저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:

저작자표시. 귀하는 원저작자를 표시하여야 합니다.

비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.

변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 이용허락규약(Legal Code)을 이해하기 쉽게 요약한 것입니다.

Disclaimer
Atopic Myelitis: An Emerging Cause of Myelitis in Korea

by

Jung Han Yoon

Major in Medicine
Department of Medical Sciences
The Graduate School, Ajou University
Atopic Myelitis: An Emerging Cause of Myelitis in Korea

by

Jung Han Yoon

A Dissertation Submitted to The Graduate School of Ajou University in Partial Fulfillment of the Requirements for the Degree of Master of medicine

Supervised by

In Soo Joo, M.D.

Major in Medicine

Department of Medical Sciences

The Graduate School, Ajou University

August, 2009
This certifies that the dissertation of Jung Han Yoon is approved.

SUPERVISORY COMMITTEE

__________________________ In Soo Joo

__________________________ Kyoon Huh

__________________________ Ji Man Hong

The Graduate School, Ajou University
June, 22nd, 2009
Acknowledgements

Almost half a year has passed since I finished residency course in neurology at Ajou University Hospital. I think it was tough but most precious moment in my life. When I have strayed, I have been able to look to Professor In-soo Joo, my supervisor for his generosity and encouragement; to Professor Kyoon Huh, for his faith and discipline; to Professor Oh-young Bang, for his careful concern and tenacity; to Professor Phil-hyu Lee, for his passion; to Professor Ji-man Hong, for limitless advice; to Professor So-young Moon for her thoughtfulness; to Professor Seok-woo Yong, for his moderation.

I am also grateful to my friends, especially Hee-young Park. As resident, we spent most of our days taking care of patients together at hospital.

It is to my family, though—my father, mother and my sister—that I owe the deepest gratitude. Without their constant love and support, I could never have finished.

Finally, I would like to thank my fiancee, Ha-young Park who passed a few months ago, for understanding and caring for me all the time. I won’t try to describe how deeply I love her still. I know that she was the kindest, most pure spirit I have ever known.

June 27th, 2009

Waiting for summer at In-Gok Jae Hospital
Atopic Myelitis: An Emerging Cause of Myelitis in Korea

Background: HyperIgEemia and atopy has recently been reported to be related with various neurological diseases such as Hirayama disease and idiopathic myelitis. We aimed to determine frequency of atopy or hyperIgEemia in idiopathic myelitis in Korea and to characterize the clinic-laboratory and MRI profiles of atopic myelitis (AM) in comparison with non-AM.

Methods: From 2006 January to 2008 August, twenty nine consecutive patients with idiopathic myelitis (14 AM and 15 non-AM) were enrolled from registry. The frequency of hyperIgEemia and two mite antigen-specific IgE positivity was examined in idiopathic myelitis patients. In addition, we compared clinical data, laboratory results including neuromyelitis optica (NMO)-IgG, autoantibodies, and radiologic findings between AM and non-AM patients.

Results: 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 following distinctive features. (1) younger age at onset (39 years vs. 51 years; p<0.0001), (2) non-acute onset (13/14 vs. 5/15; p=0.002) and long-duration of symptom at admission (76 days vs. 16 days; p<0.001), (3) predominant sensory symptom with mild weakness (4) low EDSS score (2.1 vs. 5.6; p<0.001), (5) low frequency of abnormal SEP findings (2/14 vs. 11/15; p<0.005), and (6)
increased eosinophils in peripheral blood (5.0% vs. 1.0%; p<0.001). Common MR findings of AM included eccentric lesion occupying more than two thirds of spinal cord (92%) with focal peripheral enhancement (92%) on axial image, and the lesion usually extended more than 3 to 5 vertebral segments (71%) with cord swelling (71%).

**Conclusions:** HyperIgEemia and mite antigen-specific IgE are fairly common in Korean idiopathic myelitis patients. The AM patients show relatively homogenous clinicolaboratory and radiological features. It is noteworthy that none of these patients shows brain abnormality suggestive of multiple sclerosis or neuromyelitis optica (NMO). These results suggest that AM is a distinct disease entity with different pathogenesis from multiple sclerosis or NMO.

**Key words:** Atopic myelitis, idiopathic myelitis, Neuromyelitis optica, multiple sclerosis

**Abbreviations:** EDSS, Expanded Disability Status Scale of Kurtzke; SEP, somatosensory evoked potential
# TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................... i  

TABLE OF CONTENTS .................................................................................................................. iii  

LIST OF FIGURES ............................................................................................................................... v  

LIST OF TABLES ............................................................................................................................... vi  

I. INTRODUCTION ............................................................................................................................. 1  

II. PATIENTS AND METHODS ........................................................................................................... 3  

   A. PATIENTS .................................................................................................................................. 3  

   B. CLINICAL ASSESSMENT .......................................................................................................... 3  

   C. MEASUREMENT OF TOTAL AND SPECIFIC IGE LEVEL ................................................... 4  

   D. MEASUREMENT OF NMO-IGG .............................................................................................. 4  

   E. MRI .......................................................................................................................................... 4  

   F. STATISTICAL ANALYSIS ......................................................................................................... 5  

III. RESULTS ..................................................................................................................................... 6  

   A. COMPARISON OF TOTAL IgE AND MITE-SPECIFIC IgE BETWEEN MYELITIS AND NORMAL CONTROL ......................................................................................................................... 6  

   B. COMPARISON OF CLINICAL FEATURES BETWEEN PATIENTS WITH AND WITHOUT AM ................................................................................................................................. 10  

   C. COMPARISON OF MRI FINDINGS BETWEEN PATIENTS WITH AND WITHOUT AM ............ 13  

   D. TREATMENT ............................................................................................................................. 18
E. PROGNOSIS

IV. DISCUSSION

REFERENCES

국문요약
LIST OF FIGURES

Fig. 1. Distribution of the level of total IgE (A) and *Dermatophagoides pteronyssinus* (D1) and *fubrinae* (D2)-specific IgE (B, C) in myelitis patients (n=29) and normal control (n=39) .......................................................... 8

Fig. 2. Representative MRI findings of atopic myelitis ........................................ 15

Fig. 3. Kaplan-Meier analysis for the occurrence of relapse between patients with and Without AM ............................................................................................................. 19

Fig. 4. Timeline and brain MRI classification of patients with recurrent myelitis .... 20
LIST OF TABLES

Table 1. Frequency of hyperIgEemia and mite antigen-specific IgE positivity .......... 7

Table 2. Clinico-laboratory findings between patients with and without atopic myelitis (AM) .......................................................... 12

Table 3. Radiological findings between patients with and without atopic myelitis ........ 17
I. INTRODUCTION

Atopy refers to enhanced IgE response to common environmental antigens such as foods, pollens and house dust mites. With time, the prevalence of atopy such as atopic dermatitis, bronchial asthma and allergic rhinitis has been increased in worldwide (Eder et al. 2006). Recently, various neurological diseases including Hopkins’ syndrome (Hopkins 1974), Hirayama disease (Kira and Ochi 2001; Ito et al. 2005) and idiopathic myelitis (Kira et al. 1997; Kira et al. 1998; Kira et al. 2001; Osoegawa et al. 2003) have been found to be related to atopy such as atopic dermatitis, allergic rhinitis or bronchial asthma. Kira et al firstly described 4 patients with atopic dermatitis suffering from myelitis during the exacerbation of atopic symptom (Kira et al. 1997). More recently, they found the substantial portion of idiopathic myelitis to be associated with hyperIgEemia as well as atopic disease (Kira et al. 1998; Kira et al. 2001; Osoegawa et al. 2003). 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 (Kira et al. 2001): young age onset, slowly progressive course and predominant sensory symptom with mild motor weakness, and few CSF abnormality. In addition, these findings were recently confirmed by Japan nation-wide survey. Based on these distinct clinicolaboratory features, the term “atopic myelitis (AM)” has been proposed.

However, most AM patients have been investigated in Japan, even though only a few cases of AM has been reported in western country (Zoli et al. 2005; Gregoire et al. 2006). Thus, it has been unclear whether AM is distinct entity of idiopathic myelitis or whether AM
is frequent in other Asian country as in the case of Hirayama disease.

In fact, idiopathic myelitis without previous neurological symptoms often turn out to have heterogeneous causes such as multiple sclerosis (MS), neuromyelitis optica (NMO) after long-term follow up. Thus, besides clinical follow-up, numerous efforts to find biological or radiological marker for predicting cause of idiopathic myelitis, have been made. First of all, brain MRI lesion according to Barkhof criteria is well-established radiological marker for predicting conversion to multiple sclerosis (Barkhof et al. 1997). Recently, NMO-IgG has been reported to be specific bio-marker for NMO or OSMS (optico-spinal multiple sclerosis) (Lennon et al. 2004; Nakashima et al. 2006). Especially, patients with LESCL and NMO-IgG tended to experience more subsequent myelitis or optic neuritis (Weinshenker et al. 2006). Furthermore, Pittock et al reported that asymptomatic brains are common in NMO (Pittock et al. 2006; Pittock et al. 2006), which is reflected in revised criteria of NMO (Wingerchuk et al. 2006).

To date, several lines of data have been published with focus on AM, but studies comparing clinical, laboratory results including NMO-IgG, autoantibodies, and radiological findings of AM in the context of whole spectrum of idiopathic myelitis are scarce. (Kira et al. 2001) Furthermore, treatment and follow-up of AM patients have rarely been studied.

The aims of this study are (1) to determine frequency of atopic myelitis (AM) in Korea and (2) to characterize the clinical, laboratory and MRI profiles and outcome of AM in comparison to non-AM patients.
II. PATIENTS AND METHOD

A. PATIENTS

From January 2006 to August 2008, patients with idiopathic myelitis were recruited from 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 neurological diseases or symptoms. Patients with clinical course of more than 1 month were included because long duration were frequently seen in atopic myelitis(Kira et al. 2001; Osoegawa et al. 2003). 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 symptom and CSF pleocytosis (> 50 mg/dl) 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, allergic rhinitis, or 2) hyperIgEemia and specific IgE to mite antigen (Dermatophagoides pteronyssinus, D1 and fabrinae, D2), as proposed by Kira et al(Kira et al. 1998). Thirty nine age and sex-matched subjects without history of any atopic diseases were recruited as a control.

B. 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)(Kurtzke 1983). Steroid response was considered effective if improvement of more than 1 point in EDSS score was achieved.
C. MEASUREMENT OF TOTAL AND SPECIFIC IGE

The level of total IgE and two common mite antigens, *Dermatophagoides pteronyssinus* (D1) and *fabrinae* (D2)-specific IgE were measured by Pharmacia CAP System (Pharmacia AB, Uppsala, Sweden) according to the manufacturer’s instructions. The upper normal limit of the serum total IgE and the mite antigen-specific IgE level are 250 IU/ml and 0.35 IU/ml, respectively.

D. MEASUREMENT OF NMO-IgG

Testing for NMO-IgG was performed by indirect immunofluorescence on a substrate of mouse cerebellum and midbrain, as previously described (Lennon et al. 2004). Readers were blinded to all clinical information.

E. MRI

All patients were performed spine MRI with a 1.5T 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 lesion (LESCL) (Weinshenker et al. 2006). A central linear high signal intensity seen above or below the diffuse lesion on T2WI was not considered for 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 criteria (Barkhof et al. 1997).

F. STATISTICAL ANALYSIS

Mann Whitney-U test was used for comparison of continuous variable (the level of total IgE and mite antigen-specific IgE) and Chi square or Fisher’s exact test was applied to compare frequency data. Kaplan-Meier analysis was used to evaluate the difference of relapse between patients with AM and without. A statistical significance was set at p<0.05.
### 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 as idiopathic myelitis.

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

#### A. COMPARISON OF TOTAL IgE AND MITE-SPECIFIC IgE BETWEEN MYELITIS AND NORMAL CONTROL

The level of total serum IgE and two mite antigen-specific IgE in patients with myelitis and normal control were shown in Fig 1. HyperIgEemia was more frequent in patients with myelitis (58%) than normal control (20%, p=0.005)(Table 1). The level of total IgE was significantly higher in myelitis group (median 324 IU/ml, range 18-2,345 IU/ml) than normal control (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 and in about two fifth in healthy control (p=0.05 and p=0.001, respectively)(Table 1). In
addition, myelitis patients showed significantly higher median level of *D. pteronyssinus* (0.5 IU/ml) and *fabrinae* (0.45 IU/ml)-specific IgE than normal control (*p*<0.05)(Fig. 1B and C).

### Table 1. Frequency of hyperIgEemia and mite antigen-specific IgE positivity.

<table>
<thead>
<tr>
<th></th>
<th>HyperIgEemia</th>
<th><em>D. pteronyssinus</em> (D1) IgE positivity</th>
<th><em>D. fabrinae</em> (D2) IgE positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic Myelitis (n=29)</td>
<td>17 (58%)*</td>
<td>18 (61%)*</td>
<td>19 (65%)*</td>
</tr>
<tr>
<td>Healthy control (n=39)</td>
<td>8 (20%)</td>
<td>7 (17%)</td>
<td>9 (23%)</td>
</tr>
</tbody>
</table>

*P*<0.05 compared than normal control.
Fig. 1. Distribution of the level of total IgE (A) and *Dermatophagoides pteronyssinus* (D1) and *fabrinae* (D2)-specific IgE (B, C) in myelitis patients (n=29) and normal control (n=39). 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.
B. COMPARISON OF CLINICAL FEATURES BETWEEN PATIENTS WITH AND WITHOUT AM

We compared clinical and laboratory findings between patients with and without AM (Table 2). AM patients showed male preponderance (97% vs. 56%) and were significantly younger than non-AM patients (39 years vs. 51 years; p<0.0001). Regarding the characteristics of clinical presentation at admission, non-acute onset (92% vs 33%), asymmetry (79% vs 27%) were significantly more frequent in AM patients. Among patients with non-acute onset, disease course was slowly progressive in most patients. In addition, symptom duration was significantly longer in AM patients (76 days vs. 16 days; p<0.001). While sensory symptoms were predominant during entire course as well as at onset of AM, moderate to severe motor weakness was less frequent (0% vs. 66%; p<0.05), which resulted in lower EDSS score in AM patients (2.5 vs. 3.5; P<0.005). There was no significant difference in the frequency of Lhemitte sign and urinary or sphincter symptoms between two groups.

Pleocytosis and elevated protein in CSF were more common in patients with non-AM, however, the difference was statistically significant in CSF protein (21% vs. 66%; P<0.001). None of AM patients had increased IgG index or CSF oligoclonal band, which was not different from non-AM patient. Eosinophil percentage in peripheral blood was significantly higher in AM patients (5% vs. 1%; p<0.05), although definite eosinophilia (>10% in the peripheral blood) was observed in only two AM patients. NMO-IgG was detected in only 2 non-AM patients whereas none of AM patients had NMO-IgG. Antinuclear antibody (ANA)
or extractable nuclear antigen (ENA) were detected in 3 non-AM patients while none of AM patients had autoimmune antibody. One patient of non-AM patients had autoimmune thyroid disease.

On electrophysiological studies, most non-AM patients showed abnormal findings on somatosensory evoked potentials, but did not in AM patients (73% vs. 14%; P<0.05), whereas abnormality of visual evoked potentials was not observed in both group.
Table 2. Clinico-laboratory findings between patients with and without atopic myelitis

<table>
<thead>
<tr>
<th></th>
<th>AM (n=14)</th>
<th>Non-AM (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (years, mean ± SD)</td>
<td>39 ± 6.6</td>
<td>51 ± 8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>11 (78.6%)**</td>
<td>8 (53.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Known history of atopy</td>
<td>4 (28%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mode of onset</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Acute</td>
<td>1 (7%)</td>
<td>10 (66%)</td>
<td></td>
</tr>
<tr>
<td>Non-acute</td>
<td>13 (92%)</td>
<td>5 (33%)</td>
<td></td>
</tr>
<tr>
<td>Clinical course</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Slowly progressing/Fluctuating</td>
<td>12 (85%)</td>
<td>5 (32%)</td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>2 (14%)</td>
<td>10 (66%)</td>
<td></td>
</tr>
<tr>
<td>Symptom duration (days, mean ± SD)</td>
<td>76 ± 56</td>
<td>16 ± 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>11 (79%)</td>
<td>4 (27%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Clinical symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial paresthesia</td>
<td>10 (71%)</td>
<td>5 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Motor weakness</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal to mild</td>
<td>14 (21%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe*</td>
<td>0 (0%)</td>
<td>10 (66%)</td>
<td></td>
</tr>
<tr>
<td>Paresthesia/dysesthesia</td>
<td>12 (85%)</td>
<td>7 (46%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypesthesia</td>
<td>10 (71%)</td>
<td>13 (86%)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary/Sphincter symptom</td>
<td>6 (42%)</td>
<td>11 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean EDSS at admission</td>
<td>2.1 ± 0.5</td>
<td>5.6 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eosinophil (%. mean ± SD)</td>
<td>5.0 ± 3.2</td>
<td>1.0 ± 1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SEP abnormality</td>
<td>2 (25%)</td>
<td>11 (83%)</td>
<td>0.003</td>
</tr>
<tr>
<td>VEP abnormality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Protein (&gt;45 mg/dl)</td>
<td>3 (21%)</td>
<td>10 (66%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Pleocytosis (&gt;5 cells)</td>
<td>1 (7%)</td>
<td>4 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Oligoclonal band</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated IgG index</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid effectiveness</td>
<td>1 (7%)</td>
<td>3 (21%)</td>
<td>NS</td>
</tr>
<tr>
<td>NMO IgG</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>ANA</td>
<td>0 (0%)</td>
<td>3 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>ENA</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>RF</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>0 (0%)</td>
<td>1 (13%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Kurtzke’s expanded disability status scale; SEP, somatosensory evoked potential; VEP, visual evoked potential; NMO, neuromyelitis optica; ANA, antinuclear antibody; ENA, extractable nuclear antigen; RF, rheumatoid factor
C. COMPARISON OF MRI FINDINGS BETWEEN PATIENTS WITH AND WITHOUT AM

We compared MRI findings between patients with and without AM (Table 3). Spinal cord swelling was found in 71% (10/14) in AM patients whereas only 26% (4/15) in non-AM patients. (P<0.05) In AM patients, the thoracic cord (71%) was most frequently affected, followed by the cervical cord (28%), while thoracic (33%) and thoracic to lumbar (33%) were most commonly involved regions in non-AM patients. LESCL was found in the 71% (10/14) of AM and 73% (11/15) of non-AM patients at similar frequency. Although both groups frequently showed LESCL, 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 peripherally located toward one side (eccentric large pattern), irrespective of 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; central gray matter-predominant pattern in 66% (10/15), focal peripheral white matter-predominant pattern in 20% (3/15) and holocord pattern in 13% (2/15). Most (9/10) of patients with central gray matter-predominant pattern had LESCL, whereas 2 of 3 patients with focal peripheral white matter-predominant pattern had lesion affecting less than two vertebral segments.

Thirteen (92%) of 14 AM patients had clear contrast enhancement on both axial (Fig. 2B) and sagittal T1WI (Fig. 2D). On axial T1WI, the enhancement occupied only small portion at the margin of lesion. By contrast, in non-AM patient, ill-defined (8/11) pattern was the
most common followed by focal contrast enhancement pattern (3/11).
Fig. 2. Representative MRI findings of atopic myelitis (AM). A 40-year-old man with progressive left leg paresthesia for 3 months. The patient have no brain abnormality or NMO IgG in serum. (A) On axial T2WI, high signal intensity lesion is eccentric to the right but occupies more than two thirds of the cross-sectional area of the spinal cord. (B) Only 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 T8-11 level with a cord swelling. (D) Post-contrast sagittal T1WI demonstrate focal enhancement in the middle of lesion. Three month later, most of lesion on sagittal T2WI (E) and post-contrast sagittal T1WI (F) disappeared despite mild persistent symptom.

In all of patients with AM, brain MRI showed normal findings whereas 5 of non-AM patients showed brain lesions. (P<0.05) Of these 5 patients, 2 patients had lesions suggestive of MS (perpendicular periventricular and juxtacortical lesions) and another 3 patients showed nonspecific brain lesions (corpus callosum, posterior limb of internal capsule and subcortical white matter).
Table 3. Radiological findings between patients with and without atopic myelitis (AM)

<table>
<thead>
<tr>
<th>Spinal cord MRI findings</th>
<th>AM (n=14)</th>
<th>Non-AM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Swelling</strong></td>
<td>10 (71%)*</td>
<td>4 (26%)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Axial T2WI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccentric large</td>
<td>13 (92%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central</td>
<td>1(7%)</td>
<td>10 (66%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Holocord</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral</td>
<td>0 (0%)</td>
<td>3 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Gd-Enhancement</td>
<td>14 (100%)</td>
<td>11 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td>Focal</td>
<td>13 (92%)</td>
<td>3/11 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ill-defined and patch</td>
<td>1 (7%)</td>
<td>8/11 (63%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRI spine lesion length</td>
<td>3.5 (1-6)</td>
<td>4 (1-15)</td>
<td>NS</td>
</tr>
<tr>
<td>LESCL</td>
<td>10 (71%)</td>
<td>11 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Involved Spine (total)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>4 (28%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical to thoracic</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thoracic</td>
<td>10 (71%)</td>
<td>5 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Thoracic to lumbar</td>
<td>0 (0%)</td>
<td>5 (33%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Cervical to lumbar</td>
<td>0 (0%)</td>
<td>1(7%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Brain MRI lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (0%)</td>
<td>5 (33%)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>MS-like</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atypical</td>
<td>0 (0%)</td>
<td>3 (20%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: LESCL, longitudinal extensive spinal cord lesion; MS, multiple sclerosis

*Number of patients (percentage)
D. TREATMENT

All patients were treated with high-dose intravenous steroid pulse therapy except one with side effect to steroid. Most (13/14) of AM patients showed no clinical improvement to steroid. In non-AM patients, 3/14 (21%) patients showed clinical improvement whereas one patient worsened after treatment.

E. PROGNOSIS

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). During the follow-up period, none of 14 patients with AM experienced either subsequent myelitis or optic neuritis, although mild symptoms persisted in most patients (12/14)(Fig. 3). Of these, 7 patients (50%) performed spine MRI repeatedly between 3 to 6 months after steroid pulse therapy. In all of these patients, swelling disappeared and the lesion markedly improved (Fig. 2E). Furthermore, contrast enhancement disappeared in most (6/7) of patients (Fig. 2F), although one patient still had focal enhancement but much smaller than the previous one.

In non-AM patients, 4 (27%) of 15 patients had suffered from recurrent myelitis (Fig. 3) and the relapse was severe leading to paraplegia in three patients with LESCL (patient 1, 2, 3 in Fig.4) However, in one patient with focal peripheral white matter pattern with short cord lesion, recurrent myelitis showed good recovery to steroid pulse therapy (patient 4 in Fig.4.).
Fig. 3. Kaplan-Meier analysis for the occurrence of relapse between AM and non-AM
Fig. 4. Timeline and brain MRI classification of non-AM patients with subsequent myelitis. Patient 1 to 3 have LESCL with selective gray matter involvement, whereas patient 4 have short cord lesion with focal peripheral white matter pattern.
IV. DISCUSSION

Although there are many etiology causing myelitis such as viral infection, vaccination, demyelinating diseases, collagen vascular diseases, substantial portion of myelitis turn out to be idiopathic(Jacob and Weinshenker 2008). Recently, many portion of idiopathic myelitis have been found to have hyperIgEemia and common mite-antigen specific IgE as well as atopy in Japan(Kira et al. 1998; Kira et al. 2001; Osoegawa et al. 2003). Our study also shows that hyperIgEemia and mite-antigen specific IgE are fairly common in idiopathic myelitis although atopy is less common.

In our study, patients with AM showed following distinctive features compared with those with non-AM patients:1) younger age at onset, 2) non-acute onset and long duration of symptoms, 3) slowly progressive or fluctuating course, 4) prominent asymmetrical sensory symptom 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 nation-wide survey in Japan(Osoegawa et al. 2003), several differences exist.

Firstly, there is male predominance and preferential thoracic cord involvement in AM patients in our study. The differences could be 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(Kira et al. 2001), myelitis patients with known atopic disease have a tendency to have female predominance and cervical spine involvement than myelitis with
only hyperIgEemia and mite antigen specific IgE, even though clinical features are similar each other (Kira et al. 2001). However, it is unclear whether the presence of atopy implies the different underlying pathophysiology in atopic myelitis. Secondly, the mode of onset is different. Non-acute onset is observed in most of our patients while about the half of patients have subacute or chronic onset in Japanese data. In 4 (28%) of AM patients, they did not recall the exact time at which the symptom reached maximal severity because mild symptom persisted for long time. Another 1 patient have only Lhemitte sign on flexion of the neck. These patients are considered as non-acute onset. Therefore, the fact may account for the difference in the mode of onset. It is notable that substantial portion of our patients (85%) and Japanese cases (75%) have slowly progressive or fluctuating course, giving rise to one of the distinct feature of AM. In addition, asymmetry is common and persists during course of disease in most of our patients. Considering idiopathic ATM is usually monophasic and symmetrical, asymmetry also might be one of clinical characteristics in AM.

Spine MRI findings deserve mentioning. Most of previous reports (Kira et al. 1998; Kira et al. 2001; Osoegawa et al. 2003) are limited because 1) 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 tumor, were not fully described, 3) brain MRI was not performed to all the patients with myelitis to detect asymptomatic lesion suggestive of multiple sclerosis or neuromyelitis optica (Barkhof et al. 1997; Pittock et al. 2006; Pittock et al. 2006). In this study, substantial portion of AM patients show cord swelling over three to four vertebral segments with focal contrast enhancement. Despite of long duration of symptom 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 lesion was not detected in AM patients.

Different pattern of spine and brain MRI were found in non-AM patients. Cord swelling (26%) with focal enhancement (27%) was not frequent in non-AM patients. Selective gray matter involvement on axial images with LESCL, as is frequent in NMO or OSMS (Matsuoka et al. 2007; Matsuoka et al. 2008), was observed in 9 of 15 patients, 3 of them developed recurrent myelitis causing severe paraplegia. Eccentric large lesion was found in none of this group. On brain MRI, lesion suggestive of MS were found in 2 of non-AM patients and lesion atypical for MS were seen in 3 of non-AM patients, 2 of them had LESCL with NMO-IgG.

Although distinct clinico-laboratory features of AM have been reported in our study as well as several studies in Japan, the precise pathophysiology of AM remains to be elucidated. Recent clinico-pathological findings revealed that active eosinophil infiltration with the deposition of eosinophil cationic protein, despite of mild and long duration of symptoms (Osoegawa et al. 2003; Gregoire et al. 2006). Furthermore, axon as well as myelin were severely destroyed (Osoegawa et al. 2003). These early axonal involvement, unlike to multiple sclerosis, may explain for persistent symptom despite of steroid therapy in these patients. While such a necrotizing feature is also commonly encountered in NMO, eosinophil
infiltration is rare finding. In addition, NMO-IgG and autoantibodies, which is commonly present in NMO (Hummers et al. 2004; Pittock et al. 2008), were detected in none of our AM patients, suggesting that AM is not autoimmune-related disorder such as NMO. Immunologically, AM appears to be different from other myelitis 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 (Horiuchi et al. 2000; Ochi et al. 2001; Ochi et al. 2004). More recently, CSF cytokine/chemokine analysis showing upregulation of chemokine-ligand-11/interleukin-9 which is important for eosinophil recruitment and maturation, can add more evidence for allergic nature of AM (Tanaka et al. 2008).

Previous observations has suggested that allergic mechanism is operative in AM, but can not explain why allergic mechanism occur in central nervous system such as spinal cord where external antigen is usually absent. One of the possible mechanism is a cross-reactivity between common environmental antigen and CNS antigen. Actually, mast cell, which plays important role in allergic reaction, exist in perivascular area in CNS besides tissues exposed to environmental antigens, such as the skin, intestinal tract, and trachea (Johnson et al. 1991). Thus, mast cell activation may cause a blood-brain-barrier (BBB) through the binding between CNS antigen and mast cells. Such a mechanism was suggested in presence of IgE antibodies to myelin basic protein in experimental allergic encephalomyelitis (EAE), the murin model for multiple sclerosis (Bo et al. 1991). Further studies on cross reactivity between common environmental allergen and CNS antigen, or induction of spinal cord lesion in animals by passive immunisation from serum or CSF of patients are necessary to
shed light on the exact pathogenesis of AM.

There are several limitations in our study. First, because the patients were recruited from a tertiary hospital, they may not represent patients in general population. Especially, substantial portion of AM could have been underestimated in primary care clinics because the symptom was mild and asymmetrical, which ends in false diagnosis such as radiculopathy or peripheral neuropathy. Second, no pathological verification was done. Third, follow-up duration was relatively short, and longer follow-up would permit different impact on recurrence rate between two groups. Particularly, several cases would probably have been diagnosed as NMO or MS, but did not experience a relapse during the follow up. 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 this entity have relatively homogenous clinico-radiological features different from non-AM or other central demyelinating diseases. In this regards, the recognition of this entity as a potential cause of idiopathic myelitis can be important from the therapeutic and prognostic perspective. Further multicenter studies with a prospective analysis are warranted to confirm our observations and to clarify the exact mechanisms for this entity.
REFERENCES


*Semin Neurol* 28: 105-120, 2008


아토피 척수염: 한국에서의 척수염의 새로운 원인

아주대학교 대학원의학과
윤 정 한
(지도교수: 주인수)

서론: 최근에 고IgE혈증과 아토피 질환은 여러 신경계 질환 (히라야마, 흉킨, 원인불명의 척수염)과 관계가 있음을 밝혀지고 있다. 우리는 이번 연구에서 한국에서의 원인 불명의 척수염에서 고IgE혈증과 아토피질환의 빈도를 알아보고, 아토피성 척수염의 임상, 혈청학적 및 방사선학적 특징을 비아토피성 척수염과 비교하고자 한다.

대상 및 방법: 2006년 1월부터 2008년 8월까지 총 29명의 원인 미상의 척수염 환자를 아주대학교 병원 척수염 목록으로부터 확인을 하였다. 우선, 고IgE혈증과 집먼지 진드기에 대한 특이 항체의 빈도를 원인불명의 척수염 환자들에게서 조사를 하였다. 그리고, 아토피 척수염 환자의 임상 양상, 혈청학적 검사와 방사선학적 소견을 조사하였다.

결과: 원인 불명의 척수염 환자에서 과거 아토피 질환은 4명의 환자에서만 발견이 되었지만(13%), 고IgE혈증과 집먼지 진드기에 대한 항체는 각각 56%, 61%에서 관찰되었다. 14명의 아토피성 척수염 환자는 비아토피성 척수염
환자와 비교해 볼 때, 다음과 같은 분명한 차이를 보여 주었다. (1) 발병연령이 젊은 점 (39 years vs. 51 years; p<0.0001), (2) 비급성 발현 (13/14 vs. 5/15; p=0.002) 과 입원당시 긴 증상 지속기간 (76 days vs. 16 days; p<0.001), (3) 낮은 EDSS 점수 (2.1 vs. 5.6; p<0.001), (4) 비정상 SEP의 낮은 비율 (2/14 vs. 11/15; p<0.005), 그리고 (6) 말초 혈액검사에서 증가된 호산구 비율 (5.0% vs. 1.0%; p<0.001). 아토피척수염 환자에서의 혼란 MRI 소견은 횡단면에서 전체 면적의 2/3 이상을 차지하는 타원형 (92%) 이며 주변부의 국소 조영증강 (92%) 양상을 보았으며, 척수의 세 분절 이상 (71%) 을 침범하며 부종을 동반 (71%) 하는 경향을 보였다.

결론: 고IgE혈증과 집먼지 진드기 특이 항체는 한국의 원인불명의 척수염 환자 에서 상당히 많이 존재했으며 아토피 척수염 환자는 비교적 균일한 임상, 혈척학 적 그리고 방사선학적 양상을 보여 주었다. 특히, 모든 아토피 척수염 환자의 뇌 MRI에서 다발성 경화증이나 시신경 척수염을 시사하는 소견이 없었다. 따라서 우리의 연구는 아토피 척수염이 다발성 경화증이나 시신경 척수염과는 다른 병 인을 가진 하나의 질환이라는 것을 시사한다.

핵심어: 척수염, 아토피, 아토피 척수염, 다발성 경화증, 시신경 척수염
약어: EDSS, Expanded Disability Status Scale of Kurtzke; SEP, somatosensory evoked potential