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Case Report

운동신경원성 질환과 유사하게 발현된 샌드호프병

서울대학교 의과대학 신경과학교실

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Adult Sandhoff Disease Presenting as Motor Neuron Disease Phenotype

Suk-Won Ahn, M.D., Su-Hyun Kim, M.D., Suyun Kim, M.D.,
Sung-Min Kim, M.D., Kwang-Woo Lee, M.D, Jung-Joon Sung, M.D.

Department of Neurology, Seoul National University College of Medicine,
Clinical Research Institute of Seoul National University Hospital, Seoul, Korea

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We report a 23-year-old woman with adult Sandhoff disease, who presented with motor neuron disease phenotype. The patient had experienced progressive motor weakness in four extremities since 1 year prior to admission. Electrophysiological study revealed wide-spread denervation potentials, and the assay of total hexosaminidase involving A and B activities showed decreased levels of these activities, which was consistent with Sandoff disease. This is the first Korean case of adult Sanhoff disease presented as a motor neuron disease phenotype.

Key Words: Sandhoff disease, Motor neuron disease, GM2 gangliosidosis

Introduction

Sandhoff disease is a lysosomal storage disorder that is characterized by an autosomal recessive pattern of inheritance.[1] The biochemical defect in Sandhoff diseasae is a deficiency of lysosomal hydrolase β-hexosaminidase activity (Hex).[1] This enzymatic deficiency is the result of a mutation in the gene on chromosome 5 which codes the β-subunit of Hex.[2] This subunit is common to both A and B major Hex isoenzymes. Deficiency of both A and B isoenzymes causes accumulation of water-soluble N-acetylgalactosaminides and N-acetylglucosaminides in addition to GM2 ganglioside.[1,2] This disorder displays a spectrum of clinical severity, ranging from the most severe infantile forms to juvenile, chronic and adult-onset variants. In infantile form, both Hexosaminidase A and B activities are severely deficient. In obligate Sandhoff disease heterozygotes (parents of affected infants), a partial Hexosaminidase deficiency has been described.[3] Infantile form is characterized by an early onset of symptoms, usually in the first 6~18 months of life. GM2 ganglioside and related glycolipids are stored in the brain and other tissues. Death generally occurs before 3 years of age. The adult form of Sandhoff disease usually manifests neurologic signs and symptoms in early ages, characterized by a delayed course.[3] Progression of clin-

Address for correspondence;
Jung-Joon Sung, MD, PhD.
Department of Neurology,
Seoul National University Hospital,
28 Yongon-Dong Chongno-gu, Seoul 110-744, Korea
Tel: +82-2-2072-3215 Fax: +82-2-3672-7553
E-mail: jjsung@burnham.org (jjsaint@unitel.co.kr)

ical signs and symptoms is usually slow. Although clinical phenotype of this disorder varies widely, spinocerebellar degeneration or motor neuron disease has often been reported.[4] We report a case of adult Sandhoff's disease mimicking motor neuron disease which is to our knowledge, the first report of the disease in Korean population.

Case

A 23-year-old woman presented to our department with a history of progressing general weakness. One year prior to admission, she noticed intermittent fasciculation and muscle cramp in both lower extremities. Fasciculation and cramp were gradually progressive and frequency of fasciculation and cramp increased. She began to experience difficulty in running and climbing the stairs 8 months ago. Three months previously, she found the weakness in both hand and she had difficulty in writing and lifting heavy materials. Additionally, she had difficulty in speaking for a long time and swallowing solid food. In past medical history, the antenatal and the postnatal periods had been uneventful. She had gone to school and had led an apparently normal life till she noticed neurological manifestations. Relevant neurological disease, medication, smoking, or alcohol history were not noted. However, there was a familial history of similar illness in her family. Her mother had similar symptoms of progressive motor weakness, but was not sufficiently evaluated, and she had died at thirty years of age. On examination she was a young woman with a blood pressure of 110/60 mmHg, and heart rate was 70 beats/min. Neurological examination revealed that she was alert and her orientation was intact. Cognitive impairment was not detected. Facial expression and sensory were all normal. She had no nystagmus on looking to the right and left, and slit lamp and funduscopic examination did not reveal abnormalities. There were, however, dysarthria and dysphagia on cranial nerve examination. Motor system examinations (MRC; Medical Research Council grade) revealed limb weakness involving upper and lower extremities (proximal upper extremity MRC grade 4/4, distal upper extremity MRC grade 4/4, proximal lower extremity MRC grade 4/4, distal lower extremity MRC grade 4/4), and mild muscle atrophy was found in distal extremities. Deep tendon reflexes involving knee, ankle, biceps and triceps jerk were decreased. She showed symmetric and intact responses to all sensory stimuli and his cortical senses were normal. Her neck was supple, and carotid bruit was not audible, and cerebellar function test was normal. Other systemic examination was normal. Investigations revealed a normal hemogram, serum electrolytes, renal function and thyroid function test. We performed brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), which showed normal brain parenchyma, intracerebral and carotid arteries. Cervical MRI revealed no abnormalities. Electromyography (EMG) and nerve conduction studies (NCS) were performed, and results of which showed wide spread denervation potentials in cervical, thoracic, lumbar and bulbar areas, which were coincident with motor neuron disease. Jolly test and evoked potentials (EP) were normal. She underwent muscle biopsy in vastus lateralis muscle, which revealed denervation atrophy of muscle fiber (Figure 1). Because of the early onset of motor neuron disease and family history of similar manifestations, a possibility of GM2 gangliosidosis or SMA (spinal muscular atrophy) was entertained and a quantitative estimation of Hexosaminidase A and B activity and SMN1 (survival motor neuron 1) in leukocytes was performed SMN1 deletion assessing SMA (spinal muscluar atrophy) was negative in PCR/RFLP. Fluorometric assay of peripheral blood revealed a marked reduction of both total β-hexosaminidase A and B, at 290.0 nmol /hr/mg (reference range; 620~1,000 nmol/hr/mg). In particular, the percentage of β-hexosaminidase A in total β-hexosaminidase was mildly ele-

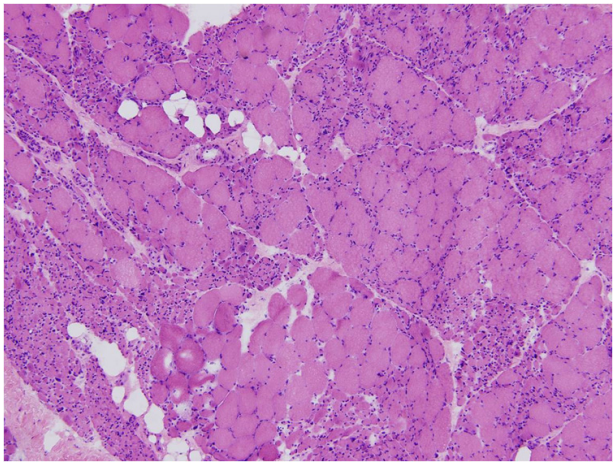

Figure 1. Muscle biopsy findings in the vastus lateralis muscle (H&E staining. ×100). Microscopic findings revealed size variation of myofibers and denervation atrophy without inflammatory cell infiltration.

Table 1. Amount of total β-hexosaminidase and β-hexosaminidase isoenzyme in leukocytes using Fluorometric assay

Enzyme activity in WBC	Results	Normal control	Normal range	Unit
Total Hexosaminidase	290.0	1,174.8	620~1,000	nmol/hr/mg
Hexosaminidase A (%)	78.5	84.3	55~72	%

vated as 78.5% (reference range: 55% to 72%, Table 1). Hence, a diagnosis of adult Sandhoff disease was made. She was discharged and has been managed in out-patients department with symptoms slowly progressing.

Discussion

The clinical features in our patient bore a distinct resemblance to motor neuron disease with the gradual onset of muscle fasciculation, cramp, motor weakness in upper and lower limbs, dysarthria and dysphagia without sensory symptoms. Because of the early onset, absence of upper motor neuron signs and family history of similar symptoms, various possible diseases involving late onset spinal muscular atrophy, multifocal motor neuropathy, mononeuritis multiplex, inflammatory myopathy, neuromuscular junction disorder, postpolio syndrome, spinal cord syndrome, demyelinating disease or Sandhoff disease, which mimic motor neuron disease, were initially considered in this patient. Therefore, electrophysiological study of NCS/EMG, jolly test and EP studies were of importance and first investigated, and imaging study and serum laboratory tests were performed in this patient. In conclusion, the enzyme studies in our patient indicate a deficiency of hexosaminidase A and B. The case is classifiable as an example of delayed onset Sandhoff disease, which usually manifests neurologic signs and symptoms in early ages, characterized by a delayed course. Actually, cases of Sandhoff disease mimicking motor neuron disease have been described in recent years.[4] The course of the disease is that of relentless and ultimately fatal progression of neurologic disease.[1]

Sandhoff disease is a storage disorder. The absence of β-hexosaminidase enzymes in this disease lead to the accumulation of GM2 gangliosides in neural tissue.[1-3] The most well known among them is Tay Sachs disease where only β-hexosaminidase A is absent. In contrast both hexosaminidase A and B are absent in Sandhoff disease. The features of both Sandhoff and Tay Sachs disease are largely similar except for the differences in bio-chemical enzyme deficiency patterns.[2] Hexosaminidase A and B are glycoprotein enzymes that have two subunits–alpha and beta. The beta subunit is common to both hexosaminidase A and B. This beta subunit is coded by a gene on chromosome 5.[2] Mutations of this gene result in abnormality of both the enzymes manifesting as Sandhoff disease. These allelic mutations are diverse and can result in varying residual of the enzymes.[5,6] This can explain certain variations in clinical presentation.[4-7] Unfortunately, genetic study was not performed in our patient because of her disapproval. Further studies on gene mutations are warranted in our patient and her family to elucidate mechanism of Sandhoff disease mimicking motor neuron disease. There is no definitive treatment yet.[1-3] A variety of innovative therapies including hexosaminidase infusions and leukocyte transfusions have been tried. Bone marrow transplantation has also been attempted.[8] However, none of these have provided a cure. For the present, preventive genetic counselling and the supportive treatment of affected individuls are the only options. Recently a new drug called N-butyl-deoxynojirimycin has been found to delay onset and progression of Sandhoff disease in animal models.[9-10] It inhibits the synthesis and storage of accumulating lipid and is a potential therapeutic strategy for other lysosomal storage diseases as well.[9-10] If future trials establish the efficacy of this drug, it could offer hope to patients afflicted with this incurable illness. Therefore Sandhoff disease must be considered in patients of early onset motor neuron disease from a therapeutic point of view, because the pathomechanism and target of treatment are different between Sandhoff disease and motor neuron disease. Sandhoff disease is rare, but there have been several case reports of this illness. However, to our knowledge, this is the first report of Sandhoff disease mimicking motor neuron disease in Korean population.

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