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Neuro-Behçet's Syndrome and Brain Stem Encephalitis. A Neuropathologic Study

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ABSTRACT. The neuropathologic findings of a case of neuro-Behçet's syndrome were described in comparison with those of a case of brain stem encephalitis of Iizuka type and the pathogenesis of the central nervous system lesions of the former case was discussed.

The patient was a 51-year-old man who had recurrent genital ulcers from an early age. Nine and a half years before death he noticed visual disturbance. Fourteen months before, dysarthria, gait disturbance and mental deterioration developed together with oral ulcers and skin eruptions.

Neuropathologic examination revealed widespread demyelinated lesions and gliosis scattered with small softened lesions and perivascular lymphocytic infiltrations mainly in the brain stem. In addition, small softened lesions were also observed in the cerebrum, cerebellum, thalamus and basal ganglia. These findings were quite similar to those for the case of brain stem encephalitis of Iizuka type. It was therefore suggested that brain stem encephalitis of Iizuka type might be a subtype of neuro-Behçet's syndrome lacking ocular and mucocutaneous lesions.

The central nervous system lesions in the case of neuro-Behçet's syndrome were suspected to have been induced not by a secondary circular disturbance due to vasculitis but by the effect of some kind of noxa resulting from a perivascular immunological reaction.

Key words : Neuro-Behçet's syndrome — Brain stem encephalitis — Neuropathology

Behçet's syndrome, which was first described by Behçet[1] in 1937, is characterized by the occurrence of relapsing uveitis, recurrent genital and oral ulcers, and erythematous eruptions of the skin.[2] It generally involves young adults of the third and fourth decades, and males are more often affected than females. Although a viral infection or an allergic mechanism is suspected, the actual etiology of the disease is still unknown.

It is now recognized that Behçet's syndrome may involve such internal organs as the intestines (intestinal-Behçet's syndrome) and the cardiovascular system (vascular-Behçet's syndrome).[3] It may further involve the central nervous system in approximately 10 to 28 percent of cases (neuro-Behçet's syndrome).[4-6] Neuro-Behçet's syndrome worsens the prognosis of Behçet's syndrome. Neuropathologically, chronic inflammatory and demyelinating lesions appear, especially in the brain stem,[7,8] although some cases[9,10] have shown fairly remarkable lesions in the cerebral hemispheres. Consequently, the difference between neuro-

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Behçet's syndrome and brain stem encephalitis as described by Iizuka[11] in 1963 has become a point of argument from the neuropathological point of view.[12,13]

It is the purpose of this paper to describe the neuropathologic findings of a case of neuro-Behçet's syndrome in comparison with those of the case of brain stem encephalitis previously described[14] and to discuss the pathogenesis of the central nervous system lesions in the case of neuro-Behçet's syndrome.

CASE REPORTS

Case 1 (B 49707) : The patient was a 51-year-old man admitted to the Kawasaki Medical School Hospital on November 9, 1982 because of diarrhea, abdominal pain and vomiting lasting one week.

The patient had exhibited a history of recurrent genital ulceration from an early age. Nine years before entry he noticed hyperemia and visual disturbance in both eyes. Within a few years he became almost blind. Ten months before admission dysarthria, gait disturbance and mental deterioration developed. One week before entry he began to have diarrhea, abdominal pain and vomiting. He entered another hospital, where he was treated conservatively, and then he was transferred to this hospital.

The patient's temperature was 36.2°C, his pulse 72 and his blood pressure 96/50 mmHg.

Physical examination revealed emaciation. Folliculitis-like eruptions were observed on the scalp and face, and erythemas were noted over the whole body. A few ulcers were observed on the scrotum. Adhesion was noted on the iris and the gingivae were reddish and erosive. The abdomen was tensed and bowel sounds were absent.

Neurologically, the patient was demented. The pupils did not react to light, and there was optic atrophy in the optic fundi. Speech was dysarthric, and the muscle strength of the extremities was weak. Deep tendon reflexes were hyperactive with bilateral Babinski signs and foot clonus.

The patient's cerebrospinal fluid contained 21 neutrophils and 13 lymphocytes per cubic millimeter ; protein was 75 mg per 100 ml, and glucose was 76 mg per 100 ml. An electroencephalogram showed a basic rhythm of alpha waves of 9 to 10 Hz with intermittent theta waves of 6 to 7 Hz. Computed tomography (CT) of the brain disclosed moderate atrophy of the cerebral cortex and marked atrophy of the brain stem with ventricular dilatation.

On the day of admission, he underwent an operation for ileus and perforative peritonitis. On November 14, melena was noted. Soon thereafter he had several dyspneic and hypoglycemic attacks, and his general condition became poor. On March 25, 1983, his temperature rose to 40.0°C. Two days later he died of septic shock, nine and a half years after the onset of ocular symptoms and fourteen months after the onset of the symptoms of the central nervous system.

A general autopsy (A 83-55) disclosed multiple ileac ulcers, multiple erythemas and ulcers on the skin, a postoperative state of partial resection of the ileum, intestinal fistula, renal abscesses, chronic cystitis, an infectious spleen, and congestion of the liver. Histologically, the ileac ulcers consisted of

a mucosal defect with underlying non-specific inflammatory granulation tissue infiltrated by lymphocytes and plasma cells. Giant cells and eosinophils were not observed in the lesions.

The brain weighed 1,140 g. The leptomeninges were slightly turbid and congested. A localized subarachnoid hemorrhage was seen on the inferior surface of the cerebellum. The cerebral gyri were slightly atrophic. The lateral and third ventricles were moderately dilated. The midbrain, pons and medulla oblongata were markedly atrophic and increased in consistency. The substantia nigra was discolored.

Microscopically, the leptomeninges of the cerebral hemispheres were fibrously thickened and infiltrated by small amounts of lymphocytes, plasma cells and macrophages. The nerve cells of the cerebral cortex were pyknotic. Small softened lesions (Fig. 1) and occasional microabscesses (Fig. 2) were found in the cerebral cortex. The white matter of the cerebral hemispheres was unremarkable except for incidental perivascular infiltration of lymphocytes. The thalamus and basal ganglia showed patchy nerve cell loss and gliosis. Remaining nerve cells were pyknotic.

In the cerebellum, a fresh subarachnoid hemorrhage and petechial parenchymatous hemorrhages were seen. Purkinje cells were pyknotic and occasionally lost. Old small softened lesions were scattered in the cerebellar cortex (Fig. 3). Many of the nerve cells of the dentate nuclei were lost, and astrocytic gliosis and capillary proliferation were seen.

In addition to mild perivascular infiltration by lymphocytes, the optic nerves were atrophic and diffusely demyelinated with marked gliosis.

In the brain stem, mild subarachnoid and perivascular lymphocytic infiltration (Fig. 10) was present. Irregularly and vaguely demarcated demyelinated lesions and softened lesions which were often cystic with lipid-laden macrophages (Fig. 9) were scattered, especially in the cerebral peduncles and tegmentum of the midbrain (Fig. 4), pontine base (Fig. 7) and pyramidal tracts of the medulla oblongata. Gliosis (Figs. 5, 8) was marked in these areas, and it frequently extended to the subarachnoid space (Fig. 6) and cranial nerve roots, making glial bundles. Lamellar fibrosis was seen in the perivascular space. IgG was not stained in the vascular walls and cerebral parenchyma by the peroxidase-antiperoxidase (PAP) method. The nerve cells of the substantia nigra and pontine nuclei were reduced in number. Remaining nerve cells were pyknotic. Nerve cells with two nuclei (Fig. 11) were observed incidentally in the pontine nuclei. The inferior olivary nuclei showed a tendency towards pseudohypertrophy, with vacuolar degeneration of nerve cells and marked gliosis (Fig. 12). Microabscesses were found also in the pons and medulla oblongata.

The distribution of the lesions is illustrated in Figure 13.

Case 2 : The patient was a 35-year-old man whose illness began with headache and double vision. Subsequent symptoms and signs included character change, facial palsy, dysphagia, dysarthria, nuchal rigidity, spastic tetraplegia, general convulsions and myoclonic seizures along with an intermittent fever. These symptoms and signs progressed slowly with transient remissions. No uveitis, and genital and oral ulcers were observed. The cerebrospinal fluid contained 15 lymphocytes per cubic millimeter ; protein was 89 mg per 100 ml, and glucose

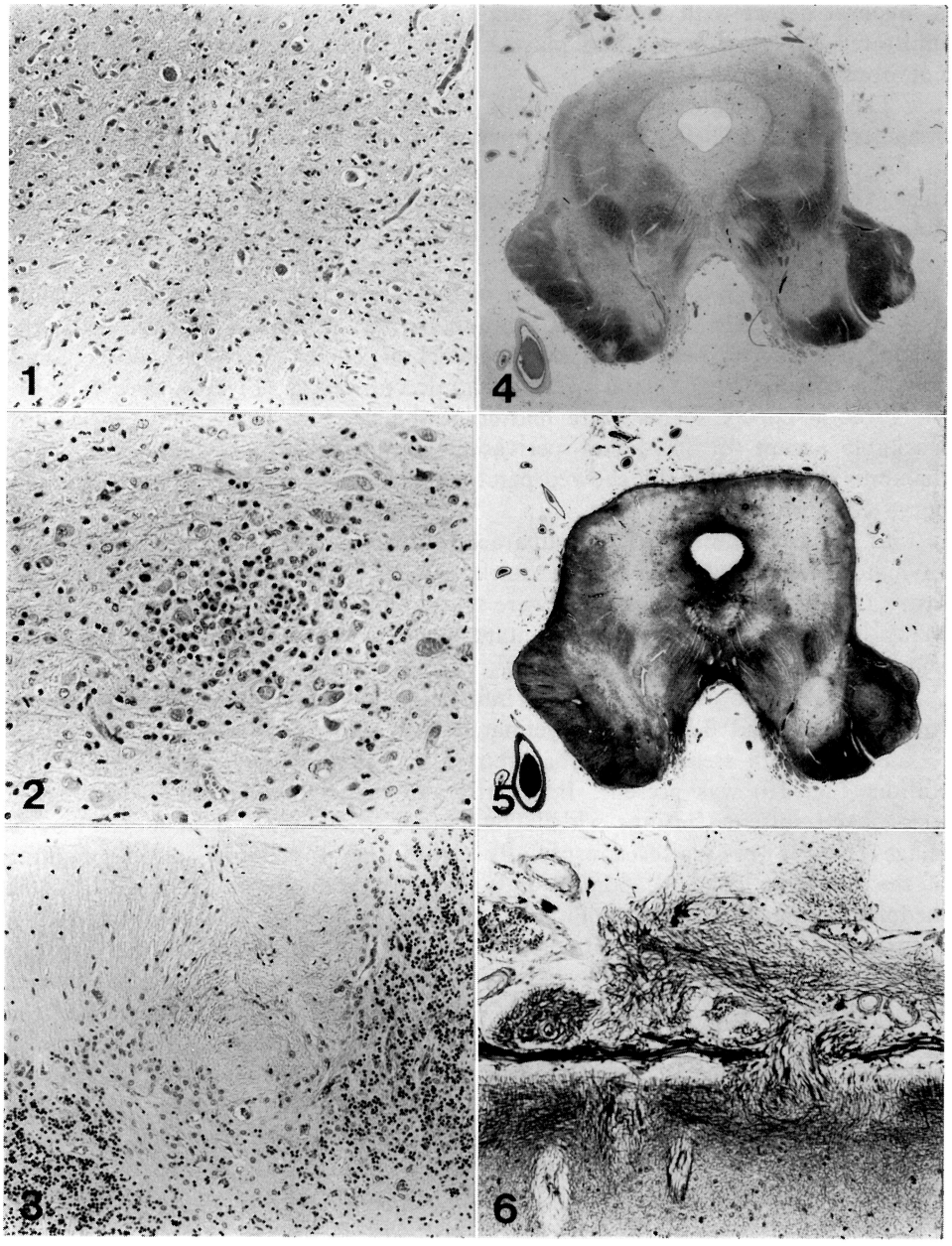

Fig. 1. Cerebral cortex showing small softened lesions. HE, ×100.
Fig. 2. Microabscess in the lateral geniculate body. HE, ×200.
Fig. 3. Old small softened lesions in the cerebellar cortex. HE, ×100.
Fig. 4. Midbrain showing irregularly and vaguely demarcated demyelinated lesions. Klüver-Barrera, ×2.6.
Fig. 5. Midbrain showing marked gliosis mainly in the cerebral peduncles and tegmentum. Holzer, ×2.6.
Fig. 6. Glial fibers proliferating into the subarachnoid space of the midbrain. PTAH, ×100.

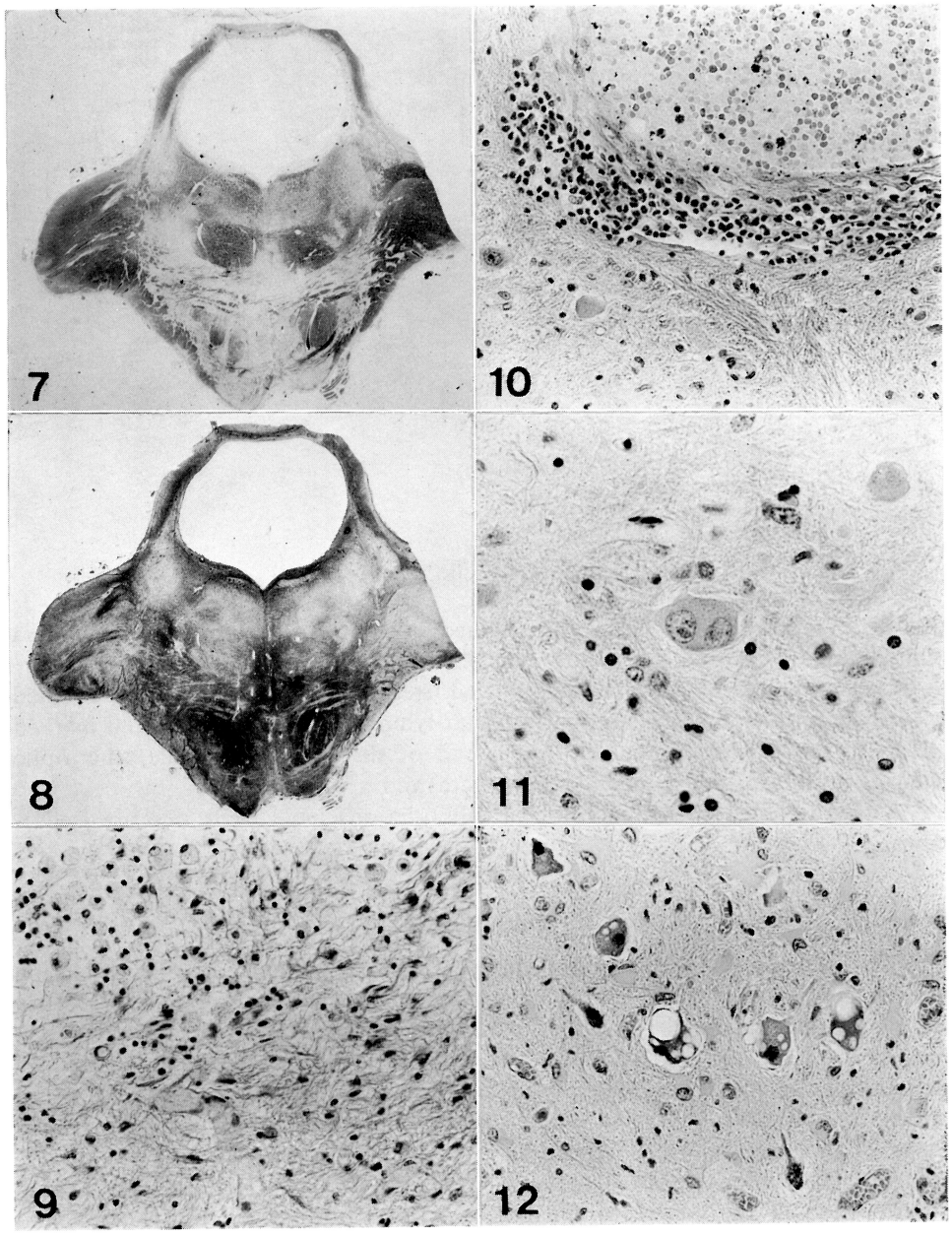

Fig. 7. Pons with irregular demyelination in the pontine base. Klüver-Barrera, ×2.4.
Fig. 8. Pons showing gliosis in the demyelinated lesions. Holzer, ×2.4.
Fig. 9. Cystic lesion with lipid-laden macrophages and gliosis in the pons. HE, ×200.
Fig. 10. Perivascular lymphocytic infiltration in the pons. HE, ×200.
Fig. 11. Nerve cell with two nuclei in the pons. HE, ×400.
Fig. 12. Nerve cells with vacuolar degeneration in the inferior olivary nucleus. HE, ×200.

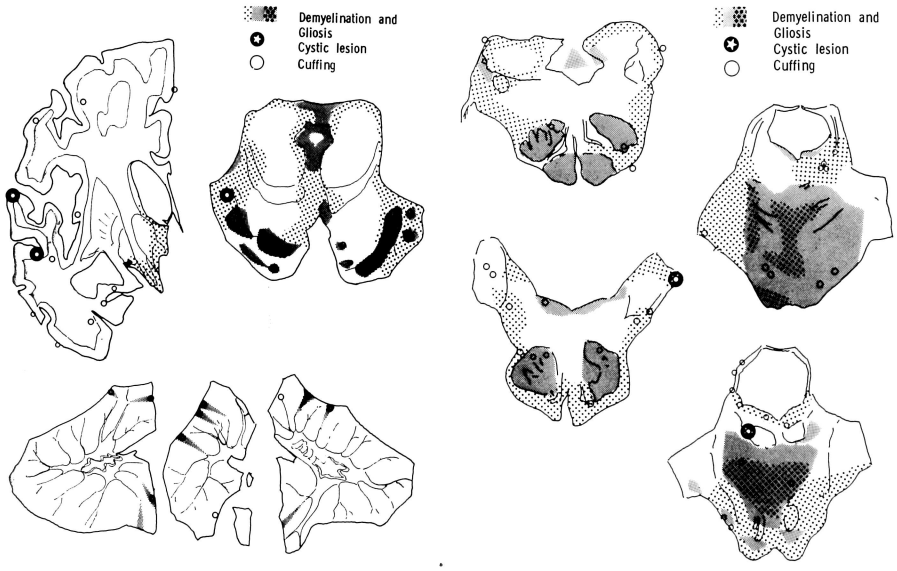

Fig. 13. Illustration of the distribution of the lesions.

was 36 mg per 100 ml. The patient died of concomitant bronchopneumonia after a three-year and six-month course of the illness.

Neuropathological examination revealed irregularly demyelinated and softened lesions with subarachnoid and perivascular lymphocytic infiltrations and marked gliosis in the hypothalamus, the lower end of the internal capsule, the optic chiasm, midbrain, pons, medulla oblongata and spinal cord.

Other detailed clinicopathological observations have been described elsewhere.[14]

DISCUSSION

The clinical symptoms and signs of the first patient, such as relapsing uveitis, genital and oral ulcers, and erythematous eruptions of the skin, satisfy the diagnostic criteria for Behçet's syndrome.[2,6] The intestinal ulcers of the patient were located in the ileum and covered with non-specific inflammatory granulation tissue infiltrated by lymphocytes and plasma cells. There was no infiltration of giant cells and eosinophils. These ulcers are consistent with those of intestinal-Behçet's syndrome.[15]

The patient developed dysarthria, weakness of the extremities and mental deterioration in the course of the illness. His cerebrospinal fluid showed mild chronic inflammatory signs. These neurological symptoms and signs were highly suggestive of neuro-Behçet's syndrome. Neuropathological examinations revealed widespread demyelinated lesions and gliosis scattered with small softened lesions and perivascular lymphocytic infiltrations mainly in the midbrain, pons and medulla oblongata. These neuropathological findings are compatible with those of neuro-Behçet's syndrome.[16,19] Pallis and Fudge[20] identified three patterns of involvement of nervous system in Behçet's syndrome, namely (a) a brain stem syndrome, (b) a meningomyelitic syndrome, and (c) an organic confusional

syndrome (possibly encephalitis). According to their classification, ours may be a brain stem syndrome.

The second patient showed slowly progressive character change, facial palsy, dysphagia, dysarthria, spastic tetraplegia and convulsions during a three-year and six-month course of the illness. There were no symptoms and signs suggestive of Behçet's syndrome, such as uveitis, and genital and oral ulcers. Neuropathological examination revealed demyelinated and softened lesions with chronic inflammatory infiltrations and marked gliosis mainly in the brain stem.

In 1963, Iizuka[11] described three fatal cases of atypical primary sporadic encephalitis with several clinical and neuropathological distinctive features. Clinically, this encephalitis is characterized by pyramidal signs and bulbar paralysis. Neuropathological findings reveal circumscribed or diffuse foci of inflammatory reactions and glial proliferations, mainly in the pons and medulla oblongata, and less frequently in the midbrain. The clinicopathological features of the second case are most similar to those of this brain stem encephalitis described by Iizuka.

Clinically, the two cases were similar in that both were young adults, both took a slowly progressive or relapsing course over a few years, both showed symptoms and signs of brain stem and pyramidal tract involvement, and both displayed a chronic inflammatory sign in the cerebrospinal fluid, although the first case had clinical symptoms of Behçet's syndrome, while the second did not. Neuropathologically, the distribution and the nature of the lesions were also quite similar. Both had chronic inflammatory and demyelinating lesions mainly in the brain stem. It is possible that the brain stem encephalitis of Iizuka type may be a subtype of neuro-Behçet's syndrome involving mainly the brain stem or a brain stem syndrome of Behçet's syndrome advocated by Pallis and Fudge, without clinical symptoms of Behçet's syndrome, as Shiraki[12] and Ishii *et al.*[13] have suggested.

In the first case, there was no evidence of active vasculitis in the vessels of the brain. Instead there was merely mild meningeal and perivascular lymphocytic infiltration and perivascular proliferation of collagen fibers. Any active vascular inflammatory reaction might have almost disappeared in the case. Shimizu *et al.*[3] have pointed out that, in Behçet's syndrome, inflammatory lesions of the veins predominate over those of the arteries, unlike vascular lesions of systemic lupus erythematosus, rheumatoid arthritis and polyarteritis nodosa. Fukuda *et al.*[21] have suggested that some factor other than circulatory disturbance as the pathogenesis of softened lesions should be taken into account. The brain stem lesions of the first case were considered to have been caused not by vascular obstruction due to vasculitis, but rather by a perivascular reaction due to the immune mechanism concerned with Behçet's syndrome. It is supposed that in Behçet's syndrome increased IgG and IgA stimulate the production of immune complex and release of active enzymes and lysosomes which injure the blood vessels and parenchymal tissue.

The viral infection theory was advocated in Behçet's original report. Nerve cells with two nuclei occasionally seen in neuro-Behçet's syndrome as in ours have been supposed to be formed by cell fusion resulting from viral infection. But viral studies of Behçet's syndrome have so far proved to be negative.[22]

Small softened lesions scattered throughout the brain may be the result of disturbance of microcirculation. Occasionally, small abscesses are found in relation to neuro-Behçet's syndrome. Kaneko *et al.*[23] observed that abscesses in their case were related to demyelination and softening, but in ours micro-abscesses may have been disseminated into the brain from the renal abscesses. In any case, these scattered softened lesions and microabscesses seem to be observed characteristically in neuro-Behçet's syndrome.

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