Bilateral Retrobulbar Optic Neuritis, Guillain-Barré Syndrome and Asymptomatic Central White Matter Lesions Following Adult Measles Infection

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Abstract

A 28-year-old woman presented with classic signs of measles and subsequently developed bilateral retrobulbar optic neuritis and Guillain-Barré syndrome. Her radiographic and CSF findings were consistent with acute measles encephalitis. However, encephalopathy, such as behavioral changes and alteration in consciousness, was not presented. Improvements in the clinical, radiographic, and electrophysiological studies were observed during the steroid therapy. The overlap of CNS and PNS involvement as neurological complications of measles infection is very rare.

Key words: optic neuritis, acute measles encephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, steroid pulse therapy

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Introduction

The neurological complications of measles infection include acute measles encephalitis, subacute sclerosing panencephalitis, Guillain-Barré syndrome (GBS), optic neuritis (ON), convulsion, and mental status changes (1-5). Most patients with measles are children and adolescents. Neurological complications of measles in adults are very rare and tend to be severe (6). While post infectious autoimmune reactions occur selectively either in the central nervous system (CNS) or peripheral nervous system (PNS), overlap of CNS and PNS immunological derangements by measles is rare (7). Herein, we present an adult woman patient who had measles and subsequently developed bilateral retrobulbar ON, GBS and asymptomatic white matter lesions on MRI.

Case Report

A previously healthy, 28-year-old woman was admitted with a 5-day history of high fever, cough and pharyngeal pain. She had no past history of measles and had never been vaccinated. Two days later, she was diagnosed with measles after appearance of the Koplik spots and characteristic maculopapular rash over the face which rapidly extended to the trunk and extremities. On the 6th day after admission, she was afibrile and complained of slight weakness of both lower extremities and difficulty in urinating. She subsequently developed a markedly unsteady gait and clumsiness in the upper extremities. On the 10th day after admission, she noticed bilateral blurred vision without eye pain.

She was referred to the department of neurology for further treatment. She denied any prior neurological illnesses or ocular symptoms. Her physical examination was normal except for pigmented macula lesions over the trunk, chest and...
arm that were healing. Neurological examination showed normal mental status and no meningeal sign. Pupillary light reflexes were sluggish. Her visual acuity was deteriorated to counting fingers (O.D. and O.S.: 0.01 (logMAR +2.0)), corrected vision O.D.: 0.01 and O.S.: 0.03 (logMAR +1.5)). Ophthalmoscopically, her optic discs and maculas were normal bilaterally. The other cranial nerves were normal. Motor examination revealed quadripareisis which was more pronounced distally (Medical Research Council rating scale 4/5), hyporeflexia (soon afterward, areflexia) of the lower extremities and absent Babinski sign. Impaired sensation to vibration in the distal lower extremities, constipation and urinary retention were also noted.

Complete blood count and urinalysis were normal. Blood gas analysis was unremarkable. Blood chemistry revealed a slight elevation of liver enzymes, but otherwise, data was unremarkable. Serological studies revealed that the measles IgM antibody titer was elevated at 9.01 (<0.8) and measles IgG antibody titer was elevated at 33.0 (<2.0), confirming the presence of recent measles infection. Other laboratory findings, including culture results, autoantibodies (antinuclear antibodies, antithyroglobulin and antineutrophil cytoplasmic antibodies) and antibodies against mycoplasma, herpes simplex virus, cytomegalovirus and Epstein-Barr virus, were negative. Three days after the neurological event, a lumbar puncture yielded clear, colorless cerebrospinal fluid (CSF) that contained 34 cells/mm³, all of which were mononuclear cells. CSF glucose was 86 mg/dL, and CSF protein was 144 mg/dL. Oligoclonal IgG band was absent, but myelin basic protein (MBP) was elevated to 350 pg/mL (102) and anti-measles IgG was elevated to 0.625 (<0.159). Chest X-ray films, electrocardiogram, electroencephalogram and auditory brainstem response were normal. An initial brain MRI showed a lesion in the right temporal subcortical white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1A). There was also a hyperintense signal lesion in the left frontal lobe, which was limited in the white matter (Fig. 1B). Both MRI lesions demonstrated linear enhancement after gadolinium injection. Diffusion-weighted brain MRI images and the apparent diffusion coefficient (ADC) maps were unremarkable. Spinal cord and optic nerve MRI showed no contrast-enhanced lesions. Visual evoked potentials with flash stimulation (VEP) showed prolonged P100 latency to 115 ms, and diminished amplitude (4.2uV) in the left eye, whereas the amplitude was absent on the right eye stimulation (Fig. 2A). Nerve conduction studies performed 7 days after the neurological event revealed slight delay in the conduction velocities and reductions in the amplitude of compound muscle action potentials (CMAPs) in the Lt-median and Lt-ulnar nerve. Sensory nerve conduction velocities were within normal limits, however, F-wave latency of the Lt-median nerve was prolonged and, H- and F-waves of the lower extremities were absent (Table 1).

The patient was tentatively diagnosed with retrobulbar optic neuritis associated with acute disseminated encephalomyelitis (ADEM) following measles infection, and was treated with a 3-day course of intravenous (IV) methylprednisolone of 1,000 mg/day, followed by oral prednisone (1 mg/kg daily). The daily dose of prednisone was reduced by 5 mg each week and discontinued within 3 months. She underwent rehabilitation. Her weakness, loss of vibration sense and urinary incontinence gradually improved after the first week of treatment. Two weeks later, a repeat MRI showed a further increase in the size of the right temporal lesion, but no change in the left frontal lesion. A repeat CSF study revealed a decrease in the cell count and protein level, but an increase in MBP level (485 pg/mL), compared with the previous CSF. CMAPs and F-wave latency of the median nerve were normal and H-wave responses of the lower extremity were observed, while those of the ulnar nerve did not show amelioration of CMAPs and nerve velocity (Table 1). Initially, the diagnosis of GBS in this patient was not established, and symptoms of increasing weakness had been attributed to ADEM. However, the diagnosis of GBS was strongly supported by the initial finding of lower limb are-
Table 1. Electrophysiological Findings of the Patient

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Day 7</th>
<th>Day 21</th>
<th>Normal limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor study</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median (Lt)</td>
<td>Distal latency (ms)</td>
<td>2.50</td>
<td>2.80</td>
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<tr>
<td></td>
<td>CMAP amplitude (mV)</td>
<td>8.50</td>
<td>12.3</td>
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<tr>
<td></td>
<td>Conduction velocity (m/s)</td>
<td>54.2</td>
<td>60.2</td>
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<tr>
<td></td>
<td>F wave latency (ms)</td>
<td>32.1</td>
<td>23.7</td>
</tr>
<tr>
<td>Ulnar (Lt)</td>
<td>Distal latency</td>
<td>2.00</td>
<td>1.90</td>
</tr>
<tr>
<td></td>
<td>CMAP amplitude</td>
<td>8.17</td>
<td>7.33</td>
</tr>
<tr>
<td></td>
<td>Conduction velocity</td>
<td>52.7</td>
<td>54.7</td>
</tr>
<tr>
<td></td>
<td>F wave latency</td>
<td>25.8</td>
<td>24.7</td>
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<tr>
<td>Tibial (Lt)</td>
<td>Distal latency</td>
<td>4.50</td>
<td>4.40</td>
</tr>
<tr>
<td></td>
<td>CMAP amplitude</td>
<td>10.2</td>
<td>6.50</td>
</tr>
<tr>
<td></td>
<td>Conduction velocity</td>
<td>43.8</td>
<td>46.9</td>
</tr>
<tr>
<td></td>
<td>H wave latency (ms)</td>
<td>absent</td>
<td>30.2</td>
</tr>
<tr>
<td><strong>Sensory study</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (Lt)</td>
<td>Conduction velocity</td>
<td>63.3</td>
<td>67.1</td>
</tr>
<tr>
<td></td>
<td>SNAP amplitude (uV)</td>
<td>61.3</td>
<td>56.7</td>
</tr>
<tr>
<td>Ulnar (Lt)</td>
<td>Conduction velocity</td>
<td>60.8</td>
<td>61.1</td>
</tr>
<tr>
<td></td>
<td>SNAP amplitude</td>
<td>42.7</td>
<td>48.0</td>
</tr>
<tr>
<td>Sural (Lt)</td>
<td>Conduction velocity</td>
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<td>Not done</td>
</tr>
<tr>
<td></td>
<td>SNAP amplitude</td>
<td>20</td>
<td>Not done</td>
</tr>
</tbody>
</table>

CMAP: compound muscle action potential
SNAP: sensory nerve action potential

flexia, the improvement of motor nerve velocity and F-wave, and the detection of H-wave response after treatment. The absence of encephalopathy in the course of the illness implies that the diagnosis of ADEM is unlikely. The definitive diagnosis is acute post-measles encephalopathy without encephalitic symptoms, with concomitant retrobulbar ON and GBS.

Just before discharge, VEPs improved with normalization of P100 latency (95ms) and amplitude (8.8uV) (Fig. 2B) despite persistent and fluctuating blurred vision (O.D.: 0.03 (logMAR +1.5) and O.S.: 0.02 (logMAR +1.7)). She was discharged on the 74th hospital day. She was kept under outpatient observation. One month after discharge, there was significant improvement in visual acuity [O.D.: 0.3 (logMAR +0.3) and O.S.: 1.2 (logMAR -0.1)]. Two months after discharge, she showed no further episodes of neurologi-
cal symptoms, and the lesions in the temporal and frontal lobe on T2-weighted and FLAIR images nearly disappeared. At 4 months after discharge (at 6-month follow-up from symptom onset), a follow-up MRI showed complete resolution of both lesions on T2-weighted and FLAIR images.

After informed consent, serum titer of antibody to water channel aquaporin-4 (AQP4) at the time of symptom onset was measured, but it was not detectable.

**Discussion**

We report a rare case of retrobulbar ON, GBS and asymptomatic brain MRI lesions after a classic measles infection. Her conditions responded well to the steroid therapy. This case was characterized by the presence of supratentorial, multifocal white matter lesions without mental status changes, and the overlap of CNS and PNS involvement.

Measles is one of the well-known neurotropic viruses; the neurological complications may vary from minor symptoms to encephalitis that can be life-threatening (8). Acute post-infectious encephalitis, which usually develops within 2 weeks after the rash, is most likely due to an autoimmune-mediated process. It more closely resembles the clinical and radiographic picture of ADEM (5, 9, 10). The present patient presented with multifocal cerebral MRI lesions and CSF cytology consistent with ADEM. Convulsion, personality changes and alteration in consciousness are frequently observed in ADEM, and the presence of encephalopathy is essential for the diagnosis of ADEM (11). However, neither behavioral change nor consciousness disturbance was observed in this case. The multifocal lesions on MRI were relatively small, and it is easily understandable why she did not have a decreased level of consciousness. FLAIR and T2-weighted images revealed reversible hyperintense lesions, whereas diffusion-weighted images and ADC maps depicted these lesions as normal. These images studies and the elevated MBP level in CSF may reflect the underlying pathology: that is immune-mediated inflammatory change and demyelination of the CNS. Therefore, this patient was diagnosed with an acute post-measles encephalopathy without encephalitic symptoms. The authors nevertheless consider this patient to have an apparent pathophysiological resemblance to ADEM.

ON is reported to occur in 7.5% of the measles encephalitis cases (12), while cases have been reported that lack both clinical symptoms and brain MRI findings as encephalitis (13-15). This case is characterized by both bilateral retrobulbar ON and asymptomatic multifocal white matter lesions. To the best of our knowledge, there have been no previous reports of such cases. Our patient regained normal vision three months after the initial steroid therapy. In previous reports (12, 13), the recovery period of visual acuity ranges from 2 weeks to several months. Full recovery of VEP findings was heralded by that of ON symptoms in this case. According to the follow-up VEP study after initial ON, it was found that 26% of the patients who showed normalization of VEP had impaired visual acuity (16). The return of the VEP to normal in ON is explained by remyelination occurring in a significant proportion of optic nerve fibers (17). Therefore, the residual blurred vision in the presence of a normal VEP in the present case may indicate that the recovery of function is incomplete.

Our case fulfills the clinical and electrodiagnostic criteria of the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) form of GBS (18, 19). The absence of CSF albumino-cytologic dissociation is the only factor which is incompatible with the diagnosis of GBS. It is likely that albumino-cytologic dissociation may have been overshadowed by the encephalitis. GBS is reported to comprise less than 2% of the measles-associated neurological complications (20). Reports of GBS coincident with acute measles encephalitis have been very rare (21, 22). ADEM-like measles encephalitis usually occurs in children; AIDP may occur in adult ADEM cases, but are considered rare in childhood ADEM (11), which may explain its very low incidence. Marchioni et al reported that 43.6% of adult ADEM patients showed PNS involvement in the form of polyradiculoneuropathy, and pure demyelination form was present in 65% of them (23). Therefore, it may be important to evaluate the peripheral nerve function in adult measles patients.

The cardinal clinical symptoms in the present case were progressive weakness of all four extremities due to GBS and acute loss of vision due to bilateral retrobulbar ON. The choice of high-dose IV methylprednisolone followed by oral prednisone or IV immunoglobulin (IVIg) as initial treatment may be controversial: steroid therapy is not considered beneficial for GBS. Since a randomized controlled trial has shown that IVIg has efficacy similar to plasma exchange, IVIg becomes accepted as the gold standard treatment for GBS because of its ease in usage (18). With regard to ON, in a double-blind, randomized trial, the effect of IVIg has not differed significantly compared with that of placebo in overall visual function and visual evoked potential (24). Since the Optic Neuritis Treatment Trial (ONTT) showed that high-dose IV methylprednisolone accelerates the recovery of visual function, the ONTT Study Group recommends the treatment with IV steroid in acute stage (25). As for measles encephalitis, most patients are treated with high-dose steroids (6, 9, 21), although others are treated with IVIg with/without steroids (10, 22). To date, there has been no study which directly compares IVIg with steroid for the treatment of ADEM including measles encephalitis. Considering the good recovery of symptoms, our experience with this case suggests that high-dose IV methylprednisolone may be useful as a first-line treatment in those with concomitant CNS and PNS involvement.

The common pathological basis for ADEM, optic neuritis and GBS is inflammatory demyelination of respective nerve tissues mediated by both cellular and humoral immune responses. The immune response of this case during the clinical course is intriguing, because it can be assumed that the acute humoral or cell-mediated response may have occurred.
simultaneously in both CNS and PNS. It is still unclear whether molecular mimicry between virus, CNS and PNS may stimulate an immunological reaction, or whether different epitopes between CNS and PNS may individually activate responses. Further data are needed to elucidate these pathophysiological mechanisms.

References