AN AUTOPSY CASE OF MYOCLONUS EPILEPSY

— GAUCHER'S DISEASE —

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A twenty-five-years-old man who had no hereditary abnormal trait but had a tendency to luxation of the omo-branchial joints since childhood. Convulsive seizures began to occur at thirteen years, myoclonia at fourteen years and cerebellar symptoms and dementia at about nineteen years, succumbed to bronchopneumonia after eleven odd years of illness.

Principal pathologic findings were splenomegaly (160 gm) and enlarged mesenteric lymph nodes in both of which Gaucher's cells containing histochemically demonstrable glycolipids were observed to be present.

At autopsy gross pathologic examination failed to reveal any significant adverse findings for the brain. Microscopically, nerve cell of the cerebellar dentate nuclei were noted to be considerably defective, hence evidence of regional neuronophagia, and defect of Purkinje's cells was also noted. A histopathologic finding of particular note was vascular changes characterized by conspicuous enlargement and proliferation of adventitial cells which were frequent in the cerebral white matter, amygdaloid nuclei, claustrum and cerebellum. Some of the enlarged adventitial cells bore resemblance to Gaucher's cells and presented histochemical findings suggestive of the presence of glycolipids. Moreover, proliferation of blood vessels was prominent in the amygdaloid nuclei.

These findings seems to represent a juvenile form of Gaucher's disease.

Myoclonus epilepsy, a condition first recognized as a clinical entity by Unverricht¹⁾ and Lundborg et al²⁾, is classified from the histopathological viewpoint into four categories³⁾⁴⁾: the Lafora-body type, degenerative type, lipidosis type and special type(?). This report describes a case of the third type experienced recently at this department which seems to represent a juvenile form of Gaucher's disease.

CASE REPORT

Patient: K.I., a 25-years-old man

Family history: Noncontributory

Past history: He occasionally experienced luxation of the arm and shoulder joints since childhood and had an operation for gonitis at eleven years of age.

Present illness and progress: The patient developed all of a sudden convul-

sive seizures, uttering a queer cry, at thirteen years of age. Thereafter, he had experienced recurrence of such seizures once to thrice every month. At fourteen years, he was begun on a combined therapy regimen of diphenylhydantoin, 0.2 gm, and primidon, 0.8 gm, under the diagnosis of epilepsy. Since around that time myoclonic jerks of the upper limbs had occasional been seen. At nineteen years of age, the patient became to show ataxic gait, incoherent speech and dementia. He became to be incapable of walking alone and experienced psychomotor excitation and transient visual hallucination at twenty. When he was about twenty-two years old, he became increasingly demented and dysarthric and in a status epilepticus with recurrent severe seizures, showing aggravation. The patient succumbed to pneumonia at twenty five years of age, or eleven years and two months after onset of illness.

Neurological findings: The pupils were regular and equal and reacted rapidly to light. Ocular movements were normal and in no way nystagmic. Myoclonia was evident with the tongue or lips of the mouth. Hypotonia, intention tremor, disturbance in coordinate movements and adiadochokinesia were noted to be present with the upper extremities whilst the lower showed increased tendon reflexes and therefore knee-heel test was impracticable.

Laboratory findings: No abnormal finding noted in the hematological examination, urinalysis, liver function tests or CSF examination. EKG and chest X-ray findings were normal. The EEG-test was grossly abnormal. The basic pattern consisted of alpha waves and theta waves. Moreover, paroxysmal poly-spike and wave complex was observed (Fig. 1).

Autopsy findings: Included (1) bronchopneumonia, (2) pulmonary edema, (3)

Fig. 1 Paroxysmal poly-spike and wave complex.

splenomegaly (160 gm), (4) enlarged mesenteric lymph nodes, (5) emaciation and so forth.

Microscopic findings for the spleen and mesenteric lymph nodes in which Gaucher's cells could be demonstrated were as follows:

1) Spleen: Large Gaucher's cells, 20 to 80 μ in diameter, were noted to be distributed in areas corresponding to red pulps. Hematoxylin and eosinstained slides of spleen showed these Gaucher's cells with slightly eosinophilic, amorphous cytoplasm and relatively small nuclei, some of the abnormal cells being dinucleated. They were more frequently distributed in splenic sinuses and in medullary cords than in other areas of the spleen, and lymph follicles were noted to be virtually all atrophic or disappeared (Fig. 2).

Fig. 2 Gaucher's cells in the spleen.

2) Mesenteric lymph nodes: Lymph sinuses were dilated and filled with

Fig. 3 Gaucher's cells in the mesenteric lymph nodes.

Fig. 4 Loss of nerve cells in the nucleus dentatus and neuronophagia.

Gaucher's cells and lymph follicles disappeared. Capillary dilatation was prominent in both of these structures (Fig. 3).

Histochemical examination of Gaucher's cells in the spleen and lymph nodes revealed RAS, (+); Sudan III, ($\pm$); Sudan black B, (+); Nile blue, ($\pm$); and glycolipids, (+) by the test of Okamoto and Ueda, (+) by Morrison-Hack test and ($\pm$) by the same test with chloroform (60°C)-methanol immersed sections; hence evidence of the presence of glycolipids.

Findings for the brain: The brain weighed 1,220 gm and gross pathologic findings were unremarkable. Microscopically, the nerve cells of cerebral cortex were noted to show a relatively well maintained architecture. There were no microscopic evidence of significant alteration in the appearance or structure of nerve cells or neuroglia in the brain stem such as basal ganglia, midbrain, pons or medulla oblongata. In the cerebellum, nevertheless, nerve cells of the Nucl. dentatus were observed to be considerably deficient and hence show features of neurophagia (Fig. 4). Purkinje cells were mostly normal but in some instances noted to be atrophic or defective. There was a slight increase in number of Bergmann's cells while the

Fig. 5 Proliferation of the adventitial cells in the granular layer of the cerebellum.

granular layer appeared to be perfectly normal.

The conspicuous findings in this case were vascular changes which were characterized by remarkable hypertrophy and proliferation of the adventitial cells thereby causing marked narrowing of the vascular lumen as if a granulomatous change (Fig. 5). Enlarged adventitial cells bore resemblance to Gaucher's cells, and the tunica adventitia showed reticular structures which contained adventitial cells when stained by silvering (Fig. 6). Such histologic alterations were frequent chiefly with blood vessels in the cerebral white matter, nucleus amygdalae, claustrum and pia mater and granular layer of the cerebellum.

Fig. 6 Enlarged adventitial cells (Gaucher's cells) in the nucleus amygdalae.

Fig. 7 Marked proliferation of blood vessels in the nucleus amygdalae.

Marked proliferation of blood vessels was also evident in the amygdaloid nucleus in addition to the above-described changes (Fig. 7).

Histochemical examination of the hypertrophied adventitial cells demonstrated PAS to be positive (+); Alcian blue, (+); Mucicarmine, ($\pm$); Sudan III, (-); and Sudan black, ($\pm$); thus suggestive of the presence of glycolipids.

DISCUSSION

At thirteen years of age the patient began to experience convulsive seizures, and shortly later myoclonia and subsequently cerebellar symptoms and dementia developed; the patient died at twenty five years. The clinical progress and manifestations observed in the case are characteristically those of myoclonus-epilepsy syndrome.

Autopsy cases of the lipidosis type of myoclonus-epilepsy syndrome have been reported by Sioli⁵⁾, Liebers⁶⁾, Ohmaru⁷⁾, Haddenbrock⁸⁾, Watson and Denny-Brown⁹⁾, Weingarten¹⁰⁾ and Sekine¹¹⁾ et al. and a case of lipidotic variety of dyssynergia cerebellaris myoclonica which shows striking resemblance to the former was also described by Hamaguchi et al.¹²⁾. These reported cases were all of amaurotic idiocy. The

patient here in described did not have hepatomegaly at any given time in the course of disease or at autopsy but apparently showed splenomegaly and enlargement of the mesenteric lymph nodes. Histologic examination demonstrated the presence of giant cells containing glycolipids. These findings are in accord with those of Gaucher's disease first described in 1882 by Phillippe C. E. Gaucher¹³⁾.

Gross and histopathologic findings for the brain of Gaucher's disease that have been reported include those by Norman et al.¹⁴⁾, Seitelberger¹⁵⁾, Inose et al.¹⁶⁾, Miyamoto et al.¹⁷⁾ and Roizin et al.¹⁸⁾. Practically all these reported cases are of the infantile form and were described to have presented such characteristic microscopic features of the brain as swollen nerve cells and vascular changes, especially hypertrophy of the adventitia and proliferation of adventitial cells among which Gaucher's cells are occasional seen.

Regional neurophagia or nerve cell defect in the cerebellar dentate nucleus was evident in the case herein reported although cellular changes characteristic of lipidosis could not be demonstrated. Pathological changes in the dentate nuclei of the cerebellum are a finding virtually common to all types of histo-

pathologic classification of myoclonus-epilepsy syndrome¹⁸⁾¹⁹⁾²⁰⁾.

Conspicuous hypertrophy and proliferation of adventitial cells of the blood vessels in the pia mater as well as cerebral parenchyme, with giant cells containing glycolipids thus being likely Gaucher's cells, were also demonstrable in the case. Such marked histologic changes of mesodermal elements correspond to those of Gaucher's disease.

Possibility of the case being Niemann-Pick disease which is also a condition due to disturbance of lipid metabolism characterized by excessive storage of phospholipids, especially sphingomyelin, in the reticuloendothelial system was ruled out by histochemical findings and intracerebral vascular alterations although no particular biochemical examination was undertaken. The case was ultimately diagnosed as juvenile form of Gaucher's disease on the ground of such clinical manifestations as luxation, arthritis, etc. that had developed since childhood and neurologic symptoms persisting since thirteen years of age as well as the above-described autopsy findings.

REFERENCES

- 1) UNVERRICHT, H.: Die Myoklonie. Deuticke Verlag, Leipzig 1891.
- 2) LUNDBORG, H.: Die Progressive Myoklonus-Epilepsie (Unverricht's Myoklonie). Almqvist & Wiskell, Uppsala, 1903.
- 3) ANRAKU, S. et al.: Special type of Myoclonus-epilepsy(?). Proceedings of 8th International Congress of Neurology, Tom IV Vienna 1965.
- 4) ANRAKU, S.: Clinical and pathological study on myoclonus epilepsy (Unverricht-Lundborg type). Recent Advance Res. nerv. Syst. (Tokyo), 11, 717, 1967.
- 5) SIOLI, F.: Über einen histologischen Befund bei familiärer Myoklonus-Epilepsie. Arch. Psychiat. Nervenkr. 51, 30, 1913.
- 6) LIBERS, M.: Zur Histopathologie der amaurotischen Idiotie und Myoklonusepilepsie. Z. Neurol. 111, 465, 1952.
- 7) OHMARU, I.: An autopsy case of unusual amaurotic idiocy (Kufs type). J. Kurume Med. Ass., 11, 28, 1948.
- 8) HADDENBROCK, S.: Zur Pathogenese systematischer Bahndegeneration bei amaurotischer Idiotie und Frage der Beziehungen dieses Leidens zur Myoklonusepilepsie. Arch. Psychiat., 185, 129, 1952.
- 9) WATSON, C. W., D. DENNY-BROWN: Myoclonus Epilepsy as a symptom. Arch. Neurol. 70, 151, 1935.
- 10) WEINGARTEN, K.: Die Myoklonischen Syndrome. Wilhelm Maudrich, Wien, Bern, 1957.
- 11) SEKINE, Y. et al.: Ein Beitrag zu Klinik der sog. Myoklonusepilepsie. Psychiat. Neurol. Jap. 60, 617, 1958.
- 12) HAMAGUCHI, K. et al.: Report of a case neuronal lipidosis. Clin. Neurol. (Tokyo), 11, 629, 1971.
- 13) YABUCHI, H.: Gaucher's disease. Metabol. Dis. (Tokyo), 8 (special number), 1280, 1971.
- 14) NORMAN, R. M. et al.: The neuropathology of infantile Gaucher's disease. J. Path. Bact., 72, 121, 1956.
- 15) SEITERBERGER, F.: Über die Gehirnbeteiligung beider Gaucherschen Krankheit im Kindesalter. Arch. Psychiat. Nervenkr., 206, 419, 1964.
- 16) INOSE, T. et al.: Beitrag zur Neuropathologie des Morbus Gaucher in Kindesalter. Acta Neuropath., 3, 297, 1964.
- 17) MIYAMOTO, M. et al.: An autopsy case of Gaucher's disease. Diag. Ther. (Osaka), 19, 1153, 1966.
- 18) ROIZIN, L. and KAUFMAN, M. A.: Dyslipidosis, Pathology of the nervous system (Minkler), McCraw-Hill Book Company, New York, 1284, 1971.
- 19) HARRIMAN, D. G. F. and MILLAR, J. H. D.: Progressive familial myoclonic epilepsy in three families: Its clinical features and pathological basis. Brain, 78, 325, 1955.
- 20) MIURA, C.: Studies on Myoclonus Epilepsy of Degenerative Type. Kyushu Neuropsychiat., 15, 295, 1969.
- 21) FUJII, K.: Clinical study on cerebral lipidosis. Kyushu Neuropsychiat., 15, 295, 1969.