parasitic migration into the spinal cord, especially in patients without previous atopic disease. But, although it is usually asymptomatic, none of our patients showed any symptoms associated with *T. canis* infection. In addition the frequency of peripheral eosinophilia, which is one of the characteristics of *T. canis* infection, was very low. Secondly, the mode of onset is different. Non-acute onset was observed in most of our patients while about the half of patients had subacute or chronic onset in Japanese data. In 4 (28%) AM patients, they could not recall the exact time at which symptoms reached maximal severity because mild symptoms persisted for long time. Another one patient had only Lhermitte's sign on flexion of the neck. These patients are considered as non-acute onset. This fact may account for the difference in the mode of onset. It is notable that a substantial portion of our patients (85%) and of the Japanese cases (75%) had slow progression or fluctuating disease course, giving rise to one of the distinct feature of AM. In addition, asymmetry was common and persisted during the course of disease in most of our patients. Considering idiopathic AM is usually monophasic and a symmetrical, asymmetry also might be one of clinical characteristics in AM.

Spine MRI findings deserve mentioning. Most of previous reports [5–7,16] have been limited because: 1) a substantial portion of suspected myelitis was not verified by spine MRI, 2) lesion length and contrast enhancement pattern on axial and sagittal images, which are important to differentiate from tumorous condition such as intramedullary tumors, were not fully described, 3) brain MRI was not performed in all patients with myelitis to detect asymptomatic lesion suggestive of multiple sclerosis or NMO [13,17]. In this study, a substantial portion of AM patients showed cord swelling over three to four vertebral segments with focal contrast enhancement. Despite of long duration of symptoms in AM, persistent cord swelling with contrast enhancement may suggest slowly progressive or persistent active inflammation. On axial images, enhancement was focally nodular and located at the margin of lesion. The enhancing area was much smaller than the extensive hyperintense lesion on T2-weighted images. Assuming that the enhancing area is the focus of active and severe inflammation, this could explain prominent asymmetry in AM. It is noteworthy that abnormal brain lesions were not detected in AM patients.

Different patterns of spine and brain MRI were found in non-AM patients. Cord swelling with focal enhancement was not frequent in non-AM patients. LESCL with selective gray matter on axial images, as is frequent in NMO or opticospinal multiple sclerosis (OSMS) [18,19], were observed in 9 of 15 patients, three of them developed recurrent myelitis. Eccentric large lesions were absent in this group. On brain MRI, lesions suggestive of MS were found in two non-AM patients and lesions atypical for MS were seen in three non-AM patients; two of them had NMO-IgG.

Although distinct clinicolaboratory features of AM have been reported in our study as well as several studies from Japan, the precise pathophysiology of AM remains to be elucidated. Recent clinicopathological findings have revealed active eosinophil infiltration with the deposition of eosinophil cationic protein, despite mild and long duration of symptoms [9,20]. Furthermore, axons as well as myelin were severely destroyed [20]. This early axonal involvement, unlike that which occurs in multiple sclerosis, may explain the persistent symptoms despite steroid therapy in these patients. While this necrotizing feature is commonly encountered in NMO, eosinophil infiltration is a rare finding. In addition, NMO-IgG, which is frequently present in NMO or OSMS [11], was detected in none of the AM patients, suggesting that AM is a different entity from NMO. Immunologically, AM appears to be different from other myelitis diseases associated with MS or HTLV-1-associated myelopathy/tropical spastic paraparesis in that type 2 helper T (Th2) cell response is predominant in the former whereas Th1 cell response is predominant in the latter [21–23]. More recently, CSF cytokine/chemokine analysis showing upregulation of chemokine-ligand-11/interleukin-9, which is important for eosinophil recruitment and maturation, has lent further supported the allergic nature of AM [24].

There are several limitations to our study. First, because the patients were recruited from a tertiary hospital, they may not represent patients in the general population. This may be especially true in that a substantial portion of AM patients could have been underestimated in primary care clinics because the symptoms were mild and asymmetrical, which often ends in false diagnosis such as radiculopathy or peripheral neuropathy. Second, no pathological verification was done. Third, follow-up duration was relatively short. A longer follow-up would allow a different impact on the recurrence rate between two groups. Finally, because all of patients in our study are Korean, our data could not be generalized to other ethnic groups.

In conclusion, our findings show that AM is fairly common in Korea and that this entity has relatively homogenous clinicoradiological

features different from that of non-AM or other central demyelinating diseases. In this regards, the recognition of this entity could be important from the therapeutic and prognostic perspective. Further studies including measurement of antibodies against *T. canis* in both sera and CSF are warranted to confirm our observations and to clarify the exact mechanisms for this entity.

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