Blindness Due to Non-Ketotic Hyperglycinemia: Report of a 38-Year-Old, the Oldest Case to Date

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We report a 38-year-old woman with a mild form of hyperglycinemia complicated with optic nerve atrophy and convulsion. She was normal at birth and showed normal mental and physical development. After the age of 13, her visual acuity rapidly decreased. At the age of 33, she had numerous episodes of tonic seizures lasting for 1–2 minutes. She had optic atrophy, but no intellectual impairment. Glycine levels of the plasma, urine and cerebrospinal fluid were markedly increased, but the CSF/serum glycine ratio was slightly higher than the normal range. Although there is one case of retinal impairment of hyperglycinemia in the literature, this is the first report of blindness with hyperglycinemia in a 38-year-old woman.

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Key words: optic atrophy, CSF/serum glycine ratio

Introduction

Hyperglycinemia is classified into ketotic and non-ketotic types. The former is hyperglycinemia secondary to abnormal inorganic acid metabolism, while the latter is primary hyperglycinemia. In general, it is rare for patients with non-ketotic hyperglycinemia (NKH) to survive to middle age. As far as we are aware, no patients with NKH have been reported to survive longer than 34 years (1). We report a 38-year-old woman with hyperglycinemia, who had complications with optic nerve atrophy and convolution.

Case Report

A 38-year-old woman was admitted to our hospital because of disturbed consciousness. Her brother was mentally retarded. Medical history of her other family members was not fully clarified. She was born without any complication, and her physical and mental development was normal. Her record at the elementary school was average, and she was slightly poor at athletics. Since her visual acuity rapidly decreased after the age of 13, she was transferred to a school for the blind. After the age of 25, she worked as a practitioner of acupuncture and moxibustion. When she was 33, she had an episode of cramps of the eye lids and cheeks, during which her consciousness was disturbed. A few months later, she had some episodes of tonic seizures lasting for 1–2 minutes. She would severely twitch and begin to cry while drinking water or driving a car. On February 27, 1990, she cried loudly and lost consciousness. She was transferred to our hospital.

On admission, she showed no intellectual impairment. There was bilateral optic nerve atrophy without retinal pigmentary degeneration. She was blind. The muscle tone and strength were normal. The deep tendon reflexes were bilaterally hyperactive, but the Babinski sign was negative. The sensation was normal about all modalities. No apparent cerebellar signs or symptoms were observed.

Laboratory tests yielded the following results; complete blood cell counts (CBC) were normal, CK (1,332 IU/l, normal range: 10–85), GOT (27 IU/l), LDH (231 IU/l), aldolase (5.2 IU/l), T3 (65 ng/dl), T4 (4.5 µg/dl), and other endocrine function tests were normal. The high CK level was probably due to convulsion. In cerebrospinal fluid (CSF), the protein level was normal (20 mg/dl), IgG level was increased (9.1 mg/dl), and oligoclonal IgG band was negative.

Amino acid analyses in the blood, urine and CSF revealed increased glycine levels (573.4 nmol/ml, 18,460.3 µmol/day, and 27.3 nmol/ml, respectively). The CSF/serum glycine ratio was 0.032 (Table 1). Other amino acids were within normal limits. Computed tomography (CT) and magnetic resonance image (MRI) of the brain showed no abnormality. Electroencephalography (EEG) revealed slightly poor continuity of alpha waves. Hyperventilation induced generalized intermittent high amplitude theta bursts, but no apparent paroxysmal waves. Somatosensory evoked potentials (SEPs) revealed a delay of N_{13-20} in the latency and absence of P_{25} and peaks of...
Table 1. Glycine Levels in Serum, Urine and CSF

<table>
<thead>
<tr>
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<th>Normal range</th>
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<tbody>
<tr>
<td>Serum</td>
<td>852.6 nmol/ml (180–370)</td>
</tr>
<tr>
<td>Urine</td>
<td>18,460.3 μmol/day (600–4,000)</td>
</tr>
<tr>
<td>CSF</td>
<td>27.2 nmol/ml (2–20)</td>
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<tr>
<td>CSF/serum</td>
<td>0.032 (&lt;0.03)</td>
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Discussion

Since the report by Childs and Nyhan (2) in 1961, nearly 100 patients including 20 Japanese patients with hyperglycinemia characterized by markedly increased levels of glycine in the blood and urine have been reported.

Carson (3) reviewed the clinical symptoms of 70 patients with hyperglycinemia, and found that 49% showed lethargy, decreased muscle tone, respiratory failure, and myoclonus or generalized convulsion within 24 hours after birth. Among patients with respiratory failure, 65% died in a mean time of 7 days after birth. Patients who had other symptoms died at a mean age of 5. Patients who had survived to adult ages were very rare, and the oldest patient ever reported in the literature is a 34-year-old (1). Therefore, to our knowledge, the present patient may be the oldest.

Optic nerve atrophy is rare in this condition. We suggest that there are two pathomechanisms of the optic atrophy caused by hyperglycinemia. Only one patient who developed optic atrophy at the age of 4 years has ever been reported (4). Hayasaka et al (5) reported another patient whose retinography was slightly abnormal, though optic nerve atrophy was absent. These findings suggest that the secondary optic damage was caused by glycine’s toxicity effecting the retina. The other pathomechanism is suggested that the optic atrophy is due to direct effects to the optic nerve because glycine is considered to play a role in the synthesis of myelin in the central nervous system, and its abnormality can cause vacuolation and cavernous changes of the myelin (6). Similar changes may be produced in the optic nerves.

In our patient, multiple sclerosis was excluded on the basis of clinical and laboratory findings, also excluded was Leber’s disease, based on the lack of family history. There was no abnormal inorganic acid metabolism suggestive of secondary hyperglycinemia, and finally a diagnosis of NKH was made.

In NKH, a high ratio of CSF/serum glycine has been reported (7) and there are three forms as distinguished by the clinical features; infantile, late infantile, and late-onset form. The infantile form is the most common, with a clinical course which is acutely progressive after birth and then death occurs in less than 2–3 weeks due to respiratory failure. The late infantile form has slow psychomotor development. Finally, in the late-onset form as in the present case, the clinical symptoms are apparent at adolescence. Flannery et al (1) reported that the ratio is lower in late-onset mild form NKH than in infantile or late infantile severe form NKH. Even when the serum glycine is a very high value, the CSF/serum ratio of glycine is low in the mild form of NKH. Since the ratio of the present case was higher than the normal range, it was possible that the glycine level in the brain of this patient was high, and it produced a very mild form of NKH.

Hyperglycinemia is caused by deficiency or a decrease in glycine cleavage proteins (P-protein, H-protein, T-protein and L-protein) in mitochondria of the liver and brain (7). Singer et al (8) reported that a 22-year-old survivor showed normal H-protein and T-protein despite markedly decreased P-protein in the liver. Therefore, partial deficiency of these proteins may allow longer survival. There may be a mild or partial deficiency of these proteins in the present patient although it has not been confirmed by liver biopsy.

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References