Chronic brainstem encephalitis with mental symptoms and ataxia

Report of three cases with necropsy

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SUMMARY Three necropsied cases of chronic, sporadic brainstem encephalitis of unknown aetiology are presented. Since their outstanding symptoms were dementia and ataxia of a progressive nature, a noninflammatory disease of the central nervous system was suspected. Neuropathological studies showed chronic inflammatory changes mainly in the brainstem without the presence of inclusion bodies or viral particles. Compared to cases previously reported as brainstem encephalitis, the clinical and pathological findings observed in these cases have rather peculiar characteristics.

Many kinds of encephalitides have been known to show localised or predominant lesions in the brainstem—namely, encephalitis lethargica, the cerebral form of the Heine-Medin disease, rabies, and equine encephalitis which has been classified by Spatz (1930) as a type of poliomyelitis with predominant involvement in the brainstem. Japanese B encephalitis (Haymaker and Sabin, 1947) or Pette-Döring type of subacute sclerosing panencephalitis (Pette and Döring, 1939) have also been known to produce intense lesions in the diencephalon or brainstem.

In contrast to the above encephalitides, aetiologically obscure encephalitis has been called “brainstem encephalitis.” Although a number of benign or fatal cases of this disease have been described, the clinical and neuropathological features have been too complicated to identify their aetiology (Möller, 1956; Bickerstaff, 1957; Möller and Nenzelius, 1961; Izuka, 1964; Tatetsu *et al.*, 1964, 1968; Mukoyama *et al.*, 1965, 1967; Gluszczyk, 1966; Verhaart, 1966; Marsal, 1967; Minauf and Tateishi, 1969; Schain and Wilson, 1971; Shirabe *et al.*, 1971, 1972; Waxman *et al.*, 1974; Yalaz and Tinaztepe, 1974).

The cases with brainstem inflammation presented in this paper, had chronic and peculiar

manifestations which have not been reported previously. We have tried to describe their clinical and pathological characteristics, as well as discuss aetiology as compared with other encephalitides.

Case reports

CASE 1

This 39 year old male (SM) had been healthy until 30 years of age. There were no remarkable abnormalities in his family. From the age of 31 years he gradually became indifferent, hypobulic, and eccentric. His manner of living became disturbed; he suffered from insomnia and was treated in a mental hospital. He was absent from work frequently, and became autistic with affective flatness. He was admitted to mental hospital in March 1961 with a provisional diagnosis of schizophrenia. During the admission, unsteadiness in walking, difficulty in speech, and hypersalivation appeared and worsened. At that time, there were no abnormal findings in the cerebrospinal fluid and electroencephalogram (EEG). In October 1962, at the age of 37 years, he was transferred to Hokkaido University Hospital.

On examination consciousness seemed clear, but he was indifferent and euphoric. There was moderate dementia. The visual acuity was reduced to less than 20/200 without correction in both eyes. The optic disc showed temporal pallor, and there was slight facial paresis on the right and

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deviation of the tongue to the right. Dysarthria was noted, and his voice had a nasal quality. The limbs were hypertonic, and there was slight weakness on the right. Tests of co-ordination, such as diadochokinesis, finger-nose, finger-finger, and heel-shin tests, were slow, unstable, and ataxic. Gait was also unstable, and ataxic. Tandem gait was impossible. Deep tendon reflexes were all hyperactive, especially on the right.

There were no abnormalities in blood, urine, liver function, serum electrolytes, basal urinary excretion of 17-KS and 17-OHCS, or serological test for syphilis. No abnormal findings were noted in the skull radiograph or on the carotid angiogram, but moderate dilatation of the third and lateral ventricles was observed on the pneumoencephalogram. The EEG showed a diffuse basic alpha pattern with sporadic or random theta activity. At lumbar puncture on 9 October 1962, the CSF opening pressure was 90 mmH₂O, and closing pressure 85 mmH₂O after withdrawal of 3 ml of clear, colourless fluid; 29 lymphocytes per mm³, protein 0.5 g/l, chloride 111 mmol/l, sugar 2.8 mmol/l, Pandy test ($\pm$), and Nonne-Apelt test ($\pm$). Electrophoresis of the protein revealed high values for beta and gamma globulin. The next test on 9 May, 1963, showed marked pleocytosis; 21 lymphocytes and 289 polymorphonuclear cells per mm³, protein 0.7 g/l, Pandy (+3), and Nonne-Apelt (+). On the third occasion on 19 May, after steroid therapy, cell count decreased to 22 lymphocytes per mm³.

Although some kind of cerebellar disease had also been suspected, the CSF findings at a later stage suggested an inflammatory disease in the central nervous system. Antibiotics and steroids were administered, but with no effect. The patient's symptoms gradually worsened, and he finally became bedridden. His general condition deteriorated with dysphagia. After about eight years, he died of pneumonia on 5 August 1963.

Necropsy findings

General pathology There was bronchopneumonia of both lungs, erosion of the stomach, haemorrhage of the gastrointestinal tract, parenchymatous degeneration of the liver and kidney, ascites, and fibrinous pleurisy on the left.

Neuropathology The brain weighed 1210 g. Macroscopically, turbidity of the meninges was observed on the convexity of the frontal lobe and the base of the brain. The frontal lobe, pons, and medulla were slightly atrophied. No gross abnormalities were noted in the basilar arteries, or on coronal sections of the brain.

Microscopically, the main pathological findings

were inflammatory changes localised in the brainstem. Perivascular lymphocytic and plasmacytic infiltration, and diffuse proliferation of glial cells, especially microglia, were prominent in the mid-brain and pons, and to a lesser degree in the thalamus, hypothalamus, medulla, and basal nucleus (Fig. 1). Only a few glial nodules were present in the parolfactory area, locus caeruleus, and inferior olive (Fig. 2). In addition, many small softening were observed in the tegmentum, crus cerebri, and inferior colliculus of the midbrain, ventral portions of the pons, and inferior olive on one side, where a number of gemistocytic astrocytes and phagocytes appeared, and patchy demyelination and fibrous gliosis were observed (Fig. 3). Such changes were also present in the lateral geniculate body. Although slight or moderate loss of the nerve cells was observed in the pontine nucleus and inferior olive mentioned above (Fig. 4), other areas of the brainstem were

Fig. 1 Perivascular cell infiltration and diffuse glial proliferation in the pons. Case 1, H & E $\times 55$.

Fig. 2 Glial nodules in the parolfactory area. Case 1, Nissl $\times 150$.

Fig. 3 Small and patchy demyelination in the midbrain (a), pons (b), and medulla (c). In these areas, fibrous gliosis of varying degrees was observed. Case 1, Heidenhein-Woelke (H & W).

Fig. 4 Marked loss of nerve cells and increase of astrocytes in the inferior olive. Case 1, Nissl $\times 55$.

relatively well preserved. No neuronophagia could be observed. Moreover, inclusion bodies were absent in the nerve cells or glial cells of the lesions. In the cerebellum, a high or moderate loss of Purkinje cells was observed with a slight glial proliferation of the white matter (Fig. 5). Moreover, nerve cells in the dentate nucleus showed a moderate degree of loss along with glial prolifera-

Fig. 5 Marked loss of Purkinje cells. Case 1, Nissl $\times 55$.

tion. Cellular infiltration was also present in the meninges of the base and brainstem. The structure of the cerebral cortex and white matter was, however, relatively preserved with only glial increase.

Electronmicroscopically, no viral particles could be observed in the nerve and glial cells in the lesions of the pons.

CASE 2

A 26 year old male (KF) had been well except for a history of acute nephritis at 4 years of age, and fracture of the right thigh bone at 13. Family history was noncontributory. He first began to have occasional headaches and insomnia at the age of 18 years. About one or two years later, he became rather talkative and sensitive to his surroundings. He also became disoriented, restless, and unkempt, and could not settle to an occupation. In July 1962, at the age of 22 years, he was admitted to a mental hospital. Because of changes in his personality, he was thought to be schizophrenic and treated accordingly for three years. Neurological symptoms, however, such as dysphagia and momentary athetotic movements of the extremities were noticed one year before admission. Unsteadiness of gait and difficulty in speaking were also evident at the time of admission. Hypersalivation and a disturbance of micturition also appeared. In June 1965, at the age of 25 years, he was transferred to our hospital.

On examination, he seemed childish and euphoric with slight dementia. The gag reflex was absent, and dysarthria and a nasal voice were observed. Muscular weakness of extremities was slight, atrophy was absent, and tone was reduced. Co-ordination tests were ataxic, particularly on the right. Deep tendon reflexes were all hyperactive especially at knee and ankle and on the right. Involuntary movement appeared in the extremi-

ties. Bladder and bowel function was disturbed. Gait was unstable and ataxic.

There were no abnormalities found in blood, urine, liver function, faeces, serum electrolytes, electrophoresis of serum protein, serological test for syphilis, or skull radiograph. Marked dilatation of the third and lateral ventricles, and cortical atrophy were demonstrated on the pneumoencephalogram. On the EEG, alpha activity was poor in the occipital area with sporadic or random theta activity in the frontal and central areas. Lumbar puncture, in August 1965, showed an opening pressure of 117 mmH₂O, a closing pressure of 80 mmH₂O, with clear colourless fluid; 8 lymphocytes per mm³, protein 0.5 g/l, chloride 124 mmol/l, Pandy test (+2), and Nonne-Apelt test (-). Electrophoresis of the protein revealed a high gamma globulin value (twice the normal value).

The patient was transferred to another hospital in September, 1965 for rehabilitation. His neurological and mental symptoms gradually became worse, and after about eight years, he died of pneumonia in February, 1966. He was suspected of having a cerebellar disease.

Necropsy findings

General Pathology There were no abnormal findings in the visceral organs except for bronchopneumonia in the lungs.

Neuropathology The brain weighed 1300 g. Macroscopically, slight atrophy of the frontal lobe, temporal lobe, pons, and cerebellum was observed. Leptomeninges in the central sulcus and parieto-occipital regions were remarkably turbid. No other gross abnormalities were observed except for dilatation of the ventricle system.

Microscopically, inflammatory changes were noted mainly in the brainstem. In the perivascular space, there were various kinds of inflammatory cells. In addition to lymphocytes and plasma cells there were large round cells, phagocytes, such as histiocytes, and fat- or iron-granule cells. A diffuse proliferation of glial cells, especially microglia, was also present. These findings were most prominent in the pons and medulla, and to a lesser degree in the thalamus, hypothalamus, and mid-brain (Fig. 6). Such findings were also observed in the basal nucleus and internal capsule to a slighter degree. On the other hand, patchy or diffuse demyelination and fibrous gliosis were demonstrated in the crus cerebri of the midbrain, middle cerebellar peduncle, ventral portion of the pons, and pyramid of the medulla (Fig. 7). There was also a small infarct in the medial longitudinal

Fig. 6 Perivascular cuffing in the medulla. Case 2, Nissl $\times 60$.

Fig. 7 Small and patchy demyelinating areas in the brachium pontis and ventral portion of the pons. Fibrous gliosis was demonstrated in these areas. Case 2, H & W.

fasciculus on one side, where many gemistocytic astrocytes and phagocytes appeared. In spite of the above changes, the nerve cells in the brainstem were relatively well preserved. Glial nodules and neuronophagia were absent. In the cerebellum, although no loss of Purkinje cells was apparent, a slight or moderate loss of nerve cells, and a glial proliferation were observed in the dentate nucleus (Fig. 8). In the cerebrum, there was slight loss of cortical nerve cells in the frontal, parietal, and temporal lobe with a few perivascular cellular cuffings in the frontal white matter. The cervical and thoracic spinal cord showed demyelination of lateral and anterior tracts without inflammatory changes (Fig. 9). In the meninges of the base and brainstem, inflammatory cells similar to those in the perivascular space were observed to some extent. There were no inclusion bodies in the lesions.

Electronmicroscopically, no viral particles could be observed in the lesions of the hypothalamus.

Fig. 8 Moderate loss of nerve cells and diffuse glial proliferation in the dentate nucleus. Case 2, Nissl $\times 100$.

Fig. 9 Demyelination of lateral and anterior tract in the cervical cord. Case 2, H & W.

CASE 3

This 50 year old female (TN) had been well until 47 years of age, when she began to show signs of difficulty in speech. The family history was not remarkable. Her voice became lower, and pronunciation obscure. Several months later, her finger movement became clumsy, and she frequently dropped food and dishes while eating. Unsteadiness in walking also appeared. She also became childish, and a decline in her intellectual faculties was noticed. She visited Kushiro Municipal Hospital in April 1969.

On examination, her face appeared apathetic and dull. Comprehension was poor, and her manner of speaking was circumstantial. Dementia of moderate degree was observed. Neurologically, ophthalmoplegia, dysarthria, clumsiness of finger movement, and ataxic gait were noted. She was hypertensive (174/90 mmHg). There were no abnormal findings on the carotid angiogram and pneumoencephalogram. Lumbar puncture in April 1969, showed an opening pressure of 155 mmH₂O, a closing pressure of 105 mmH₂O, with clear, colourless fluid; Pandy test (—), and

Nonne-Apelt test (—), 4 lymphocytes per mm³, protein 0.175 g/l, sugar 3.3 mmol/l, chloride 111 mmol/l.

She was readmitted in May 1969, with suspected cerebrovascular disease or presenile dementia. On admission, reacting to a trivial matter, she became negativistic and regressed. Suspected of being in a hysterical state, electric convulsive therapy was given, but it was ineffective in regard to the psychiatric and neurological symptoms. In addition, administration of various drugs and physical therapy were not helpful. About one year later, dysphagia developed, and her nutritional state became worse. Muscular tone of the extremities became hypotonic, and their movement more ataxic. Finally, the patient could not stand and walk at all, and became bedridden. Facial paresis on the left, asymmetry of deep tendon reflexes, and Hoffman's reflex on the left were observed in the course of illness, but they were slight and transient in their occurrence. At a later stage, generalised tonic convulsions began to occur once a month. In December 1972, after about four years, she died of pneumonia.

There were no abnormal findings from examinations of blood, urine, liver function, serum electrolytes, serological test for syphilis, ECG, and skull or chest radiographs. Moderate dilatation of the third and lateral ventricles was revealed by pneumoencephalography in January 1971. An EEG was carried out every year, but only low voltage and irregular alpha waves were observed without slow components or paroxysmal discharge. Cerebrospinal fluid, which was examined in January 1971, revealed a cell count of 7 lymphocytes per mm³, protein 0.25 g/l, sugar 4.0 mmol/l, chloride 120 mmol/l, with clear and colourless fluid.

Necropsy findings

Necropsy was confined to the brain which weighed 925 g. Macroscopically, it was small, and the cerebral hemispheres showed marked cortical atrophy, especially in the frontal lobe. Pons and medulla were also atrophied. Moderate atherosclerotic changes were observed in the basilar artery. No other gross abnormalities were noted in the leptomeninges and coronal sections of the brain.

Microscopically, inflammatory changes were located mainly in the grey matter of the brainstem. Perivascular infiltration with lymphocytes and plasma cells, and diffuse proliferation of glial cells, especially microglia, were prominent in the thalamus, hypothalamus, and midbrain, and to a lesser degree in the pons, medulla, and basal

Fig. 10 Perivascular cuffing and diffuse proliferation of glial cells of high degree in the lateral nucleus of the thalamus. Case 3, H & E $\times 60$.

nucleus (Fig. 10). In the dentate nucleus of the cerebellum, glial cells showed a moderate increase (Fig. 11). Slight diffuse demyelination and loss of nerve cells were demonstrated in the lateral nucleus of the thalamus, tuber cinereum of the hypothalamus, and red nucleus and tegmentum of the midbrain (Fig. 12), where the inflammatory changes were greatest. Relatively few glial nodules, light in appearance, were observed in the hypothalamus and dentate nucleus. Nerve cells in the other areas of the brainstem were relatively well preserved, and necrosis or neuronophagia were absent. In the cerebellum there was no loss of Purkinje cells or granular cells, although a slight loss in the dentate nucleus was observed. Moreover, a slight degree of demyelination and fibrous gliosis were demonstrated in the superior cere-

Fig. 11 Marked glial increase in the dentate nucleus. Case 3, H & E $\times 80$.

Fig. 12 Diffuse demyelination in the thalamus and centrum semiovale. Case 3, H & W.

bellar peduncle. In the cerebral cortex, a slight loss of nerve cells was observed in the frontal and parietal lobe, although the structure of the nerve cell layer was relatively preserved without senile changes such as senile plaque or Alzheimer's fibril. In the cerebral white matter, however, diffuse demyelination of the centrum semiovale and temporal lobe was present with slight glial increase (Fig. 12). Leptomeninges of the brainstem showed slight cellular infiltration. There were no arteriosclerotic changes of the small arteries or arterioles in the meninges and parenchyma, and no inclusion bodies in the nerve cells and glial cells of the lesions.

Electronmicroscopically, no viral particles could be found in the lesions of the midbrain.

Discussion

The cases presented in this paper have several points in common.

1. The age of onset of the illness was in adult life—from 21 to 47 years.
2. The occurrence was sporadic, and insidious. The course was chronic and slowly progressive without an acute stage or remission. The duration was four to eight years.
3. The outstanding symptoms were progressive dementia and ataxia. In the initial stage, however, personality change and abnormal behaviour were so prominent, as in cases 1 and 2, that they were suspected of schizophrenia, and treated in mental hospitals. Also, case 3 was suspected of a

hysterical state, and treated with electric convulsive therapy. As incidental symptoms to dementia, there were euphoria in cases 1 and 2, and hypochondriacal mood or emotional incontinence in case 3. Neurologically, it is characteristic that although bulbar signs such as dysarthria, dysphagia, and pyramidal signs were observed in all cases, other signs of brainstem lesions were rather poor or slight; only facial paresis or ophthalmoplegia were noted to some extent in cases 1 and 3, involuntary movement and bladder-bowel dysfunction in case 2, and generalised convulsions in case 3.

4. Medical and neurological symptoms or signs, which suggested an inflammatory process of the central nervous system, were so inadequate that making an exact diagnosis of "encephalitis" was difficult. Cases 1 and 2 were suspected of a cerebellar disease, and case 3 of some presenile dementia or cerebrovascular disease. Headache at the initial stage, and occasional slight fever during the fourth year after onset were notified in case 2 only.

5. Laboratory examinations also demonstrated minor inflammatory findings. Haematological examinations revealed no abnormalities except during the last stage of the illness, when pneumonia was present. Cerebrospinal fluid showed pleocytosis of slight or moderate degree at a later stage in case 1 only, and total protein was slightly raised in cases 1 and 2.

6. Pathologically, chronic inflammatory changes were observed, predominantly in the brainstem, and to a lesser degree in the cerebellum or subcortical grey matter, but scarcely extended to the cerebral cortex and white matter. In the brainstem, white as well as grey matter was involved in cases 1 and 2, but changes in white matter were not so prominent in case 3. Although perivascular cell infiltration and diffuse glial proliferation were prominent, only a few glial nodules were observed in cases 1 and 3. Moreover, nerve cells in the brainstem except for some regions were relatively well preserved. Necrosis and neuronophagia were absent. No inclusion bodies nor viral particles could be found in the nerve cells and glial cells of the lesions.

It is clear from the above that clinical and pathological features of our cases differ from encephalitides of known cause which were briefly mentioned in the introduction. Behçet's syndrome also shows inflammatory lesions in the brainstem (Rubinstein and Urich, 1963), but there were no signs suggestive of this syndrome, such as cutaneous or ocular lesions, in our cases. In addition, similar inflammatory changes of the brainstem

have reportedly been induced by the remote effects of cancer, particularly lung cancer (Russell, 1961; Henson *et al.*, 1967; Henson and Urich, 1970). In this disease, a subacute course and symptoms of myeloradiculoneuropathy are commonly described, and it is said to be easily diagnosed as cancer before death. The necropsies of our cases 1 and 2, however, clearly negate the possibility of cancer. From clinical and radiological points of view, case 3 can hardly be suspected of cancer and remotely induced brainstem lesions, although there have been descriptions of a few chronic cases whose cancer was discovered only at necropsy (Croft *et al.*, 1967).

It is most probable that the inflammatory lesions in our cases were produced by chronic infection of some yet undescribed virus which had a predilection for the brainstem region in the central nervous system. The biological properties, however, could not be clarified, since viral particles could not be observed under electron microscopy. Moreover, virological studies were not done because of our initial suspicion of a non-inflammatory disease. From the epidemiological point of view, it is of interest that this kind of chronic encephalitis with these peculiar features has been observed only in the Hokkaido region, the northern part of Japan, where there has been no epidemic of Japanese B encephalitis. Some endemic factors might have to be taken into account in association with their occurrence, but the details remain unclear.

Various neurological symptoms or signs have been described in brainstem encephalitis. Ataxia has been observed in a relatively large number of cases (Bickerstaff, 1957; Möller and Nenzelius, 1961; Tatetsu *et al.*, 1964; Mukoyama *et al.*, 1965; Verhaart, 1966; Marsal, 1967; Minauf and Tateishi, 1969; Schain and Wilson, 1971; Waxman *et al.*, 1974) though few showed ataxia as the predominant symptom, or were suspected of having cerebellar disease. Mental symptoms, except for disturbance of consciousness, were noted in only a few cases, and were not so prominent as in our cases (Iizuka, 1964; Tatetsu *et al.*, 1964, 1968; Shirabe *et al.*, 1972). On the other hand, it is interesting that the mental symptoms and the clinical course of our patients were similar to those of chronic panencephalitis of unknown aetiology (Peters and Struck, 1959; Boudoresques *et al.*, 1969; Ishino *et al.*, 1971); at onset, they were in the fourth or fifth decade of life, and had been suspected of mental diseases such as general paresis, presenile dementia, and schizophrenia, for they manifested dementia, euphoria, or dysarthria as the main symptoms.

Pathologically, severe inflammatory changes had been observed with numerous glial nodules in the grey matter of the cerebrum and brainstem. In our cases, however, only a few glial nodules were observed in the lesions of the brainstem. In addition, inflammatory changes in our cases did not extend to the cerebral cortex, although severe damage of the cerebrum was suspected from their mental changes and the abnormal findings of pneumoencephalography and EEG. Kersting (1952) suggested that encephalitis of adult onset had a tendency to show more intense changes in the brainstem and subcortical grey matter. According to his suggestion, our cases might be a type with more localised lesions in the brainstem. But our cases can hardly be considered the same as the type of panencephalitis mentioned above, or to be caused by the same aetiology as that of panencephalitis, from the pathological point of view.

It is certain that the mental abnormalities in our three cases are closely correlated with involvement of the brainstem and diencephalon, where several lesions were present, at the same time, without apparent changes in the cortex. Although the aetiology is still obscure, we are sure that it will be clarified in the near future by the development of virological and immunological studies.

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