Rapidly Progressive Tabes Dorsalis Associated with Selective IgA Deficiency

Satoshi Nishimura, Hideaki Miura, Haruki Yamada, Tomiko Ryu and Yasusada Miura

Abstract

Tabes dorsalis is uncommon and progresses slowly from infection to clinical manifestation. We report a rare case of rapidly progressive tabes dorsalis associated with selective IgA deficiency (slgAD). A 28-year-old man was hospitalized with lightning back pain, nausea, and bladder bowel dysfunction. Serum and cerebrospinal fluid (CSF) revealed high titers of Treponema pallidum antibody, and the serum IgA level was less than 5 mg/dl. Th1-dominant cytokine expression was observed, as is usually seen in neurosyphilis. He was treated with Ceftriaxone and CSF pleocytosis disappeared. We postulate slgAD influenced the atypical rapid clinical course of tabes dorsalis in this patient.

Key words: neurosyphilis, Treponema pallidum, cytokines

Introduction

Neurosyphilis is an uncommon disease. Its pathogenesis remains unclear, and it was thought to be a disease of the past. However, the spread of HIV infection has led neurosyphilis to become a problem again, because co-infection with HIV leads syphilis to show an atypical and rapid clinical course, with resistance to the previously recommended treatment (1–3). Selective IgA deficiency is also uncommon, and its pathogenesis and clinical importance are not well understood. Here we report a 28-year-old man who had rapidly progressive tabes dorsalis associated with selective IgA deficiency. The present case may shed light on the role of IgA.

Case Report

A 28-year-old man was admitted to our hospital because of lightning back pain, nausea, vomiting, and bladder bowel dysfunction. He had noticed anisocoria three years before admission, and intermittent nausea gradually appeared from the next year. He lost weight because of worsening nausea and vomiting. He had sharp and stabbing pain around the lumbar and sacral vertebrae, and bladder bowel dysfunction occurred six months before admission. Both gastroscopy and colonoscopy were performed, but nothing abnormal was found.

The patient had been born after an uncomplicated full-term pregnancy and developed normally. Appendectomy was performed at the age of ten without transfusion, but HBs-antigen was detected when he attempted to make a blood donation at the age of twenty-one. He had no episode of urinary tract infection, no skin lesions, and no increase of other infections.

He smoked one pack of cigarettes a day, and drank alcohol occasionally. He was not married, but he had been sexually active since his first sexual intercourse when he was seventeen. He was heterosexual, and sexual intercourse was generally performed without protection.

On admission, the body temperature was 36.9°C, the pulse rate was 76/min, and the respiration rate was 13/min. His blood pressure was 122/62 mmHg. His height was 168 cm and his weight was 42.5 kg. Physical examination showed no specific findings, except for small palpable cervical and inguinal lymph nodes. No skin lesions, no Hutchinson’s teeth, and no skin ulcers were found. Fundus examination showed normal optic discs. Neurological examination revealed normal mental state, anisocoria (the right pupil was 4 mm in diameter and the left was 7.5 mm, respectively), a reduced light reflex in the left eye, vertical nystagmus, dysesthesia of the palms, lightning back pain, areflexia, generally reduced muscle tonus, ataxia with positive Romberg’s sign, and bladder bowel dysfunction.

Laboratory tests were performed (Table 1). He had normal blood cell counts and a normal differential white cell count. The urine was normal. Normal liver function tests with positive HBs antigen and anti-HBe antibody suggested that he was a healthy HBV carrier. The serologic tests for syphilis (STS) and the Treponema pallidum hemagglutination test (TPHA) were positive with high titers, indicating active syphilis infection. Examination of the cerebrospinal fluid (CSF) revealed elevated pressure, pleocytosis, and a high TPHA titer. He was negative for HIV tests.

In analyses for associated immunodeficiency, the serum IgA
Tabes Dorsalis with IgA Deficiency

Table 1. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>7,400/μl</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>61%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>26%</td>
</tr>
<tr>
<td>(CD4 47%, CD8 29%, CD20 7%)</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>9%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2%</td>
</tr>
<tr>
<td>Basophils</td>
<td>2%</td>
</tr>
<tr>
<td>RBC</td>
<td>449×10⁴/μl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.3 g/dl</td>
</tr>
<tr>
<td>Platelet</td>
<td>22.2×10⁴/μl</td>
</tr>
</tbody>
</table>

Blood chemistry

<table>
<thead>
<tr>
<th>Total Protein</th>
<th>7.4 g/dl</th>
<th>6.5–8.0 g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>5.0 g/dl</td>
<td>4.1–5.0 g/dl</td>
</tr>
<tr>
<td>AST</td>
<td>29 IU/l</td>
<td>10–33 IU/l</td>
</tr>
<tr>
<td>ALT</td>
<td>30 IU/l</td>
<td>4–30 IU/l</td>
</tr>
<tr>
<td>LDH</td>
<td>299 IU/l</td>
<td>210–500 IU/l</td>
</tr>
<tr>
<td>GTP</td>
<td>26 IU/l</td>
<td>10–75 IU/l</td>
</tr>
<tr>
<td>T.Bil</td>
<td>0.8 mg/dl</td>
<td>0.2–1.2 mg/dl</td>
</tr>
<tr>
<td>BUN</td>
<td>19 mg/dl</td>
<td>8–20 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 mg/dl</td>
<td>0.6–1.1 mg/dl</td>
</tr>
<tr>
<td>CRP</td>
<td>0.3 mg/dl</td>
<td>0.0–0.4 mg/dl</td>
</tr>
</tbody>
</table>

Serology

Serologic tests for syphilis (STS)
(+, ×32) (the rapid plasma reagin method)
(+, ×32) (Venereal Diseases Research Laboratory Test)

Treponema pallidum hemagglutination test (TPHA)
(+, > ×5,120)

HBs-antigen (+)
HBe-antigen (–)
anti-HBe (+)
anti-HCV (–)
anti-HIV (–)

Cerebrospinal fluid

Pressure 120 mmH₂O
Cell count 20 cells/μl
(100% mononuclear cells, CD4 35%, CD8 22%, CD20 37%)
Protein 23 mg/dl

Treponema pallidum hemagglutination test (TPHA) (+, ×320)


Serology

Serologic tests for syphilis (STS)
(+, ×32) (the rapid plasma reagin method)
(+, ×32) (Venereal Diseases Research Laboratory Test)

Treponema pallidum hemagglutination test (TPHA)
(+, > ×5,120)

HBs-antigen (+)
HBe-antigen (–)
anti-HBe (+)
anti-HCV (–)
anti-HIV (–)

Cerebrospinal fluid

Pressure 120 mmH₂O
Cell count 20 cells/μl
(100% mononuclear cells, CD4 35%, CD8 22%, CD20 37%)
Protein 23 mg/dl

Treponema pallidum hemagglutination test (TPHA) (+, ×320)


level was found to be less than 5 mg/dl, whereas IgG and IgM were within the normal limits, and serum protein immunoelectrophoresis revealed the complete absence of precipitation between serum from the patient and specific anti-IgA serum (Fig. 1). Selective IgA deficiency was diagnosed and serum anti-IgA antibodies were observed. The serum level of cytokines showed increased IFN-γ, and a normal range of interleukin (IL)-5, 6, and 10 (Table 2). Magnetic resonance imaging (MRI) of the head and spinal cord with gadolinium enhancement showed an enhancing lesion anterior to the pons on T1-weighted images that suggested pachymeningitis (Fig. 2).

He was treated with Ampicillin (ABPC) and Ceftriaxone

Figure 1. Results of immunoelectrophoresis, showing the complete absence of precipitation between serum from the patient and specific anti-IgA serum (arrow).

Table 2. Cytokine Levels on Admission

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Serum Level</th>
<th>CSF Level</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>0.2 IU/ml</td>
<td>&lt;0.1 IU/ml</td>
<td>&lt;0.1 IU/ml</td>
</tr>
<tr>
<td>IL-5</td>
<td>&lt;5 pg/ml</td>
<td>&lt;10 pg/ml</td>
<td>&lt;10 pg/ml</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.3 pg/ml</td>
<td>&lt;4 pg/ml</td>
<td>&lt;4 pg/ml</td>
</tr>
<tr>
<td>IL-10</td>
<td>&lt;2 pg/ml</td>
<td>&lt;5 pg/ml</td>
<td>&lt;5 pg/ml</td>
</tr>
</tbody>
</table>

Figure 2. MRI showing an enhanced lesion anterior to the pons on a T1-weighted image (arrow).
(CTRX) 2 g/day intravenously. Pleocytosis disappeared, and the pressure of CSF decreased. The serum STS value decreased, but his clinical findings did not change (Fig. 3). He was readmitted to our hospital six months later for re-treatment, and the gadolinium enhancement lesion on magnetic resonance imaging had decreased.

**Discussion**

This is the first reported case of rapidly progressive tabes dorsalis associated with selective IgA deficiency. Tabes dorsalis is the late stage of neurosyphilis and has been uncommon in the first three decades of penicillin use. It is known to progress slowly from infection to clinical manifestation, usually over more than 20 years. But, in the past decade, neurosyphilis has been more common in younger patients. The reason may be an impaired host immune response caused by additional infection including human immunodeficiency virus (HIV). In patients with both HIV infection and syphilis, there have been several reports of atypical clinical symptoms, rapid progression, and resistance to penicillin (1–3). Regarding T-cell response against syphilis, a recent study showed that a Th1-predominant local cellular response such as interferon (IFN)-γ, interleukin (IL)-2, 10, and 12, promoted macrophage activation and Spirochaeta clearance during early syphilis (4–6). T-cell responses later in syphilis are believed to play a role in the development of immunity to re-infection. The present case was atypical in that the clinical course was thought to have been no longer than seven years, although HIV infection was denied. The levels of serum cytokines showed increased IFN-γ, and normal range of IL-5, 6, and 10, indicating Th1-predominance, which is typical of the local immune response against neurosyphilis.

In this case, selective IgA deficiency was revealed, which is very uncommon in Japan; its incidence is approximately 1 in 18,500. IgA deficiency is associated with autoimmune diseases and more than 20% of patients have significant levels of antibodies to IgA (7–9). In some instances it is familial. Half of the IgA-deficient individuals remain healthy, but others may experience an increased frequency of infections or unusual types of infections. The pathogenesis is heterogeneous and many types of immune system defects may be involved (9). Arrested differentiation of IgM B cells into IgA-secreting plasma cells is suspected to occur, but the precise point at which differentiation is arrested remains a subject of controversy. The presence of IgA-positive B cells in IgA-deficient patients appears to place the defect downstream of isotype switching and implicates problems in the triggering of IgA B cells. Various experimental models of IgA deficiency support this hypothesis. Mice with targeted inactivation of the T cell receptor, NF-κB, and various cytokines or cytokine-related genes (IL-4, 6, 7 etc.) have low IgA levels or no IgA secretion (9). In the present case, a Th1-dominant cytokine pattern was observed, as is usually seen in neurosyphilis (4–6). This suggested that selective IgA deficiency did not affect the cellular or cytokine immune response.

This patient was atypical in that the clinical course was rapid. The appearance of intermittent nausea and vomiting before admission suggests the onset of meningeal syphilis, but only an additional three years had led to his clinical presentation of tabes dorsalis, late syphilis. Tabes dorsalis tends to present with
the longest latency of all neurosyphilis syndromes, occurring 25 to 30 years after primary infection (10). The peak of incidence of tabes dorsalis is in the fourth and fifth decades of life, but the present patient was only 28 years old on admission. The atypical rapid course of this patient was possibly due to his selective IgA deficiency. Defective mucosal immunity because of the absence of IgA or an incomplete immune response against syphilis may have led to early- and re-infection, and failure to eliminate the organism, but the precise mechanism is unknown.

The patient was successfully treated using Ceftriaxone. Ceftriaxone has been recommended as an established alternative in patients with both infections of syphilis and HIV, because it penetrates and achieves high concentrations in the cerebrospinal fluid (3, 11).

In conclusion, this patient with two uncommon diseases, tabes dorsalis and selective IgA deficiency, may provide some insight into IgA function and the immune defect in selective IgA deficiency.

References