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Neuropathology Education

A 53-year-old woman with muscular atrophy showing hypersomnia and respiratory failure

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CLINICAL HISTORY

A 53-year-old female patient noticed weakness and wasting of limb muscles at age 30 years. Over the following years, the sternocleidomastoid muscles became atrophic and wasted, with frontal baldness. At age 43, her eyesight began to fail because of bilateral cataracts. She had experienced increasing sleepiness since adolescence. She was always very apt to drop off to sleep and always had difficulty in getting up in the morning. Examination at age 45 years revealed a hatchet face with frontal baldness, bilateral ptosis, grasp and percussion myotonia, and muscular atrophy of the four limbs, greater distally, and at the sternocleidomastoid. Pulmonary function tests revealed ventilatory insufficiency of a restrictive type with reduction of vital capacity (1800 mL, 55% of predicted), total lung capacity (2500 mL) and maximum breathing capacity (24 I/min, 25% of predicted). The ratio of the forced expiratory volume in 1 second to the forced vital capacity was 80%, showing no sign of airway obstruction. Arterial gas analysis values at rest while awake showed marked hypercapnea and hypoxia with respiratory acidosis (PaO_2 40 mmHg; $PaCO_2$ 68 mmHg; pH 7.29). The maximum inspiratory and expiratory pressure (71.3 cmH_2O and 83.2 cmH_2O) and the diffusion capacity for CO (15.3 mL/min/mmHg) revealed no abnormality. The ventilatory response to CO_2 inhalation was markedly impaired. However, voluntary hyperventilation lowered the CO_2 by 23 mmHg. Mental changes such as inattention, apathy and memory defect, which were not noticed in her childhood, were observed. Her IQ was 48. Brain CT scan disclosed enlargement of the lateral ventricles. At age 46, the patient experienced sudden respiratory insufficiency caused by local anesthesia for a cataract operation. She died of acute pneumonia at 53 years of age.

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PATOLOGICAL FINDINGS

The weight of the brain was 1050 g. On gross inspection, the brain was of normal external appearance. Histologically, intracytoplasmic inclusion bodies were present in the thalamus. The bodies were oval or elongated with smooth, sharply defined contours, usually located at the periphery of the cell, and occasionally surrounded by a halo. Each body was approximately 4–8 μm in maximum size. In HE preparations they appeared homogeneously eosinophilic (Fig. 1). The proportion of the inclusion bodies of the total cell population in the thalamus was 15.7%. The inclusion bodies were more abundant in the dorso-medial and anterior nuclei of the thalamus. Irregular intracytoplasmic inclusion bodies, ranging 1–8 μm in maximum size, often multiple and not surrounded by a halo, were found at the periphery or within accumulations of neuromelanin granules in the pigmented cells of the substantia nigra. With HE stain, the bodies appeared refractile and brightly eosinophilic (Fig. 2); 15.2% of the pigmented cells were affected. In addition, there were état crible in the cerebral deep white matter and neurofibrillary tangles immunoreactive for phosphorylated tau in the hippocampus and entorhinal cortex. The neuronal migration defect in the cerebral cortex was not observed.

As the ultrastructural features of the intracytoplasmic inclusion bodies of the thalamus and the substantia nigra were almost identical, they are described together. At the ultrastructural level, the intracytoplasmic inclusion bodies of the thalamus and the substantia nigra were composed of stacks of alternating, parallel, light and dark rectilinear profiles oriented perpendicularly to the long axis of the bodies (Fig. 3). At higher magnification, they were found to have internal structures composed of parallel alternating dark and light lines, the distance between the center of one dark line and the next being about 14 nm (Fig. 3). Where inclusions were sectioned transversely, they appeared as arrays of punctuate densities with a uniform center-to-center spacing of 13–15 nm (Fig. 4).

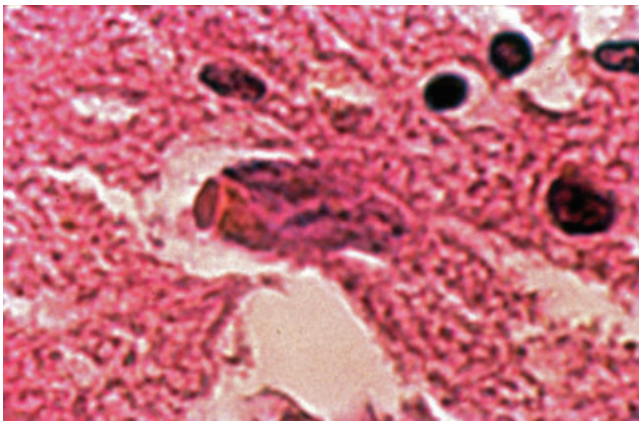

Fig. 1 Intracytoplasmic inclusion body of the thalamus. The inclusion is oval with smooth and sharply defined contours, located at the periphery of the cell. HE staining.

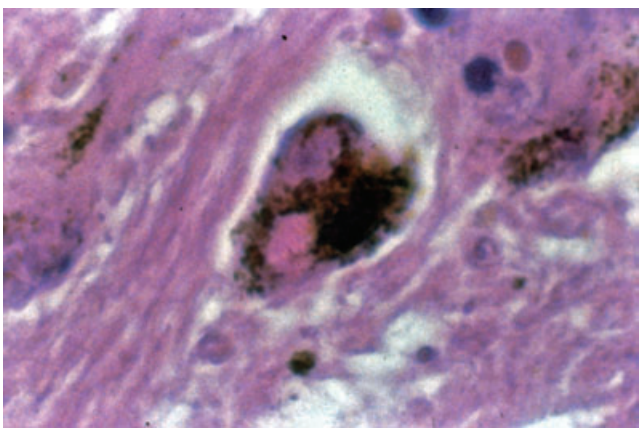

Fig. 2 Intracytoplasmic inclusion body of the substantia nigra. The inclusion is irregular, located within the accumulation of neuromelanin granules. HE staining.

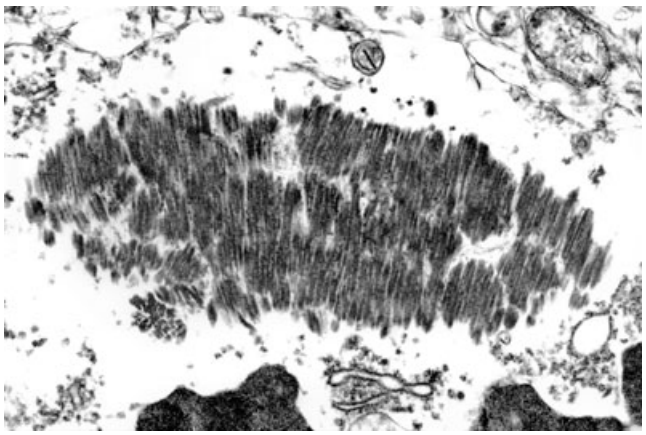

Fig. 3 Electron micrograph of intracytoplasmic inclusion body of the thalamus. The inclusion body is composed of assemblies of parallel alternating dark and light rectilinear profiles (×13 000).

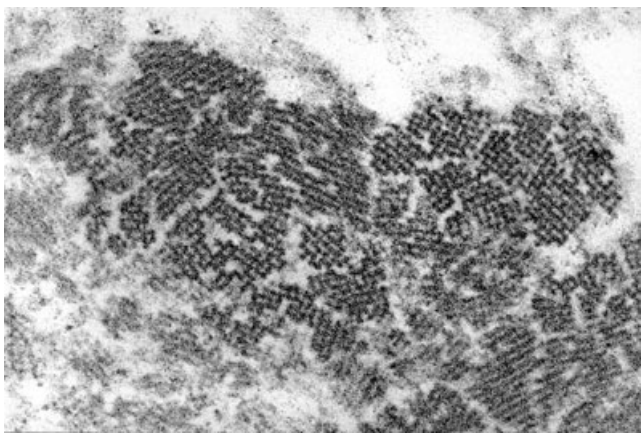

Fig. 4 Electron micrograph of intracytoplasmic inclusion body of the thalamus. The inclusion body shows a tetragonal lattice pattern in which the center-to-center distance of one punctuate density to another is approximately 14 nm (×84 000).

Severe neuronal loss and gliosis were observed in the midbrain and pontine raphe, particularly in the dorsal raphe nucleus (DRN) and superior central nucleus (SCN), with few abnormalities detected in the raphe of the medulla oblongata (Fig. 5). Pontine and medullary reticular formations also showed a marked cell loss and fibrillary griosis (Fig. 6), which were not limited to any particular nuclear group, and their remaining neurons were atrophic.

DIAGNOSIS

Myotonic dystrophy (MyD).

DISCUSSION

Ono *et al.*[1] reported that in controls the frequency of the neurons with intracytoplasmic inclusion bodies in the thalamus and the substantia nigra remained well under 1% and 3%, while in patients with MyD these were increased to over 10%. It is remarkable that the inclusion bodies of the thalamus on the substantia nigra were found with a far higher frequency in patients with MyD than in controls. It is suggested that the presence of a high frequency of these bodies[1] is not an incidental finding but may have an intimate and important relationship with the pathogenesis of MyD. Lesions of the thalamus are characterized clinically by sensory disturbances, motor deficits, cerebellar dysfunctions, involuntary movements and psychiatric disturbances. Psychiatric disturbances were found in our patient. However, the author fails to explain the absence, except for psychiatric disturbances, of clinical features characterized by thalamic lesions; in other words, it seems unlikely that the thalamic lesion alone causes psychiatric symptoms in MyD. The patient's mental problems developed in her

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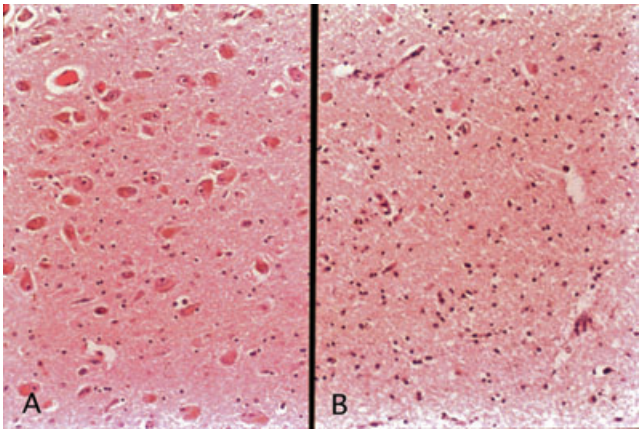

Fig. 5 Dorsal raphe nucleus in the midbrain from a control (A), as compared to our patient (B). (B) shows a decrease in the number of neurons. HE stain.

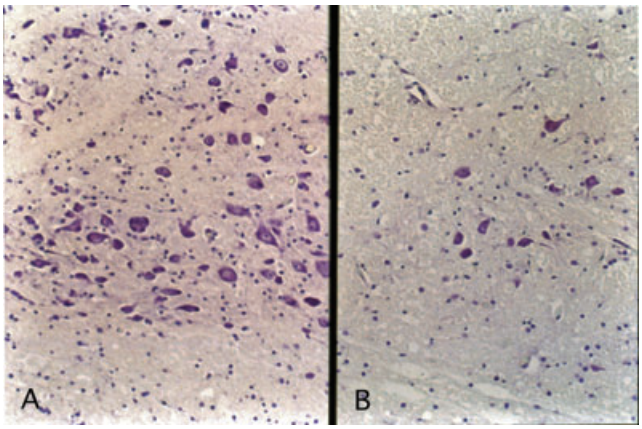

Fig. 6 Reticular formation in the medulla oblongata from a control (A), as compared to our patient (B). (B) shows a decrease in the number of neurons. KB stain.

adulthood, suggesting that it is related to dementia. Further studies are required to clarify the etiology of mental symptoms.

The ultrastructure of intracytoplasmic inclusion bodies of the thalamus and the substantia nigra are quite similar; both of them had an internal structure composed of parallel alternating dark and pale lines. Although the mechanism of formation of these inclusion bodies is unknown, the results strongly suggest that these bodies appear to consist of protein probably derived from the union of many identical macromolecules and the similarity may represent an expression of almost the same pathological mechanism associated with MyD.

The raphe nuclei play an important role in the regulation of the awake-sleep rhythm and are considered to be related to non-REM sleep.[2] Kitamura *et al.*[3] reported five patients who showed sleep disturbance and the central type of sleep apnea, and pointed out the relationships between sleep apnea and abnormalities in monoamine metabolism of the raphe nuclei. The neuronal loss in the DRN and the SCN was significantly greater in MyD patients with hypersomnia than in MyD without hypersomnia and control subjects, and that there was an appreciable positive correlation in the density of neurons between the DRN and the SCN in all MyD patients.[4] Several studies have revealed a lack of age-related changes in the raphe.[5] Therefore, based on our neuropathological findings, we conclude that extensive neuronal loss within the DRN and the SCN may correspond to the presence of hypersomnia in MyD.

Respiration is controlled by two systems, the voluntary and autonomic. Voluntary respiratory dysfunction has been demonstrated in patients with cerebral and bilateral pyramidal tract lesions or respiratory muscle weakness, while autonomic control has been localized to the reticular formation of the medulla oblongata and the pons.[6] There is an hypothesis that alveolar hypoventilation arising in the course of MyD may be due to the extension of the myopathy to the respiratory muscles.[7] Pulmonary function tests in our patient showed some restrictive impairment. However, our patient revealed a reduced ventilator response to carbon dioxide, which is attributed to a central origin.[8] A pulmonary, thoracic or diaphragmatic cause for the diminished response to carbon dioxide are ruled out, because our patient was able to lower pCO_2 considerably by voluntary hyperventilation, suggesting a central defect in respiratory regulation as a cause of alveolar hypoventilation in our case. The neuronal loss in the medullary reticular formation was significantly greater in MyD patients with hypoventilation than in those without hypoventilation and controls.[9] The present case disclosed cell loss and gliosis in the reticular formation of the medulla oblongata, thus implying together with the previous studies,[7–9] that these specific morphologic findings are related to the alveolar hypoventilation of this disorder.

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