An Autopsy Case of Schilder's Variant of Multiple Sclerosis (Schilder's Disease)

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Dear Sir,

Schilder's disease or myelinoclastic diffuse sclerosis is a rare form of primary demyelinating disease, which is now considered to be a variant of multiple sclerosis (MS) [1, 2]. In 1912, Schilder described a case of a 14-year-old girl who had signs of mental deterioration associated with an increased intracranial pressure. She died after 19 weeks of her illness, and autopsy revealed large areas of sharply demarcated plaques of demyelination in both hemispheres [3]. Subsequently, Schilder reported two addi-

tional cases under the same eponym, but the case reported in 1913 was later identified to be adrenoleukodystrophy, and the 1924 case subacute sclerosing panencephalitis. The diagnostic criteria of 'true' Schilder's disease have been proposed in 1986 [1]. There should be large (at least 3 × 2 cm) bilateral plaques in the centrum semiovale of the cerebral hemispheres with histological characteristics identical to MS.

Here, we report the first case of elderly onset Schilder's disease confirmed by au-

topsy. Because the patient rapidly deteriorated and died, the relationship between the patient's condition with Marburg's variant of MS is also discussed.

Case Report

A 69-year-old previously healthy woman was admitted to a hospital because of left hemiparesis on May 26, 2002. Magnetic resonance imaging (MRI) revealed bilateral lesions in the centrum semiovale (fig. 1). She was initially diagnosed as having cere-

Fig. 1. MRIs on May 27. **a–c** T₂-weighted images. **d** Diffusion-weighted image. Bilateral small hyperintense areas are present in the white matter.

Fig. 2. MRIs on June 4. **a, b** T₂-weighted images. **c** Diffusion-weighted image. **d** T₁-weighted image. **e** T₁-weighted gadolinium-enhanced image. Hyperintense areas on T₂- and diffusion-weighted images are markedly expanded. There is little contrast enhancement.

Fig. 3. MRIs on June 12. **a, b** Axial sections. **c** Coronal section. Hyperintense lesions are further enlarged, and corpus callosum is involved (**c**).

Fig. 4. **a** Coronal section of the brain showing large, sharply demarcated area of demyelination with the sparing of U fibers (Kluver-Barrera stain). **b** Axons are relatively preserved (Bodian silver stain). **c** Perivascular lymphocytic infiltration (HE stain). **d** CD45-immunoreactive lymphocytes (arrows) in the perivascular region. **e** CD68-positive macrophages in the parenchymal demyelinating lesion. **f** Glial fibrillary acidic protein-positive astrocytes with long processes are distributed throughout the demyelinating lesions.

bral infarction. She was treated with 400 ml of glycerol and 160 mg of sodium ozagrel. Despite the treatment, she deteriorated and became quadriplegic and aphasic in 3 days. Since the lesions were enlarged on MRI and neoplastic lesions were also considered, she was transferred to our hospital on June 4, 2002. Her previous medical history was unremarkable.

On admission, she was afebrile and general examination did not reveal abnormal findings. She was mute and apallic with her eyes open. Her neck was supple. The optic fundi were normal, and the light reflex was prompt. The oculocephalic reflex was present. The extremities showed flaccid paralysis. Deep tendon reflexes were normal. Babinski's response was bilaterally positive.

The results of laboratory studies including complete blood counts and routine chemistries were unremarkable. The C-reactive protein level was normal. Cerebrospinal fluid (CSF) examination revealed a normal opening pressure, a normal cell count (1/μl) with a slightly elevated glucose level of 86 mg/dl and a normal protein level. The CSF myelin basic protein level was 207 ng/ml (normal < 4). Oligoclonal band was not observed. MRI revealed large bilateral lesions in the subcortical white matter of both cerebral hemispheres (fig. 2).

She was treated with intravenous beta-methazone 16 mg/day with no resolution of her symptoms. After 1 week of such treatment, MRI revealed an enlargement of the white matter lesions, which extended to the corpus callosum (fig. 3). She had fever and an increased blood C-reactive protein level since June 12; therefore, the administration of antibiotics was started. On June 19, she developed disseminated intravascular coagulation secondary to sepsis, and died on June 22, 27 days after the onset.

Autopsy was performed only for the brain. Macroscopically, the brain was slightly swollen with multiple subarachnoid hemorrhages. The coronal sectioning of the brain revealed large, sharply demarcated areas of demyelination with the sparing of U fibers (fig. 4a). Small plaques, which were not visible on the MRI, were present in the temporal lobe. There was no lesion in the brainstem and cerebellum. Microscopically, the lesion was characterized by the loss of myelin, while axons were relatively preserved (fig. 4b). In the active lesion, there was perivascular infiltration of lymphocytes (fig. 4c), and some of them were CD45 immunoreactive (fig. 4d). Numerous CD68-

positive foamy macrophages (fig. 4e) and glial fibrillary acidic protein-positive astrocytes with long processes (fig. 4f) were distributed throughout the demyelinating regions.

Discussion

The present case demonstrated the subacute deterioration of consciousness and motor function with roughly symmetrically large plaques in the centrum semiovale of both cerebral hemispheres. Autopsy disclosed extensive acute inflammatory demyelination, characterized by presence of perivascular T lymphocytes, parenchymal macrophages and astrocytes, which is compatible with acute MS [4]. These clinical and pathological features meet the criteria of Schilder's disease or Schilder's variant of MS [1, 2]. Although this disease has mainly been reported in children, some adult cases have been reported [5–7]. We believe this is the first report of Schilder's disease with serial MRI and autopsy findings in an elderly.

The autopsy finding of Schilder's original case showed bilateral large white matter demyelination involving the corpus callosum [3]. However, the lesions in the subsequent reports of Schilder's disease were not always symmetric, or even unilateral [5–7]. The present case, in terms of the callosal involvement and roughly symmetrical lesions, may closely resemble the extension of the lesions in Schilder's original case. There have also been reports involving the corpus callosum. Mehler and Rabinowich [5] described a 12-year-old girl with bifrontal lesions involving the anterior corpus callosum. Kurul et al. [8] reported a 9-year-old girl with lesions in bilateral parieto-occipital subcortical areas and genu and splenium of the corpus callosum. However, the pattern of extension to the corpus callosum seems to vary in each case. Serial MRI findings in our patient suggested that two distinct lesions expanded in each hemisphere and finally involved the corpus callosum.

Patients with Schilder's disease sometimes show radiological findings mimicking cerebral tumor. A 5-year-old boy and a 40-year-old woman in the reports of Poser and Brinar [2] and Dresser et al. [7], respectively, were initially suspected to have brain neoplasm. Diagnosis was made by cerebral biopsy in these patients. Conversely, some patients with MS or primary demyelinating disease who had radiological features of brain tumor meet the criteria of Schilder's disease [9–11]. Some of them had callosal

lesions simulating infiltrating gliomas [12, 13]. Our patient was also referred to our institute on the suspicion of cerebral neoplasm. Brain biopsy was planned, but it was not performed because of the deterioration of her general condition. The diagnosis was confirmed by autopsy.

Acute disseminated encephalomyelitis (ADEM) was also considered, but roughly symmetrically large plaques in the centrum semiovale of both cerebral hemispheres without brainstem lesions indicate Schilder's type MS more likely. In addition, the present patient did not have a history of prior infection or vaccination. Schwarz et al. [14] reported that presence of antecedent infection and infratentorial lesions both favored the diagnosis of ADEM rather than MS.

The other interesting features of our patient are the rapid deterioration of her condition and her subsequent death within weeks. A fulminant monophasic variant of MS was initially described by Marburg [15]. Interestingly, Mendez and Pogacar [16] described a case of Marburg's variant of MS with large bilateral white matter demyelination. Although the patient had brainstem lesions on autopsy, large bilateral white matter demyelination in the patient resembles that in Schilder's disease. Therefore, there may be an overlapping of features between Marburg's variant of MS and Schilder's disease, and as mentioned above, between Schilder's disease and MS with tumor-like plaques as well. This suggests that these three unusual entities may have common features.

In conclusion, we described an elderly patient with Schilder's disease. Schilder's variant of MS should be considered even when the patient is elderly, or when there are rapidly developing neoplasm-like lesions in the white matter of the brain.

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