Neuronal Ceroid Lipofuscinosis with Early-onset Dementia and Periventricular Leukoencephalopathy in which a Skin Biopsy was Diagnostically Useful

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Abstract

Neuronal ceroid lipofuscinosis (NCL) is a rare disease with onset typically during childhood; however, that developing during adulthood can lead to early-onset dementia. We report a 54-year-old man whose onset coincided with speech impairment, amnesia and dyscalculia. On brain MRI, marked diffuse leukoencephalopathy with periventricular predominance was observed. On a skin biopsy, characteristic fingerprint images were noted, and the patient was diagnosed with NCL. The differential diagnosis of cognitive impairment with leukoencephalopathy is wide ranging; however, when marked symmetrical periventricular-predominant leukoencephalopathy is prevalent and no peripheral neuropathy or gait disorders are evident, a diagnosis of NCL should be suspected and a skin biopsy should be performed.

Key words: dementia, periventricular, leukoencephalopathy, neuronal ceroid lipofuscinosis, skin biopsy, fingerprint profiles

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Introduction

Neuronal ceroid lipofuscinosis (NCL) is a disease in which ceroid lipofuscins accumulate in the lysosomes of neurons, leading to the progressive loss of vision and neuronal degeneration, with autosomal recessive inheritance often being noted.

Classically, the disease is categorized into four types based on the age of onset (infantile, late-infantile, juvenile and adult), with more than 151 genetic defects having been reported to date (1). There are no accurate epidemiological data for Japanese NCL patients; however, in northern Europe, NCL is a rare disease, with a rate of 1 in 12,500. Of the 36 reported Japanese cases, two were infantile, 15 were late infantile, 15 were juvenile and four were adult (2). Awareness of the adult form of NCL is insufficient; however, the condition is suspected based on clinical observations and the brain MRI findings, thereby making the diagnosis of the disease possible based on the results of skin biopsies.

Case Report

The patient had no problems regarding birth or development and was educated until high school. After graduation, he worked as a restaurant manager. At 54 years of age, he developed a speech impairment. At 55 years of age, he suffered from forgetfulness and miscalculation. At 56 years of age, a frontal lobe disorder, constructive apraxia, visuospatial agnosia, mild aphasia and memory disturbance were diagnosed at another hospital. Marked leukoencephalopathy was observed on MRI and single photon emission computed tomography (SPECT) showed a generalized reduction in blood flow. However, the cause of these conditions was not identified. At 59 years of age, the patient was able to follow simple instructions; however, his speech function was almost entirely lost. At 60 years of age, he visited our hospital after entering a residential care home. No convulsions or vision-related symptoms were noted throughout the pa-

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Figure 1.  T2-weighted image. Marked, confluent periventricular-predominant leukoencephalopathy is observed.

Figure 2.  Electron microscopic findings on skin biopsy. Fingerprint structures can be seen.

tient’s entire clinical course.

He had no medical history of particular note, except for dementia. There was no history of psychoneurological illness among the patient’s grandparents, parents, two brothers and two sisters. Both of his parents were from Kyoto. No medications had been taken before the onset of symptoms. The patient had never smoked, although he had drunk 700 mL of beer every day before onset.

The patient’s blood pressure was 109/69 mmHg, his heart rate was 74 beats/min and regular, his body temperature was 36.8 degrees, his respiratory rate was 18 breaths/min and his SpO2 was 98% (room air). There were no malformations or facial features of note. The patient sometimes understood simple instructions communicated with body language; however, he was almost mute. There were no behavioral problems, except for occasional loitering. The conjunctivae were not pale, and there was no jaundice. The patient’s lung sounds were clear, with no heart murmurs, and his abdomen was flat and soft, with no tenderness. Regarding the neurologic findings, no ocular motility disorders, nystagmus, orthostatic hypotension or muscle weakness of the limbs or trunk were observed, the patient consumed food with a spoon, there were no distinctive disorders of fine movement, the patient’s superficial sensation and muscle tone were normal and deep tendon reflexes were pronounced in both the upper and lower limbs, with no bilateral differences. Babinski, Chaddock, Oppenheim, root and palomental reflexes were negative. The snout reflex was positive bilaterally, and the left grasp reflex was also positive. Although the patient exhibited brachybasia while walking, his steps were stable and not wide, and no pulsion was observed.

Blood test parameters (blood count, hemogram, the liver function, the kidney function, electrolytes, blood sugar, urine, the thyroid function, syphilis and HIV antigen antibodies) were all normal.

Marked confluent periventricular-predominant leukoencephalopathy was observed on MRI (Fig. 1). There were no cerebral infarctions or hemorrhagic lesions. No arterial irregularities were noted on magnetic resonance angiography (MRA).

A skin biopsy of the thigh was performed. Ceroid lipofuscin was seen in the duct and gland cells of the eccrine sweat glands and cytoplasm of Schwann cells on electron microscopy, while some cells exhibited characteristic stratified fingerprint images (Fig. 2) considered to be indicative of ceroid lipofuscinosis.

Overall, the clinical and MRI findings and skin biopsy results led to a diagnosis of neuronal ceroid lipofuscinosis.

Discussion

Adult-form NCL is also called Kufs disease. Its characteristic features include myoclonus, cognitive impairment, motor ataxia and behavioral disorders; however, it does not cause visual impairment. Typical onset occurs in the 20s and 30s, although onset in the 50s and 60s, as in the present case, is sometimes reported (3-8).

The aphasia and constructional apraxia observed in this case can be generally categorized as cortical symptoms. However, subcortical lesions caused by cerebrovascular diseases (9) and leukodystrophy, such as autosomal dominant leukodystrophy with axonal spheroids and pigmented glias (10), are known to cause aphasia. Diseases that present with subcortical lesions have been reported to be associated with a decreased cortical blood flow on brain SPECT (11). The present patient exhibited cortical symptoms, such as aphasia and constructional apraxia, and brain SPECT per-
formed in a previous hospital showed a diffusely decreased blood flow. These findings can be explained as indicating secondary changes caused by the subcortical lesions.

Detecting leukoencephalopathy on head MRI is important for diagnosing NCL. In a review of head MRI findings in 30 cases of juvenile neuronal ceroid lipofuscinosis, leukoencephalopathy was reported to be the most important change (12). In particular, leukoencephalopathy in the periventricular area on MRI was marked compared to that observed in the subcortical area (13).

There is no consensus regarding the MRI findings of adult neuronal ceroid lipofuscinosis. Some studies have reported brain atrophy, low signal intensity on T2-weighted MR images of the putamen (14), high signal intensity on T2-weighted MR images of the cortex (15), high signal intensity on T2-weighted images of the cortex and basal ganglia (16) and periventricular-predominant leukoencephalopathy (3). Other studies have demonstrated the markedly localized accumulation of neuronal lipofuscin mimicking mass lesions (17), suggesting the presence of a heterogeneous pathological condition. The relationships between genetic mutations and MRI findings in patients with adult neuronal ceroid lipofuscinosis remain unclear; however, periventricular-predominant leukoencephalopathy can be considered to be a finding suggestive of adult neuronal ceroid lipofuscinosis.

On the other hand, more than 50 diseases are known to be associated with leukoencephalopathy, and identifying the causative disorder is often difficult in patients with leukoencephalopathy. In 2009, Schiffmann et al. categorized patterns of leukoencephalopathy based on MRI findings (18). According to this classification, leukoencephalopathy exhibits 10 patterns, each of which comprises four to 13 diseases or disease groups. The presence of periventricular predominance, as observed in this case, reduces the number of causative disorders to eight.

Of these diseases, metachromatic leukodystrophy and adult polyglucosan body disease present with peripheral neuropathy, while Krabbe disease is associated with peripheral neuropathy and gait disorders caused by spastic paralysis. In leukoencephalopathy patients with brain stem and spinal cord involvement and lactate elevation, gait disorders are the primary symptom; therefore, these disorders can be clinically ruled out. Sjögren-Larsson syndrome is a disease with the three main symptoms of mental retardation, congenital ichthyosis and spastic paraplegia and quadriplegia. Periventricular leukomalacia is a disease that develops in low-birth-weight infants; hence, these conditions can also be ruled out. Based on this background, the present patient’s clinical features and MRI findings are consistent with HIV encephalopathy and/or later-onset neuronal degenerative disorders (neuronal ceroid lipofuscinosis) only. The HIV antigen antibody test was negative for HIV infection. These results suggest that NCL should be considered the tentative diagnosis.

More than 90% of cases of lysosomal disorders are positively diagnosed on electron microscopy after a skin biopsy. Therefore, a definitive diagnosis can be made, even in patients with NCL or mucolipidosis type IV (19). It has been reported that making a diagnosis based on the findings of a skin biopsy was possible in 32 of 34 cases of NCL, with findings suggestive of NCL observed in the other two cases (20). Fingerprint and curvilinear structures are known to be characteristic electron microscopic findings of NCL. In this case, we found the former, which led to a definitive diagnosis. Since skin biopsies can be performed easily and are not markedly invasive procedures, they should be carried out when a diagnosis of NCL is suspected.

The authors state that they have no Conflict of Interest (COI).

References


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