Autoimmune Neurological Diseases

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Abstract: Multiple sclerosis, myasthenia gravis, and Guillain-Barré syndrome are neurological diseases induced by abnormal autoimmunity. Since these diseases show characteristic clinical courses and neurological symptoms, they can be diagnosed with appropriate examinations. However, it is necessary to note that the common types of these diseases in Japan are not always the same as those in Western countries. Based on an increasing knowledge of the pathological mechanisms of the diseases, various immune therapies are being developed.

Key words: Autoimmune neurological diseases; Multiple sclerosis; Myasthenia gravis; Guillain-Barré syndrome

Introduction

This paper describes some representative autoimmune neurological diseases. As described later, the common types of the diseases in Japan are different from those in Western countries; for example, the optic-spinal form of multiple sclerosis and the axonal form of Guillain-Barré syndrome are more common in Japan than in Western countries. This suggests that the development of autoimmune neurological diseases varies among races and is substantially influenced by environmental factors. Therefore, care is needed in interpreting medical textbooks and literature published in Western countries.

Multiple Sclerosis

The diagnosis of multiple sclerosis (MS) is made according to the conventional clinical description of “spatially and temporally separated multifocal central nervous lesions”.1) Pathologically, MS presents perivascular inflammation and myelin sheath destruction (demyelination plaques) in the white matter.

The prevalence of the disease in Caucasians is 40 to 100 per 100,000 individuals, while it is only about one-tenth of this figure among the Japanese. The disease type is also different between Caucasians and Japanese — the cerebral and optic-spinal forms are predominant in the former and the latter, respectively.

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The examination of evoked potential is useful for detecting clinically asymptomatic potential lesions that cannot be read in MR images. It is performed for visual, auditory, and somatic sensation — when any of the sensory pathways is abnormal, its signal latent time is prolonged.

2. Clinical course

MS mainly develops in patients in their twenties to fifties, with a peak being noted between 25 and 30 years. Most patients are classified into relapsing/remitting MS in which periods of exacerbation and periods of stable or improved clinical state occur alternately. Symptoms may recur from several times a year to only once every several years.

Primary progressive MS that progresses chronically from the onset has been reported in about 10 to 15% of Western patients,2) but only in 5% of Japanese patients. This form of MS has to be differentiated from neurodegenerative diseases or cerebral tumors.

In about 10% of patients with relapsing/remitting MS, the disease gradually becomes progressive within 10 years (secondary progressive MS). Although this form of MS is observed in 20 to 40% of patients in Western countries, it is less frequently observed in Japan.

3. Neurological symptoms

MS has a large variety of neurological symptoms. It often occurs with vision disorder or acute transverse myelitis in Japanese because many Japanese MS patients are classified into optic-spinal MS. The symptoms that may develop during the clinical course of MS include reduced vision, double vision, dyskinesia/paresthesia, spasm, dysuria, ataxia, tremor, cognitive dysfunction, and Lhermitte’s sign (an electric shock-like sensation running from the back to the limbs when the neck is bent forward, and associated with lesions in the cervical-spinal cord posterior funiculus). In addition, paroxysmal symptoms may occur,
including trigeminal neuralgia, paroxysmal articulation disorders, and dystonic paroxysm (often called tonic convulsions).

4. Treatment

Adrenocortical steroids have long been used for the treatment of relapsing/remitting MS. The most reliable therapy is the intravenous drip infusion of 1,000 mg of methylprednisolone (for 3 days), followed by the oral administration of prednisolone. Although these steroids shorten the periods of administration or symptomatic relapse, they do not reduce the relapse rate or change the long-term prognosis. Plasmapheresis may be effective for patients who do not respond to a massive dose of methylprednisolone.

Amantadine and selective serotonin reuptake inhibitors serve as useful symptomatic treatment for relieving fatigue. Carbamazepine is often effective for trigeminal neuralgia and Lhermitte’s sign. Carbamazepine or phenytoin is used to treat dystonic paroxysm.

Interferon β-1b (Betaferon®) was approved in Japan in September 2000 for relapsing/remitting MS and secondary progressive MS to reduce the relapse rate. It is also effective for optic-spinal MS. It is used by subcutaneously injecting 8 MIU (million international units) every other day. It has been reported to cause adverse effects such as influenza-like symptoms, redness/pain/necrosis at the injection site, and depression.

Myasthenia Gravis

The prevalence rate of myasthenia gravis (MG) has been reported to be 5 to 7 per 100,000 people. It occurs relatively frequently in females in their twenties and thirties, but tends to more frequently occur in males in their forties or older.

1. Clinical symptoms

The most evident symptom is tiring easily. The repeated use of muscles causes muscular weakness, which quickly becomes evident as fatigue. The fatigability may be improved by taking a rest. In addition, MG is subject to intraday or interday variation (for example, it is more severe in the evening than in the morning).

MG often develops with blepharoptosis and double vision owing to extraocular muscle weakness, although it may develop with bulbar paralysis (articulation disorders and dysphagia) or muscular weakness of the limbs (with proximal muscles being dominant). The symptoms are not always symmetrical.

2. Diagnosis

(1) A diagnostic test is performed with edrophonium hydrochloride (Tensilon®), a short-acting anticholinesterase agent. Its solution (dissolved in 9 ml of physiological saline at 10 mg/ml) is intravenously administered to determine whether it improves muscular weakness or not.

(2) A repeated stimulation test using a surface electromyogram is performed at 1, 3, 5, 10, and 20 Hz. The patients with MG show a waning phenomenon (reduced amplitude of provoked potential as compared with the first trial) in response to either high or low frequency stimuli.
(3) A blood test is performed for anti-acetylcholine receptor antibody. The antibody is positive in about 80% of MG patients, although the antibody titer does not always correlate with the severity of the disease.

(4) Imaging diagnosis (CT or MRI) is performed for the anterior mediastinal region because MG is often complicated with thymoma or thymic hyperplasia (Fig. 2).

3. Treatment

An appropriate treatment should be selected, depending on the symptoms of each patient. Basically, MG is treated with anticholinesterase agents or adrenocortical steroids to be administered every other day, or thymectomy. Oral anticholinesterase agents, such as Mestinon® and Mytelase®, inhibit acetylcholinesterase, and mild MG may be resolved with anticholinesterase therapy alone.

However, they do not treat the basic mechanism of MG lesions, that is, they are not effective for the actions of the autoantibodies against postsynaptic receptors or adjacent muscle membrane. Therefore, an adrenocortical steroid is administered every other day for MG, except the ocular muscle form. It is started at a dose of 20 to 30 mg/day and maintained at 60 to 100 mg/day for several weeks followed by gradual dose reduction.

Immunosuppressive agents such as azathioprine and cyclosporin can be used in intractable cases that do not respond to anticholinesterase agents or adrenocortical steroids. (These immunosuppressive agents are not covered by the Japanese medical insurance scheme.)

In September 2000, tacrolimus (Prograf®) was approved for coverage by Japanese medical insurance for patients who do not respond well to steroids or for whom steroids are contraindicated. A recent study reported that the drug was markedly effective in some cases.3)

Plasmapheresis or massive γ-globulin administration (intravenous immunoglobulin: IVIG) is performed in severe cases or in those who developed a crisis. The effects of plasmapheresis are not significantly different between the double filtration and immune adsorption techniques. IVIG is generally administered at 400 mg/kg for 5 days.

Thymectomy is essential for patients with thymoma. In patients without thymoma, residual fat tissue in the anterior mediastinal region is removed.

Guillain-Barré Syndrome

It is important to differentiate the demyelinating and axonal forms of polyneuropathy by performing a nerve conduction test and checking for F wave abnormality. The most common type of demyelinating polyneuropathy results from the inflammation of myelin sheaths and is therefore called inflammatory demyelinating polyneuropathy. Its acute form is Guillain-Barré syndrome (GBS). It should be noted that GBS is different in Japanese and Westerners — the axonal form accounts for about 30% in Japanese patients.

1. Clinical course and prognosis

In typical patients with GBS, tetraplegia rapidly progresses and the progression stops within 4 weeks. After an average plateau period of 2 weeks, the patients start to recover. However, some patients may show different clinical courses, including the suspension of the progression, phased exacerbation of tetraplegia, and recurrence of symptoms during recovery.

Although plasmapheresis and IVIG, which are described later, may modify these clinical courses, the prognosis of GBS is poor in the elderly, patients with rapidly progressing symptoms, those requiring artificial respiration, and those with electrophysiologically low amplitude of complex muscular action potential. Further, the patients with axonal GBS generally have a poorer prognosis than those with demyelinating GBS.
Although more than 75% of GBS patients have complete functional recovery within 6 months of its onset, about 15% have sequelae that limit daily activities. GBS recurs infrequently, with a recurrence rate of 5% or lower.

2. Etiology and mechanism

About two-thirds of patients with GBS have a history of prior infections (such as upper respiratory inflammation or diarrhea). The pathogens involved include *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr (EB) virus, mycoplasma, HIV, and influenza bacillus.

The most common in Japan is infection with *C. jejuni*, which is an important bacterium responsible for bacterial diarrhea. It should be noted that GBS associated with *C. jejuni* infection is frequently observed in China. GBS associated with *C. jejuni* often develops as a purely motor axonal form.⁴

The annual prevalence of GBS in Japan is 1 to 2 individuals per 100,000, which is comparable to that in Western countries.

3. Treatment

The main treatment for GBS is to remove anti-ganglioside antibodies and TNF-α, which are considered to be involved in the onset of GBS and increase in the acute phase of the disease. Adrenocortical steroid therapy had previously been used, but it was proved ineffective when administered alone. Therefore, plasmapheresis, IVIG, and pulse therapy with methylprednisolone are currently used. Other standard treatments include those for respiratory disorders, arrhythmia, abnormal blood pressure, and complications such as infections and pulmonary infarction, as well as rehabilitation during the recovery phase.

Plasmapheresis is roughly divided into simple plasmapheresis, plasmapheresis based on double filtering, and plasma adsorption using an immune adsorber. Plasmapheresis inhibits exacerbation, shortens the morbid period (including artificial respiration period or period until the patient can walk), and relieves sequelae.

Plasmapheresis is generally indicated for the following patients:

1. Patients with moderate or severe symptoms (Grade 4 or higher as evaluated with the Hughes’ functional grade (Table 1)) or those classified into Grade 3 who have progressive muscular weakness
2. Patients within 14 days of onset
3. Patients without serious circulatory, renal or hepatic diseases
4. Patients at 16 years old or older without septic shock, a history of myocardial infarction within 6 months, marked autonomic disorder, or tendency to hemorrhage.

The following frequency is considered appropriate for plasmapheresis depending on severity:³

1. Two times for mild patients (who can walk and stand, but cannot run)
2. Four times for moderate patients (who need assistance standing) and severe patients (who need artificial respiration)

Any of the above plasmapheresis techniques usually improves GBS symptoms and suspends the progression of GBS within one week after the start of the treatment.

IVIG has been demonstrated to improve motor function, shorten the morbid period, and reduce the rate of patients who need artificial respiration 4 weeks after the start of the

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Normal</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>Has mild neurological symptoms</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Can walk for 5 meters without a cane</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Can walk for 5 meters with a cane or supporting device</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Is restricted to bed or wheelchair</td>
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<tr>
<td>Grade 5</td>
<td>Requires assisted ventilation</td>
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<tr>
<td>Grade 6</td>
<td>Dead</td>
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AUTOIMMUNE NEUROLOGICAL DISEASES

Table 1 Hughes’ Functional Grade
IVIG is expected to provide an almost comparable effect to plasmapheresis. IVIG is performed by intravenous drip infusion of 400 mg/kg/day of a human immunoglobulin preparation (Venilon-I®) for 4 to 6 hours once daily for 5 straight days.

The pulse therapy with methylprednisolone is not effective when given alone. However, it has been reported to improve motor function at week 4 or to shorten the period until independent gait when combined with IVIG. The pulse therapy is performed by the intravenous drip infusion of 500 mg/day of methylprednisolone together with human immunoglobulin preparation for 5 days continuously.

Because of the low prevalence rate, it is difficult for patients and their families or other people, including paramedical staff, to obtain detailed information on GBS. With support from the Guillain-Barré Syndrome Foundation International, an international GBS organization, we have prepared a General Guide to Guillain-Barré Syndrome (Fig. 3), which is available at no cost.

**Conclusion**

This paper discussed three autoimmune neurological diseases, multiple sclerosis, myasthenia gravis, and Guillain-Barré syndrome. We would like to emphasize again the importance of understanding their specific characteristics in Japanese patients in order to provide appropriate treatment.

**REFERENCES**


