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# Adrenoleukodystrophy -A Case Report-

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=Abstract=We describe a 9-year-old boy who showed typical neurologic manifestations i.e., progressive behavioral changes, intellectual impairment, visual disturbances and hearing loss, cerebellar and pyramidal signs with characteristic neuroimaging features, which led us to make a clinical deagnosis of ALD. It was confirmed later by demonstration of increased VLCFA levels in RBC membrane using HPLC. He has no family history of neurologic or endocrine disorder. Prophylactic antiepileptic medicaion could not prevent the development of seizure disorder.

Key words: ***Adrenoleukodystrophy, Very long chain fatty acids, High-performance liquid chromatography, MR imaging.***

## INTRODUCTION

Adrenoleukodystrophy (ALD) is an X-linked recessive disease of childhood associated with rapidly progressive demyelination of cerebral white matter and varying degrees of adrenal cortical failure (Schaumburg *et al.* 1975).

Most affected boys are between the ages of 5 and 10 years when the first symptoms are noted; the initial clinical presentations are usually an alteration in behavior ranging from a withdrawn state to aggressive outbursts and intellectual impairment. Neurologic deterioration is then relentlessly progressive and includes loss of vision and/or hearing, disturances of gait and coordination, long tract signs, and ultimate deterioration to a vegetative state and finally death. Seizures are a late manifestation. Although the primary enzymatic defect in ALD is still unknown, recent investigations have disclosed that the metabolic defects occur in the oxidation of very long chain fatty acids (VLCFA) (Igarashi *et al.* 1976; Moser *et al.* 1981; Kobayashi *et al.* 1983; Moser *et al.* 1984).

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## CASE REPORT

H.Y., a 9-year-old boy, was admitted to the Seoul National University Hospital because of progressive visual disturbance and hearing loss that had begun at 8 $\frac{1}{2}$ years of age.

He was the first child of healthy young parents. He had no family history of neurologic or endocrine disorder. Following an unremarkable pregnancy and delivery, he weighed 3.15 kg at birth. Growth and development milestones were normal. He appeared to be a bright child and was in perfect health until 8 months prior to study when he became poorly attentive and his school performance began to decline. Over the next few months, he developed a gait disturbance, dysarthria and drooling.

His examination on admssion revealed a small wasted and somewhat dull-looking child. He was alert but expressionless. There was no abnormal skin pigmentation, and blood pressure was 90-100/60-70. Visual acuity was below 0.04/0.04, and visual field examination on perimetry revealed right upper quadrant islands. Audiometry disclosed a bilateral sensorineural hearng loss (SNHL). Strength and sensations

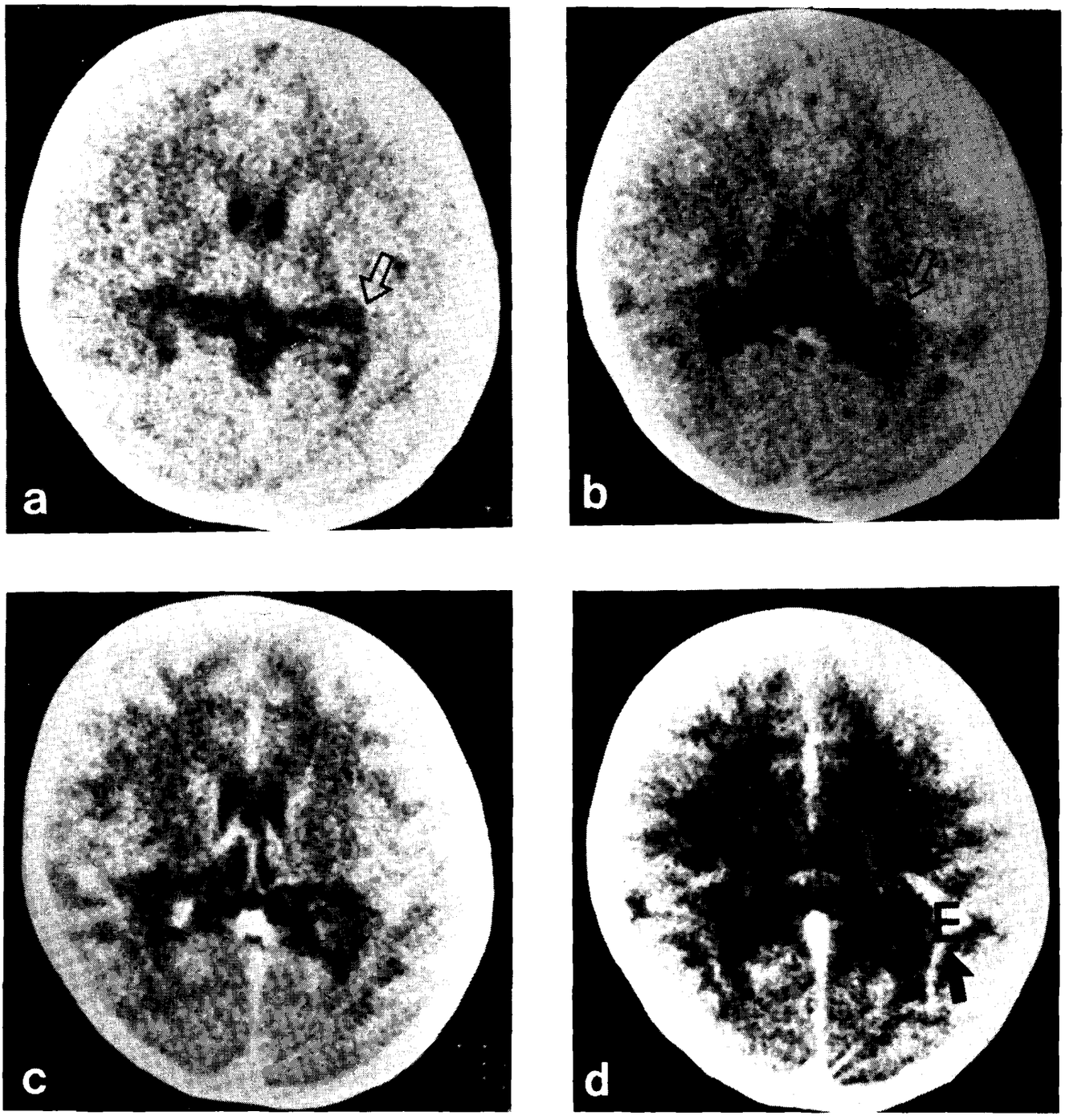


Fig. 1. a-d
Non-contrast scans show areas of decreased attenuation in the deep white mater (arrows) around the ventricular trigone (a,b).
Contrast scan shows characteristic peripheral enhancement (E, arrow) (c,d).

were normal, but he had spastic lower limbs. Tendon stretch reflexes were exaggerated with extensor plantar responses and sustained ankle clonus, bilaterally. He also showed bilateral dysmetria on finger to nose testing and showed spastic awkward gait. Laboratory studies were as follows; normal hemogram and blood smear, urinalysis, calcium 10.0 mg/100 ml, phosphorus 5.0 mg/100 ml, and serum aspartate aminotransferase (SGOT) 13 units. Metachromatic granule was negative in the urine. Serum cortisol was 4.3 $\mu$g/ml in a morning sample and 20.3 $\mu$g/ml in an evening sample. ACTH stimulation test revealed normal response.

A Computed Tomography (CT) of the brain performed elsewhere demonstrated low density

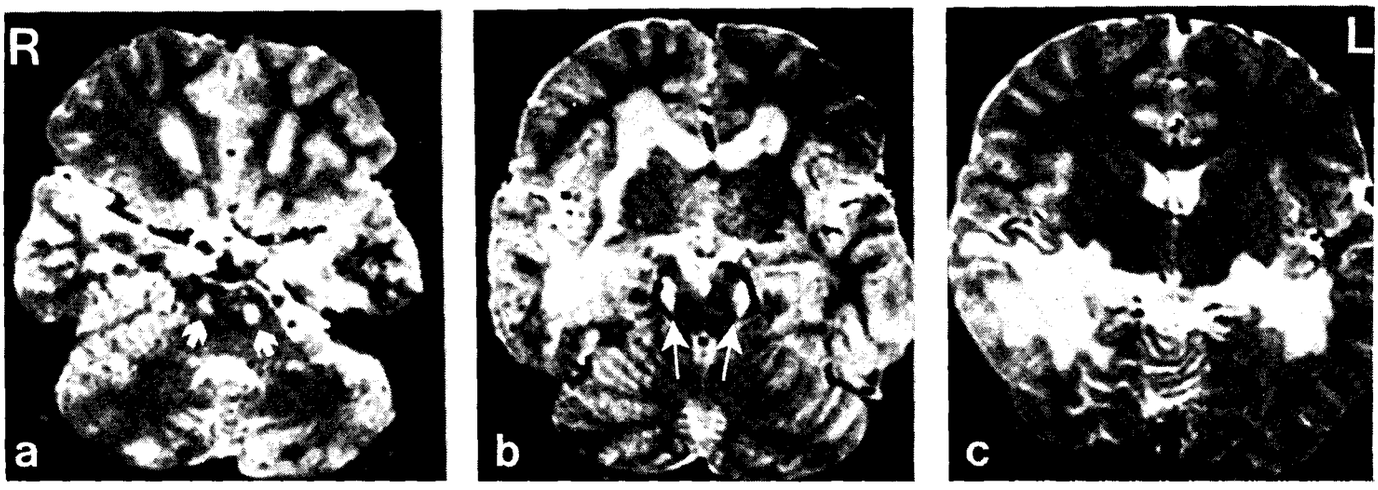


Fig. 2. High-field strength MRI (2.0 Tesla) precisely showing various levels pathways affected by disease (Spin Echo TR = 3,000 ms, TE = 80 msec).
a. Section at the level of the pons shows discrete pyramidal tract involvement (arrows).
b. MR image at the level of midbrain discloses cerebral peduncle involvement (arrows).
b. MR image at the level of frontal horns reveals involvement of splenium of corpus callosum and parieto-occipital white matter.

lesions of the subcortical white matter adjacent to the ventricular trigone, extending into parieto-occipital areas (Fig.1-a) with an enhancing rim that is more prominent anteriorly (Fig.1-b). A Magnetic Resonance Imaging (MRI) scan (GS SPECTRO-20,000) revealed an area of high-intensity, symmetric, periventricular signal in the white matter of parietal lobes, discrete pyramidal tract involvement within the brainstem, lesions of the lateral cerbral peduncle and involvement of splenium of corpus callosum (Fig.2). Electroencephalography (EEG) showed localized frontal slowing but no definite epileptiform activity. After initial diagnostic work-up, he was put on an antiepiliptic medication (Phenytoin 200 mg/day) to prevent possible seizure attacks.

Two months after discharge, he developed a focal seizure with secondary generalization while his serum phenytoin level was maintained within the therapeutic ranges. On his second admission, all other clinical features got worse than before. His speech deteriorated almost to unintelligibility. He could hardly walk out alone without assistance.

On his third admission 6 months after initial diagnosis, he developed status epilepticus. During his last admission, for the analysis of VLCFA, venous blood was obtained with heparin-Na as an anticoagulant from the patient and the plasma and washed RBC's were prepared as suggested by Kobayshi *et al* (1983). The samples were stored at −60°C until analyzed. Although the active seizure ceased, he could not regain his consciousness. The child was discharged to the care of his parents in a vegetative state.

## DISCUSSION

Adrenoleukodystrophy (ALD) refers to a group of degenerative disorders characterized by widespread demyelination and relentless neurological deterioration. Because the phenotype is varied, it has been classified into three main subtypes; childhood ALD, adrenomyeloneuropathy (AMN) and neonatal ALD (Moser *et al.* 1984).

As previously mentioned, the most common childhood form is distinguished by its prominent clinical features; slowly progresive behavioral changes, intellectual impairment, loss of vision and/or hearing, cerebellar and pyramidal signs with or without evidence of adrenal insufficiency in a boy who has been in perfect health.

Childhood ALD and AMN are frequently observed in the same kindred and have an X-linked hereditary trait. AMN usually does not begin until the second or third decade or even later, and the disorder is characterized by adrenal insufficiency, variable hypogonadism, a slowly progressive demyelination in the spinal cord and

in peripheral nerves that causes spastic paraparesis and distal polyneuropathy (Griffin *et al.* 1977). So it is now considered to be a more indolent variant of childhood ALD. Another form, neonatal ALD is now obviously different from childhood ALD, not only in inheritance pattern (autosomal recessive) but also in clinical manifestation; abnorml facial features, moderate to severe hypotonia, hepatomegaly and retinitis pigmentosa (Moser *et al.* 1980; Aubourg *et al.* 1986).

Because all neurological features were typicl of ALD, the clinical diagnosis was not so difficult in this patient, No family history of adrenal or neurologic disease could be elicited.

After completing the initial diagnostic work-up, the boy was on prophylactic antiepileptic medication, but it was impossible to prevent, as might have been expected, the seizure attack caused by the progression of disease.

Since Igarashi *et al.* (1976) found abnormal accumulation of VLCFA in cholesterol ester fractions from cerebral white matter and adrenal glands of a patient with ALD, increased VLCFA levels have been found in other tissues and body fluids suggesting that ALD is a systemc metabolic disorder of this class of fatty acids (Igarashi *et al.* 1976; Kobayashi *et al.* 1983; Moser *et al.* 1984; Rizzo *et al.* 1984; Singh *et al.* 1984).

Although the specific enzymatic defects in ALD remain to be further established, studies showing impaired VLCFA oxidation in fibroblasts and leukocytes suggest that it is one of the peroxisomal disorders. Because of functional derangement in peroxisomes, where the $\beta$-oxidation of fatty acids occurs, there results in accumulations of VLCFA in the tissues (Lazarow 1987). The most consistently observed increase is that of hexacosanoic acid (C26:0) (Watkins *et al.* 1987). Although typicl ALD shows clinical signs of adrenal failure such as cutaneous pigmentation, hypotension or vomiting, drenal insufficiency is not always clinically manifested.

There are numerous reports of CT findings in ALD. The typical CT features, as seen in our patient, were large symmetric, low-density lesions with peripheral enhancement that involved white matter of the occipital, posterior parietal, and temporal lobes (i.e., peritrigonal areas). Extension of these lesions progressively involves the splenium of corpus callosum (Greenberg *et al.* 1977; Chiro *et al.* 1980; Aubourg and Diebler 1982). However, atypical findings, i.e., frontl lobe involvement, predominantly unilateral involvement, calcifications within the white matter lesion, and mass effect were also described (Chiro *et al.* 1980; Inoue *et al.* 1983).

Recently a few reports have described MRI appearance of ALD and concluded that MRI is superior to CT in the demonstration of nervous system involvement (Bewermeyer *et al.* 1985; Young *et al.* 1983; Huckman *et al.* 1986). Kumar *et al.* (1987) described more detailed MR images in their six patients with ALD and suggested that MRI is the first imaging modality to demonstrate both auditory and visual pathway structural disease in ALD.

The present case certainly emphasizes the importance of the MRI. The scan obtained on the 7th hospital day revealed discrete pyramidal tract involvement within the brainstem, involvement of auditory and visual pathways and extensive white matter lesion. These MRI findings are so characteristic that anyone can make diagnosis of ALD in a appropriate clinical settings.

Open adrenal biopsy has been the most reliable test for the diagnosis of ALD, but there have been a few autopsy proven cases with normal adrenal function (Schaumburg *et al.* 1975; Kim *et al.* 1988). Lamellar inclusions observed in conjunctival or skin biopsies may help the diagnosis but are still not confirmative (Arsenio-Nunes *et al.* 1981).

Therefore, demonstration of increased hexacosanoic acid (C26:0) becomes indispensable for the confirmation of ALD, and it is possible to identify female carriers of ALD by verifying the increased plasma VLCFA level (Moser *et al.* 1983). Techniques for the prenatal diagnosis of ALD were also established (Moser *et al.* 1982). In our case, the increased plasma VLCFA level was demonstrated using HPLC during the third hospital admission (Table 1). In an analysis of VLCFA the hexacosanoate (C26:0) was most notably increased.

We're planning to measure the plasma VLCFA levels of this patient's mother and his younger sister.

Recently some reports (Rizzo *et al.* 1986; Aubourg and Diebler 1982) have demonstrated that dietary restriction of C26:0 with oleic acid sup-

Table 1. Very long chain fatty acids of sphingomyelin in erythrocyte memberanes

| | C 24 : 0 | C 25 : 0 | C 26 : 0 |
|---|---|---|---|
| Patient | 3.00 | 0.079 | 0.206 |
| Control | 2.45 | 0.060 | 0.100 |
| (n=18) | ±0.21 | ±0.012 | ±0.015 |

Values are expressed on the basis of C 22:0.
Control values are expressed as mean ± SD.

plementation lowers plasma VLCFA levels, but its clinical implication needs further refinement.

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## REFERENCES

Arsenio-Nunes ML, Goutieres F, Aicardi J: An ultrascopic study of skin and conjunctival biopsies in chronic neurological disorders of childhood. Ann Neurol. 1981, 9:163-173

Aubourg P, Diebler C: Adrenoleukodystrophy-Its diverse CT appearances and an evolutive or phenotypic variant. The leukodystrophy without adrenal insufficiency. Neuroradiol. 1982, 24:33-42

Aubourg P, Scotto J, Rocchiccioi F, Feldmann-Pautrat D, Robain O: Neonatal adrenoleukodystrophy. J. Neurol Neurosurg Psychiat. 1986, 49:77-86

Bewermeyer H, Bamborschke S, Ebhardt G, Hunermann B, Heiss WD: MR imaging in adrenoleukomyeloneuropathy. J Comput Assist Tomogr. 1985, 9:793-796

Chiro GD, Eiben RM, Manz HJ, Jacobs IB, Schellinger D: A new CT pattern in adrenoleukodystrophy. Radiology. 1980, 137:687-692

Greenberg S, Halverson D, Lane B: CT scanning and diagnosis of adrenoleukodystrophy. Neurology. 1977, 27:884-886

Griffin JW, Goren E, Schaumburg H, Engel WK, Loriaux L: Adrenomyeloneuropathy: A probable variant of adrenoleukodystrophy. I. Clinical and endocrinologic aspects. Neurology. 1977, 27:1107-1113

Huckman MS Wong PWK, Sullivan T, Zeller P, Geremia GK: Magnetic resonance imaging compared with computed tomography in adrenoleukodystrophy. AJDC. 1986, 140:1001-1003

Igarashi M, Schaumburg HH, Powers J, Kishimoto Y, Kolondy E, Suzuki K: Fatty acid abnormality in adrenoleukodystrophy. J Neurochem. 1976, 26:851-860

Inoue Y, Fukuda T, Takashima AS, Onoyama Y, Kusuda S, Matsuoka O, Murata R: Adrenoleukodystrophy: New CT findings. AJNR. 1983, 4:951-954

Kim YH, Kim SK, Yang SW, Moon HR, Chi JG: A case of adrenoleukodystrophy. Seoul J Med. 1988, 29:195-200

Kobayashi T, Katayama M, Suzuki S, Tomada H, Goto I, Kuroiwa Y: Adrenoleukodystrophy: detection of increased very long chain fatty acids by high-performance liquid chromatography. J Neurol. 1983, 230:209-215

Kumar AJ, Rosenbaum AE, Naidu S, Wener L, Citrin CM, Lindenberg R, Kim WS, Zinreich SJ, Molliver ME, Mayberg HS, Moser HW: Adrenoleukodystrophy: Correlating RI images with CT. Radiology. 1987, 165:497-504

Lazarow PB: The role of peroxisomes in mammalian cellular metabolism. J Inher Metab Dis 10 Suppl. 1987, 1:11-22

Moser HW, Moser AB, Frayer KK, Chen W, Shulman JD, O'Neill BP, Kishimoto Y: Adrenoleukosystrophy: Increased plasma content of saturated very long chaing fatty cids. Neurology. 1981, 1:1241-1249

Moser HW, Moser AB, Kawamura N, Barbara M, O'Neil BP, Fenselau C, Kishimoto Y: Adrenoleukodystrophy: Studies of the phenotype, genetics and biochemistry. Johns Hopkins Med J. 1980, 147:217-224

Moser HW, Moser AB, Powers, Nitowsky HW, Schaumburg HW, Norum RA, Migeon BR: The prenatal diagnosis of adrenoleukodystrophy: Demonstration of increased hexacosanoic acid levels in cultured amniocytes and fetal adrenl gland. Pediatr Res. 1982, 16:172-175

Moser HW, Moser AE, Trojak JE, Supplee SW: Indentification of femle carriers of adrenoleukodystrophy. J Pediatr. 1983, 103:54-59

Moser HW, Moser AE, Singh I, O'Neill BP: Adrenoleukodystrophy: Survey of 303 cases: Biochemistry, diagnosis and therapy. Ann Neurol. 16:628-641

Rizzo W, Watkins PA, Phillips MW, Cranin D, Campbell B, Avigan J: Adrenoleukodystrophy: Oleic acid lowers fibroblast saturated C22-26 fatty acids. Neurology. 1986, 36:357-361

Rizzo W, Watkins MW, Dammann AL, Leshner RT, Jennings SS, Avigan J, Proud UK: Adrenoleukodystrophy: Dietary oleic acid lowers hexacosanoate levels. Ann Neurol. 1987, 21:232-239

**Rizzo WB, Avigan J, Chemke J, Schulman JD**: Adrenoleukodystrophy: Very long-chain fatty acid metabolism in fibroblasts. Neurology. 1984, 34:163-169

**Schaumburg HH, Powers JM, Raine CS, Suzuki K, Richardson EP**: Adrenoleukodystrophy. A clinical and pathological study of 17 cases. Arch Neurol. 1975, 32:577-599

**Singh I, Moser AE, Moser HW, Kishimoto Y**: Adrenoleukodystrophy: Impaired oxidation of very long chain fatty acids in white blood cells, cultured skin fibroblasts and amniocytes. Pediatr Res. 1984, 18:286-290

**Watkins PA, Naidu S, Moser HW**: Adrenoleukodystrophy: Biochemicl procedures in diagnosis, prevention and treatment. J Inher Metab Dis 10 Suppl. 1987, 1:46-53

**Young IR, Randell CP, Kaplan PW, James A, Bydder GM, Steiner RE**: Nuclear magnetic resonance (NMR) imging in white mater disease of the brain using spin-echo sequences. J Comput Assist Tomogr. 1983, 7:290-294

=국문초록=

## Adrenoleukodystrophy 1례

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저자들은 정상적인 발육 및 성장을 보이다가 서서히 진행하는 행동장애, 지능저하, 시력 및 청력감퇴, 소뇌 및 추체로 징후 등의 임상양상을 나타내고 특징적인 신경방사선학적 소견을 보인 9세 환아에서 HPLC 검사상 증가된 VLCFA치를 나타내 ALD로 확진된 1례를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.