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Clinical Observations

A New Cholesterol Biosynthesis and Absorption Disorder Associated With Epilepsy, Hypogonadism, and Cerebro-Cerebello-Bulbar Degeneration

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ABSTRACT

BACKGROUND: Cholesterol is one of the main components of human cell membranes and constitutes an essential substance in the central nervous system, endocrine system, and its hormones, including sex hormones. **PATIENT:** A 19-year-old male patient presented with failure to thrive, psychomotor deterioration, intractable epilepsy, hypogonadism, and cerebro-cerebello-bulbar degeneration. His serum level of cholesterol was low, ranging from 78.7 to 116.5 mg/dL. **RESULTS:** The serum concentrations of intermediates in the cholesterol biosynthesis pathway, such as 7-dehydrocholesterol, 8-dehydrocholesterol, desmosterol, lathosterol, and dihydrolanosterol, were not increased. In addition, the levels of the urinary cholesterol biosynthesis marker mevalonic acid, the serum cholesterol absorption markers, campesterol and sitosterol, and the serum cholesterol catabolism marker, 7α-hydroxycholesterol, were all low. **CONCLUSIONS:** A serum biomarker analysis indicated that the patient's basic abnormality differed from that of Smith-Lemli-Opitz syndrome and other known disorders of cholesterol metabolism. Therefore, this individual may have a new metabolic disorder with hypocholesterolemia because of decreased biosynthesis and absorption of cholesterol.

Keywords: hypocholesterolemia (Oita), cholesterol metabolism, intractable epilepsy, hypogonadism, cerebro-cerebellar-bulbar degeneration, dysmyelination

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Introduction

Cholesterol is one of the main components of human cell membranes and constitutes an essential substance in the central nervous system, endocrine system, and its hormones, including sex hormones.[1,2] Hypocholesterolemia is rare and a characteristic finding of several disorders, such as central nervous system ontogenesis disorder, hypogonadism, and psychomotor deterioration.[3]

We describe a patient with a distinctly different from previously reported cholesterol metabolic disorders.

Case report

A male patient was the first child of nonconsanguineous healthy Japanese parents. The pregnancy was uneventful. At birth, his weight, height, and head circumference were 3210 g, 50.6 cm, and 34.4 cm, respectively. His developmental milestones had been delayed; standing alone, meaningful speech, and two-word sentences were acquired at an age of 1 year and 7 months, 1 year and 6 months, and 8 years, respectively.

Thereafter, distinct deterioration was noticed, including the development of a low and slow voice, wide-based gait, and ataxia. At age 8 years, he presented with a rounded face, small head with narrow frontal area, open mouth, thickened antihelix, bilateral blepharoptosis, astigmatism, hypermetropia, and right exotropia (Fig. 1). He was able to eat regular meals slowly. He also developed myoclonus of the upper limbs, head nodding, and versive seizures with secondary generalized

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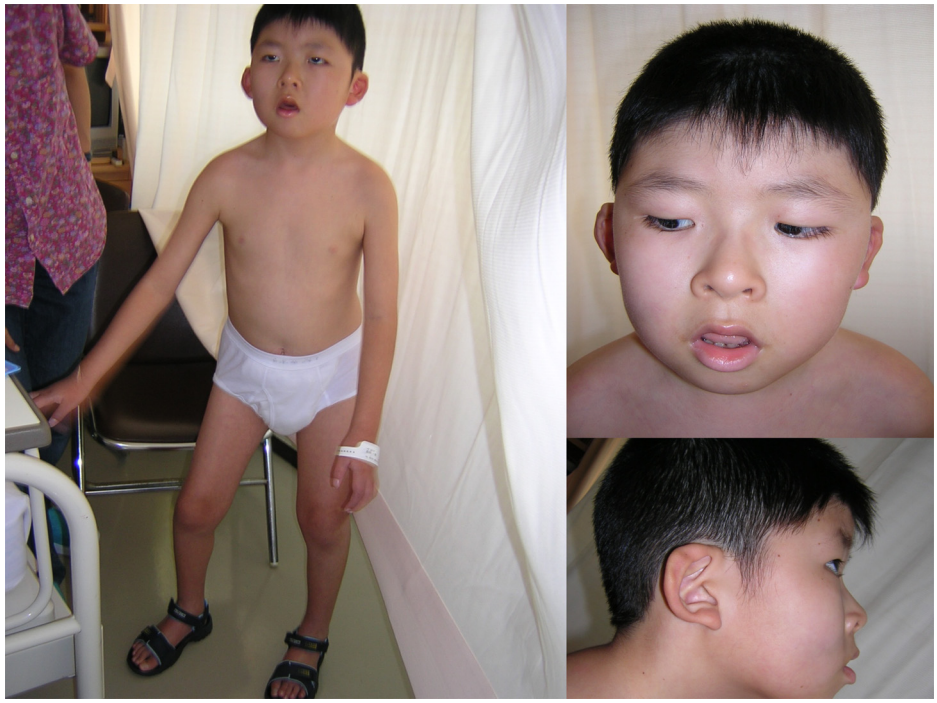

FIGURE 1.
Physical findings at an age of 10 years. Physical findings in the present patient with hypocholesterolemia, intractable epilepsy, hypogonadism, and cerebro-cerebello-bulbar degeneration. Distinct deterioration was noticed, including the development of a low and slow voice, wide-based gait, and ataxia. The patient presented with a rounded face, open mouth, thickened antihelix, bilateral blepharoptosis, astigmatism, hypermetropia, and right exotropia (with informed consent for academic use only). (Color version of figure is available in the online edition.)

tonic seizures, that were resistant to various antiepileptic drugs, including valproic acid, carbamazepine, ethosuximide, zonisamide, and clobazam. At an age of 14 years, he had become unable to speech or walk.

At 19 years of age, the patient's physical findings presented with failure to thrive (weight, −3.6 S.D. for his age-matched control), small head (−1.8 S.D.), and hypoplastic external genitalia without pubic hair. He could not produce speech or sit alone. He sometimes aspirated chopped foods. His hypotonia and generalized muscle atrophy had become exacerbated with an intelligence quotient <20. His deep tendon reflex revealed flaccid pendulation. Generalized tonic seizures with vocalization were noticed one to two times per day. In addition, limb myoclonus was frequently observed, although no cataracts or steatorrhea were noted.

Routine blood examinations were essentially normal, including blood cell counts and parameters of serum biochemistry, serum levels of transaminases and creatine kinase at 32 IU/L. The serum cholesterol level, however, has ranged from 78.7 to 116.5 mg/dL during the previous 5 years. A lipoprotein fraction analysis revealed a high-density lipoprotein level of 43% (22-50), a low-density lipoprotein level of 42% (44-69), and a very-low-density lipoprotein level of 11% (5-20). The serum level of testosterone was low at 183 ng/dL (250-1100), whereas both luteinizing hormone and follicle-stimulating hormone were within the normal ranges at 1.0 mIU/mL (1.0-7.1) and 6.2 mIU/mL (2.0-8.3), respectively. Other endocrinological findings were all within the normal ranges, including the levels of cortisol at 15.6 μg/dL (6.4-21.0), adrenocorticotropic hormone at 27.9 pg/mL (7.4-55.7), free triiodothyronine at 2.46 pg/mL (1.71-3.71), free thyroxine at 1.13 ng/dL (0.70-1.48), and thyroid-stimulating hormone at 2.918 μIU/mL (0.35-4.94). The patient chromosome was 46, XY, and there were no abnormalities on a urine amino acid analysis or cerebrospinal fluid examination, including the levels of protein, lactate, and pyruvate.

An interictal electroencephalography demonstrated multifocal spikes on the right occipital, right anterior-temporal, bilateral front polar, and left posterior-temporal areas, independently. In addition, an ictal electroencephalography revealed a left hemisphere–dominant recruiting rhythm with left parietal–posterior-temporal spikes followed by secondary generalization.

Head magnetic resonance imaging performed at the age of 11 and 18 years disclosed hypoplasia of the corpus callosum and demyelination of the bilateral peri-posterior horns of the lateral ventricles. Compared with the findings observed at the age of 11 years, progressive cerebro-cerebello-brainstem atrophy was obvious at the age of 18 years (Fig. 2). The results of an electromyography and the patient's motor and sensory nerve conduction velocities were normal, and a muscle biopsy did not reveal any myogenic or neurogenic abnormalities.

A serum sterol analysis revealed that the levels of 7-dehydrocholesterol and other intermediates in the cholesterol biosynthesis pathway, such as desmosterol, lathosterol, and dihydrolanosterol, were not increased.[1] In addition, the levels of the cholesterol biosynthesis marker urinary mevalonic acid and the serum cholesterol absorption markers, campesterol and sitosterol, were low.[4] Cholesterol catabolism (bile acid synthesis) was evaluated by measuring the 7α-hydroxycholesterol concentration, and the levels of feedback regulators of cholesterol biosynthesis and absorption, such as 24S-hydroxycholesterol and 27-hydroxycholesterol,[5] were also determined (Table). However, neither increased cholesterol catabolism nor elevated concentrations of the feedback regulators were observed.

Discussion

Our patient presented with failure to thrive, psychomotor deterioration, intractable epilepsy, hypogonadism, and cerebro-cerebello-bulbar degeneration associated with hypocholesterolemia. Cholesterol is a major component of myelin and a contributor to signal transduction in the development and maintenance of the central