Case Report

Adult Adrenoleucodystrophy with Hypercortisolemia

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A 39-year-old male showed rapid progression of cerebral white matter involvement after 8 years' duration of adrenomyeloneuropathy. Increased ratio of C:26 to C:22 in the fatty acid composition of sphingomyelin in the blood and needle-like cytoplasmic inclusions in the biopsied peripheral nerve were indicative of adrenoleucodystrophy or adrenoleucomyeloneuropathy. Plasma ACTH levels were extremely elevated, but most of ACTH immunoactivity was eluted at the molecular weight of 55000. Plasma cortisol levels were initially within normal range and were elevated in the final stage. Possible mechanism of elevated ACTH in this disorder was briefly discussed.

Key Words: Adrenoleucodystrophy, ACTH, ALMN, Hypercortisolemia, Spastic paraplegia

Adrenoleucodystrophy (ALD) is a disease of children characterized by involvement of adrenal glands and the white matter of the brain, and the spinal cord and the peripheral nerves are also known to be involved^{1, 2)}. On the other hand, another disease with the same combination of adrenal insufficiency and neurological disorders has also been reported to occur mainly in adults affecting only the spinal cord and the peripheral nerves without any apparent lesions in the brain. This type has been called adrenomyeloneuropathy (AMN)³⁾. Since ALD and AMN were recognized in a single kindred⁴⁾, and also since the biochemical abnormalities in fatty acid composition were common in both disorders⁵⁻⁷⁾, they were considered to be two different expressions of a single disease, and an inclusive term adrenoleucomyeloneuropathy (ALMN) has been postulated⁸⁾. However, there still have been very few papers in which the clinical characteristics of both ALD and AMN were recognized in the same patient. In this paper, a case is described who presented with rapid progression of involvement of the frontal lobe white matter during the pro-

longed course of AMN. His endocrinological findings were also unique in that his ACTH was largely of big molecular weight and he finally showed hypercortisolemia.

REPORT OF A CASE

A 39-year-old male was admitted for evaluation of mental disturbance. The patient had been healthy until about 8 years prior to admission when he was gradually noticed to have clumsy gait. Since then, disturbance of gait had been progressively worse, and he was diagnosed as having spastic paraplegia. About 6 months prior to admission, he began to show abnormal behavior and some personality changes, and frequently made easy mistakes in his daily work as a clerk. He also became easy to get angry, and abnormal behavior increased in frequency. He also complained of cold sensation on the legs and feet, and numbness and tingling were gradually increased. Since his mental deterioration progressed, he was admitted to our hospital at the age of 39. He had no previous illness. Family history of neurological or endocrinological diseases was

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negative.

On admission, his height was 160.7 cm and weight 54.5 kg. His skin was pigmented. Excessive pigmentation was also seen in the buccal mucous membrane. Hair was thin, and the axillary hair was lost, though the pubic hair was preserved. Facial expression was poor. Blood pressure was 108/40 mmHg. Chest and abdomen were intact. Neurologically, consciousness was clear. Orientation was fairly well preserved. Severe disturbance of recent memory was present. Dyscalculia was severe. Judgement was poor. Intellectual function test of WAIS revealed verbal scores and performance scores being 54 and 60 respectively. Cranial nerves were intact except slight loss of visual acuity and positive jaw jerk. Muscle strength was decreased in the lower extremities, and especially dorsiflexion of the ankles was most severely weak. Deep tendon reflexes were bilaterally exaggerated. Babinski and Chaddock reflexes were bilaterally positive. Gait was spastic, and slight dystonic movement of the shoulders and the arms was noted while he was walking. Cerebellar signs were negative. There was a stocking-type sensory loss of all modalities below the level of the knee. Routine laboratory examinations on admission were essentially normal. X-ray films of the chest and skull were also normal. CSF protein was 51 mg/100 ml and cells were 22/3 cubic mm with 11 polymorphonuclear cells. EEG showed diffuse slow activities in the frontal areas with more dominant slowness on the right. Peripheral nerve conduction velocities were slightly slow, measuring 41 m/sec in the peroneal nerves. Endocrinologically, thyroid function tests were within normal range. Parathyroid was also normal. Serum cortisol was 7.8 microg/100 ml. Urinary excretions of 17-KS and 17-OHSC were 6.1 and 3.6 mg/24hrs respectively. ACTH administration test revealed normal response of plasma cortisol which elevated up to 26.2 microg/100 ml 60 minutes after the administration. Plasma ACTH was 1,000 pg/ml by direct assay and was 390 pg/ml by extraction method with QUSO. Dexamethasone suppression test with 8 mg oral administration revealed significant decrease of the plasma cortisol levels, but no significant effect on ACTH levels. When the patient's plasma was

applied on a Sephadex G 75 SF column (2.6 × 90 cm), most of ACTH immunoactivity was eluted in a single peak corresponding to the molecular weight of approximately 55,000. The details of the endocrinological study are to be described elsewhere.

Fatty acid composition of the sphingomyelin in the blood was studied and the ratio of C26 to C22 was 0.0217 (0.0044 ± 0.0003 in the control subjects).

Brain scintigram with ^{99m}Tc showed a positive uptake in the right frontal area (Fig. 1), and CT scan showed bilateral low attenuation in the frontal lobe white matter with atrophy of the frontal lobes and ventricular enlargement (Fig. 2). Contrast enhancement was evident in the right frontal white matter corresponding to the positive area demonstrated by ^{99m}Tc scintigraphy. The enhancement effect was maximal about 40 minutes after the intravenous injection of the contrast medium. Biopsy of the sural nerve revealed endoneurial fibrosis with moderate loss of myelinated fibers, and numerous lamellar bodies were observed chiefly in the Schwann cells (Fig. 3). The shape of these bodies was consistent with so-called needle-like trilaminar cytoplasmic inclusion bodies.

After the admission, his mental symptoms constantly progressed and personality changes were severe. Hallucination started to appear and verbal communication was completely lost. At that time, brain CT scan showed increased low density areas over the entire white matter bilaterally. One year after the admission, repeated

Fig. 1. ^{99m}Tc brain scintigram showing positive uptake in the right frontal area.

Fig. 2. Brain CT scan showing low attenuation in the bilateral frontal lobe white matter more dominantly on the right hemisphere. Contrast enhancement (right) was evident in the small area of the right frontal lobe.

Fig. 3. Needle-like trilaminar cytoplasmic inclusion bodies in the Schwann cells from the sural nerve biopsy.

Table. Values of adrenal cortical function tests of the patient.

	Normal range	Initial stage		Final stage	
		Basic level	After* admin.	Basic level	After* admin.
Plasma ACTH (pg/ml)	10–90	640	580	480	570
Plasma cortisol (μg/dl)	3.7–13.0	7.1	1.0	20.8	1.4
Urinary 17-OHCS (mg/day)	1.6– 6.7	4.1	1.2	11.6	2.0
Urinary 17-KS (mg/day)	2.0– 7.6	7.8	3.0	6.0	3.1

*The second day after administration of 8 mg of dexamethasone.

determinations of plasma cortisol level showed significant elevation. Administration of 2 mg dexamethasone failed to show adequate suppression, but 8 mg brought normal response of plasma cortisol level (Table).

He died of pneumonia about 16 months after the admission.

COMMENT

Clinical features, biochemical changes of plasma sphingomyelin fatty acid compositions⁹⁾, pathological findings of the Schwann cells²⁾, the brain CT scan and scintigram findings and elevated plasma ACTH levels are helpful for making the diagnosis of ALD, and the findings in the present case fully satisfied these criteria. Though ALMN has been proposed as an inclusive term of ALD and AMN, ALD has already been known to involve both the spinal cord and the peripheral nerve in addition to the white matter of the brain^{1,2)}. Therefore, ALMN is not necessarily needed as an inclusive term to cover ALD. Instead, ALD can include AMN as one of its variant forms, and the term ALMN is useful only in distinguishing those who show signs and symptoms of the brain involvement after AMN has already appeared. Namely, ALD consists of 3 subtypes; typical ALD, AMN and ALMN. Typical ALD occurs predominantly in children in the latter half of the first decade with mental and/or visual disturbance as an initial symptom. However, there have been a few adult cases with fairly typical ALD such as described by Weiss et al.¹⁰⁾ or seen in the *New England Journal of Medicine*¹¹⁾. On the other hand, AMN essentially occurs in adults, but there are also occasional cases whose onset of the disease was in childhood. One of such examples was reported by Gumbinass et al.¹²⁾ who presented a 10-year-old boy whose pathological changes were limited to the spinal cord without any loss of myelin in the brain, though the boy had some personality changes and seizures. ALMN is the most rare, and only a few cases have been seen in the literature. Case 4 in Griffin's paper showed a striking mental deterioration 14 years after the onset of spastic paraplegia³⁾, and neuropathologically involvement of the white matter was confirmed throughout the

cerebral hemispheres, brain stem and the spinal cord⁷⁾. A case reported by Yoshida et al.¹³⁾ was also able to be encountered in this subgroup. It is assumed that AMN has some basic abnormalities in the brain tissue regardless the absence of the clinical symptoms of the brain damage, because biochemical changes were observed in pathologically normal brain¹²⁾. Abnormal auditory brain stem responses were also reported in AMN¹⁴⁾ suggesting subclinical changes in the intracranial nervous system. However, it is also true that most cases with AMN showed no signs or symptoms of the brain lesions even many years after the onset of spastic paraplegia. Therefore, length of the duration of the disease itself is not the critical factor between AMN and ALMN.

ALD or ALMN presenting with the clinical pictures of spinocerebellar degeneration was first reported by Marsden et al.¹⁵⁾ and similar cases have been seen in the literature¹⁶⁾. Possibly this is the fourth subtype of ALD.

As for the adrenal functions, the present case initially showed normal plasma cortisol levels, urinary excretions of 17-KS and 17-OHCS, and also normal response of plasma cortisol levels to administration of ACTH. These results suggested that the adrenal function of the patient was normal. However, plasma ACTH levels were extremely elevated. Reviewing 60 cases with ALD and AMN in the literature¹⁻²⁰⁾, approximately 60% of them were described as having some clinical features of adrenal insufficiency, and also 60% of the cases examined endocrinologically had laboratory data indicating hypofunctions of adrenal cortex such as decreased plasma cortisol levels or urinary excretions of 17-KS or 17-OHCS. On the other hand, approximately 90% of the cases in whom ACTH administration test was performed showed poor or no response of plasma cortisol levels or urinary excretions of 17-KS or 17-OHCS to ACTH. As for the basic ACTH levels, 85% of the cases had abnormally high values though only recently reported cases were examined and the number of such cases was relatively small. Therefore, severity of adrenal dysfunctions in this disorder widely ranged, and elevated plasma ACTH levels and poor response of the adrenal cortex to ACTH administra-

tion were the most frequent features.

Plasma ACTH levels determined by the direct assay greatly differed from those by the extraction method in the present case. Similar discrepancy in this disorder was also reported by Ide et al.¹⁷⁾ Therefore, elevated ACTH values frequently recognized in ALD or AMN might be derived partly from natural ACTH but partly from other similarly immunoactive materials. Most of ACTH immunoactivity in our patient was eluted in a single peak corresponding to the molecular weight of approximately 55,000. ACTH precursors or precursor-like materials have been reported to be of larger molecules than natural ACTH, and to be present in normal extrapituitary tissues^{21, 22)}. It might be possible to consider that ACTH immunoactivity in our patient was largely due to such materials though whether they were of pituitary or extrapituitary origin was obscure.

It was difficult to explain for existence of hypercortisolemia in ALD. One of the possible explanations is that those ACTH-precursor-like materials in our patient was weakly bioactive. Longstanding high concentrations of such materials in the blood might have caused hypersecretion of cortisol in our patient. The fact that sufficient dose of dexamethasone showed significant suppression of plasma cortisol but failed to suppress ACTH levels might suggest that an abnormality was present above the level of the pituitary gland. Secretion of corticotropin releasing factor (CRF) might be abnormal as a result of lesions in the hypothalamus or higher central nervous system. Namely, two different pathogeneses might be considered to be present for the endocrinological disturbance in this patient; one is direct involvement of the adrenal cortex by the disease process of ALD itself resulting in adrenal insufficiency in various extent, and the other is neuroendocrinological abnormalities caused by the damage of the central nervous system due to ALD. Elevated plasma ACTH levels are possibly attributable to both factors. Further careful observations are necessary on the functions of the hypothalamus and the pituitary gland to clarify the mechanism of elevated ACTH and the role of CRF in this disorder.

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