Central Diabetes Insipidus and Hypothalamic Hypothyroidism Associated with Aceruloplasminemia

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Abstract

Aceruloplasminemia is a rare autosomal recessive disease first reported by Miyajima et al. (Neurology 37: 761-767, 1987); it is clinically characterized by diabetes mellitus, retinal degeneration and neurological abnormalities, such as cerebellar ataxia, extrapyramidal signs and dementia. Aceruloplasminemia is caused by mutations in the ceruloplasmin gene, which results in the absence of serum ceruloplasmin and iron overload in the brain, liver, pancreas and other organ tissues. However, little is known about endocrine diseases associated with aceruloplasminemia. We report herein a case of aceruloplasminemia accompanied by central diabetes insipidus and hypothalamic hypothyroidism.

Key words: aceruloplasminemia, central diabetes insipidus, hypothalamic hypothyroidism

(Inter Med 49: 1581-1585, 2010)
(DOI: 10.2169/internalmedicine.49.3508)

Introduction

Aceruloplasminemia is an autosomal recessive disorder of iron metabolism, first reported by Miyajima et al (1). This disease is clinically characterized by the triad of retinal degeneration, diabetes mellitus and neurological symptoms, including ataxia, involuntary movements and dementia (2).

Ceruloplasmin (CP) is the major copper-carrying protein containing more than 95% of the copper in plasma. CP plays a role in the mobilization and oxidation of iron from tissue stores with subsequent incorporation of ferric iron into transferrin (3). Although CP is mainly synthesized in the liver, the CP gene is widely expressed in many organs, including the central nervous system (4). CP deficiency induces iron accumulation in the liver, pancreas, central nervous system and other organs (2). Aceruloplasminemia is caused by mutations in the CP gene, which encodes CP (5). To date, more than 30 aceruloplasminemia-causing mutations have been identified (6, 7). More than half of the mutations in the CP gene are truncated types, leading to the formation of a premature stop codon, and those result in formation of a protein lacking copper-binding sites presumed to be critical for enzymatic function (6). Therefore, molecular analysis of the CP gene is crucial for the diagnosis of aceruloplasminemia. Diabetes mellitus often precedes neurological abnormalities in aceruloplasminemia. However, in the typical cases, aceruloplasminemia is not diagnosed until progressive neurological abnormalities are apparent (8-10). Furthermore, endocrine complications associated with aceruloplasminemia are rarely reported with one exception of primary hypothyroidism in Japan (11). We report herein a case of aceruloplasminemia accompanied by insulin-dependent diabetes mellitus, central diabetes insipidus and hypothalamic hypothyroidism without retinal degeneration and neurological abnormalities.

Case Report

In April 2009, a 44-year-old Japanese man was admitted to our hospital because of poor glycemic control. The health checkup in his company in 2007 revealed that he had diabetes mellitus, and he was treated with oral hypoglycemic agents (glibenclamide, pioglitazone and voglibose) by a local medical doctor. As his glycemic control had become...
progressively poorer, he was referred to our hospital. He had no other past medical history and no family history of diabetes mellitus. His body temperature was 35.8°C, blood pressure was 108/56 mmHg, and the heart rate was 66 beats/minute. His body mass index (BMI) was 18.2 kg/m². Laboratory tests showed that his fast plasma glucose level was 250 mg/dL and his HbA1C was 14.5% (reference range: 4.3-5.8%).

We diagnosed him as secondary diabetes mellitus induced by aceruloplasminemia (Fig. 1B). Laboratory findings showed that his serum CP was below the detection level (21-37 mg/dL), his serum iron concentration was 32 μg/dL (54-181), his transferrin saturation was 22% (45-60%), his serum ferritin concentration was 961 ng/mL (54-181), his transferrin saturation was 2 μg/dL (5-9), and his serum iron concentration was 0.50 ng/mL (<0.17); serum insulin-like growth factor 1 (IGF-1) level, 164 ng/mL (41-272); serum lutenizing hormone (LH) level, 0.97 mIU/mL (1.8-5.2); serum follicle stimulating hormone (FSH) level, 3.59 mIU/mL (2.9-8.2); serum testosterone level, 4.42 ng/mL (2.07-7.61); and serum prolactin level, 9.51 ng/mL (3.58-12.78). Although we at first suspected that abnormalities of thyroid function were due to nonthyroidal illness, these inappropriate levels continued after improvement of glycemic control (serum free T3: 1.91 pg/mL, serum free T4: 0.64 ng/dL, serum TSH: 3.03 mIU/mL). To investigate the existence of central hypothyroidism, a thyrotropin-releasing hormone (TRH) loading test was done. His serum TSH concentration increased from 1.31 μIU/mL at 0 min to 8.73 μIU/mL at 30 min, 9.43 μIU/ mL at 60 min, 9.01 μIU/mL at 90 min and 8.16 μIU/mL at 120 min (normal time of maximum: 30 min), and his serum T3 concentration changed from 0.88 ng/mL at 0 min to 1.02 ng/mL at 120 min (normal rate of increase: 30% or greater progression).
above basal level). These data indicated a delayed response of TSH and a blunted response of T₃, suggesting the existence of hypothalamic hypothyroidism. Thus, we treated him with 25 μg of levothyroxine sodium (T₄-Na), but he showed no improvement after therapy.

To determine the function of the hypothalamus, an insulin tolerance test (ITT) was performed. Insulin-induced hypoglycemia with intravenous injection of 0.1 IU/kg regular insulin increased his serum GH and plasma ACTH levels (data not shown).

After obtaining written informed consent, molecular analysis of the CP gene was performed at Hamamatsu University School of Medicine. Sequencing analyses of genomic DNA showed a 5-bp insertion at amino acid 446 in exon 7 of the CP gene (nt1286 TACAC ins), resulting in a frameshift mutation and premature stop codon.
Aceruloplasminemia is one of the iron overload diseases characterized by the absence of serum CP, low serum iron, and low serum copper (1). While the histopathologic features of the liver are comparable (12), aceruloplasminemia is distinguished from hemochromatosis by having low transferrin saturation (<45%) and an undetectable level of CP in cases of anemia and/or neurological symptoms (13). Another apparent difference from hemochromatosis is iron accumulation in the brain in aceruloplasminemia (2). Although hemochromatosis is one of the most common genetic disorders in Western countries (13), aceruloplasminemia has been reported mainly in Japan. The incidence of a homozygote with aceruloplasminemia in the Japanese population is estimated to be approximately 1 per 2,000,000 for non-consanguineous marriages (14).

Aceruloplasminemia is clinically characterized by diabetes mellitus, retinal degeneration and neurological abnormalities such as cerebellar ataxia, extrapyramidal signs and dementia (2). Muroi et al (9) suggested that aceruloplasminemia should be considered in patients with insulin-dependent diabetes mellitus who develop progressive neurological abnormalities. In addition, our findings suggested that CT and MRI are potential tools for differentiating aceruloplasminemia-induced diabetes from other types of insulin-dependent diabetes.

None of the endocrine diseases except primary hypothyroidism have been reported in aceruloplasminemia (11). Because iron accumulation in the brain is characteristic of aceruloplasminemia (2), it is natural that the synthesis or secretion of hypothalamic hormones could be impaired due to iron accumulation in the hypothalamus as in the present case. AVP is synthesized within the neurons of hypothalamus and released into the circulation from the nerve endings (15). Rapid secretion of AVP is mainly controlled by plasma osmolality (15, 16). This stimulus is sensed at the osmoreceptors or the input from the osmoreceptors to AVP-synthesizing neurons, usually controlling AVP release, were damaged by iron accumulation in the hypothalamus. On the other hand, it is reported that the TSH release response to TRH is delayed, exaggerated or prolonged (21), and that T3 release response to TRH does not increase (22) in patients with hypothalamic disorders, demonstrating the secretion of biologically inactive TSH (23). In the present case, TRH loading test resulted in a delayed response of TSH and a blunted response of T3, suggesting the existence of hypothalamic hypothyroidism.

The function of the other hypothalamic hormones, as seen from the results of ITT conducted to evaluate hypothalamic function, was not affected in the present case. Iron accumulation may accidentally be serious in the neurons synthesizing AVP and TRH, or tend to occur in those neurons. Moreover, while the distribution pattern of iron deposition is the same in the reported cases, the degree of iron deposition is varied (24). Thus, the clinical onset and manifestations could vary among the patients with aceruloplasminemia.

This is, to our knowledge, the first case report of aceruloplasminemia accompanied by endocrine complications, such as central diabetes insipidus and hypothalamic hypothyroidism. We must keep in mind that endocrine diseases may be the clinical manifestations in aceruloplasminemia with insulin-dependent diabetes mellitus but without neuro-

### Table 2. Hypertonic Saline Infusion Test (A) and AVP Test (B)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma sodium concentration (mmol/L)</td>
<td>143</td>
<td>147</td>
<td>146</td>
<td>149</td>
<td>149</td>
</tr>
<tr>
<td>Plasma osmolality (mOsm/kg)</td>
<td>296</td>
<td>313</td>
<td>317</td>
<td>318</td>
<td>321</td>
</tr>
<tr>
<td>Plasma AVP (pg/mL)</td>
<td>2.1</td>
<td>1.6</td>
<td>1.5</td>
<td>1.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

(B) AVP was given intramuscularly at 0 min

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>-30</th>
<th>-15</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma osmolality (mOsm/kg)</td>
<td>318</td>
<td>304</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary osmolality (mOsm/kg)</td>
<td>154</td>
<td>131</td>
<td>135</td>
<td>141</td>
<td>461</td>
<td>561</td>
<td>647</td>
<td>717</td>
<td>817</td>
</tr>
<tr>
<td>Urinary volume (mL)</td>
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<td>75</td>
<td>75</td>
<td>40</td>
<td>15</td>
<td>15</td>
<td>15</td>
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</tbody>
</table>
logical abnormalities. Additional cases are necessary for further investigation of the clinical manifestations in aceruloplasminemia.

References


