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Case report

Congenital disorder of glycosylation type Ic: Report of a Japanese case

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Abstract

Congenital disorders of glycosylation (CDG) are inherited metabolic diseases affecting N-linked glycosylation pathways with variable clinical presentations characterized by psychomotor retardation, seizures, ataxia and hypotonia. CDG-Ic is caused by mutation in the ALG6 gene encoding alpha-1,3-glucosyltransferase. We present a 9-year-old girl diagnosed as having CDG-Ic. She developed severe psychomotor retardation, epileptic seizures, muscle hypotonia, strabismus and some dysmorphic features without inverted nipples or fat pads. She showed a fluctuating serum transaminase level with or without some infection, and a characteristically low level of antithrombin III. MR imaging of the brain at age 2 years demonstrated the lower limit of normal myelination, mild atrophy of the cerebrum, and mild hypoplasia of the brainstem and cerebellum. The patient exhibited a CDG type I pattern of serum transferrin on isoelectric focusing and mass spectrometric profiling. Sequence analysis of the ALG6 gene showed two heterozygous mutations, c.998C>T (A333V) and c.1061C>T (P354L). The patient was diagnosed as having CDG-Ic with a novel mutation, making her the first Japanese case. It was suggested that the severe psychomotor retardation in the patient was due to the existence of multiple mutant ALG6 alleles.

Keywords: Congenital disorder of glycosylation; CDG-Ic; ALG6; Glucosyltransferase; Transferrin; Psychomotor retardation; Antithrombin III

1. Introduction

Congenital disorders of glycosylation (CDG), previously called the carbohydrate-deficient glycoprotein syndrome, are inherited autosomal recessive disorders caused by defects in the pathways of N- and O-linked glycosylation [1]. The CDG type I group encompasses defects that affect the biosynthesis of the lipid-linked oligosaccharide (LLO) precursor for N-linked glycosylation, while type II defects disturb processing of the oligosaccharide chains already transferred to a protein. Over the last decade, 500–1000 CDG patients have been diagnosed with a disorder of dolichol-linked oligosaccharide assembly. Clinically, the patients suffer from psychomotor retardation, dysmorphic features, coagulation abnormalities and dysfunction of many organs. Furthermore, the spectrum of symptoms and degree of severity may be highly variable even within the same group [2]. The defective glycosylation is usually recognized on isoelectric focusing (IEF) of serum glycoproteins such as transferrin. Normal serum transferrin contains two diasialo-biantennary N-glycans, and then mainly composed of tetrasialotransferrin. In CDG type I, a subpopulation of transferrin carries either only one N-glycan or none. In type II, truncation of one branch

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of the biantennary N-glycans of transferrin occurs. CDG type I is characterized by an increase of di- and asialotransferrin and a decrease of tetrasialotransferrin, where as type II pattern shows additional tri- and monosialotransferrin involvement. CDG-Ia, caused by a deficiency of phosphomannomutase (PMM) activity, is found in 80% of CDG type I patients. It was described in 2003 that at least 10 CDG-Ia patients had been identified in Japan.

CDG-Ic is caused by defects in the ALG6 gene encoding Dol-P-Glc:Man9GlcNAc2-P-P-Dol alpha-1,3-glucosyltransferase [3]. The clinical manifestations of CDG-Ic are reported to be milder than those of CDG-Ia. To date more than 30 patients worldwide have been diagnosed as having CDG-Ic. There have only been a small number of reports on CDG-Ic. We describe a case of CDG-Ic, the first reported Japanese case, and discuss the clinical features and genotypes.

2. Case report

A Japanese girl aged 9 years was referred for evaluation of psychomotor retardation and hypotonia. She was born at 40 weeks gestation after a normal pregnancy and delivery with a birth weight of 2752 g. She was the second child of healthy nonconsanguinous parents. There was no family history of neurological disorders. She exhibited premature ventricular contraction without any abnormality on cardiac echography in early infancy. At 6 months of age, she developed complex partial epileptic seizures, and thus was treated with some antiepileptic drugs. On physical examination, the patient showed severe developmental delay, being unable to sit alone, nonverbal and completely dependent on the family for care. She had external strabismus, a low nasal bridge, a high-arched palate, wide set nipples, tapered fingers, and small feet (Fig. 1). She had no inverted nipples or fat pads, or an abnormal distribution of subcutaneous fat tissue. She exhibited muscle hypotonia and decreased deep tendon reflexes. She showed mild scoliosis with age. Retinal degeneration was not observed. Hematological examination revealed normal blood cell counts, electrolytes and renal function. The serum transaminase levels were fluctuated between normal and nearly double the normal with or without infection. The serum lactate, pyruvate, glucose and ammonia levels were normal. Coagulation tests consistently showed a prothrombin time of 12.7–17.8 s, an active partial thromboplastin time of 40.3–82.6 s, and an antithrombin III level of 13–49%. The protein S and protein C activities were 31% and 42%, respectively. The clotting factor XI level was not known. Serum amino acid and

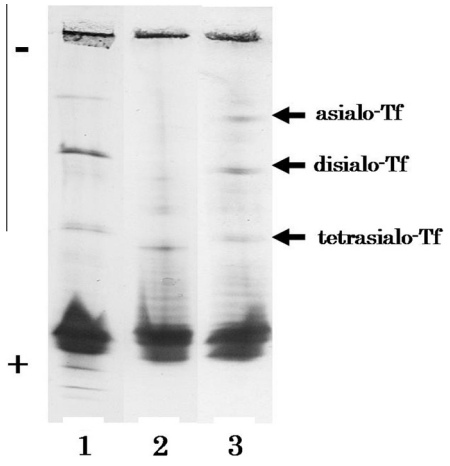

Fig. 2. Isoelectric focusing of serum transferrin from the patient (lane 1), a normal control (lane 2), and a CDG type I patient (lane 3). The patient showed a CDG type I pattern with increased frequencies of di- and asialotransferrin.

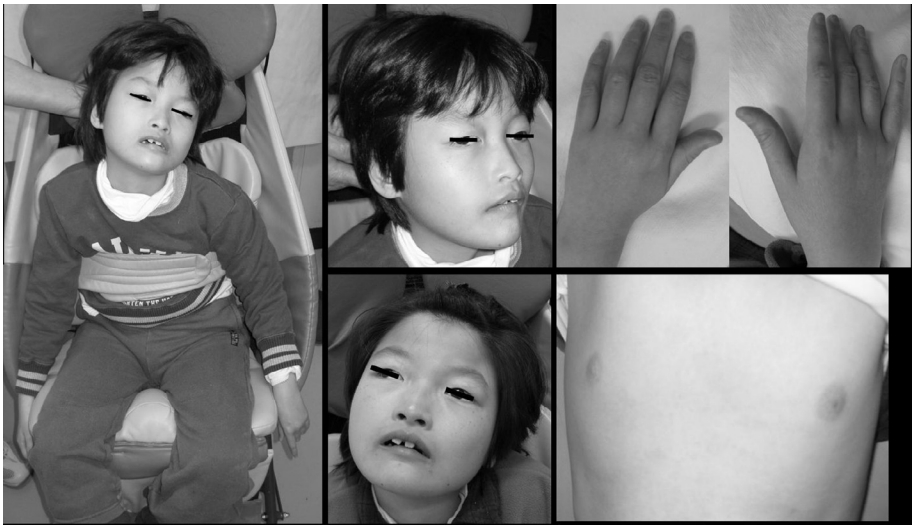

Fig. 1. The patient showed external strabismus, a low nasal bridge, tapered fingers and wide set nipples.