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ALG3-CDG (CDG-Id): Clinical, biochemical and molecular findings in two siblings

Suzi Riess [a], Dinah Susan Reddihough [a,b], Katherine Brooke Howell [c], Charuta Dagia [d], Jaak Jaeken [e], Gert Matthijs [f], Joy Yaplito-Lee [g,*]

[a] Developmental Medicine, Royal Children's Hospital, Melbourne, Australia
[b] Department of Paediatrics, University of Melbourne, Australia
[c] Department of Neurology, Royal Children's Hospital, Melbourne, Australia
[d] Medical Imaging Department, Royal Children's Hospital, Melbourne, Australia
[e] Center for Metabolic Diseases, University Hospital Gasthuisberg, Leuven, Belgium
[f] Center for Human Genetics, University of Leuven, Leuven, Belgium
[g] Metabolic Genetics, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia

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ABSTRACT

Congenital disorders of glycosylation (CDG) represent an expanding family of metabolic disorders with a wide range of biochemical, molecular and clinical phenotypes. ALG3-CDG (CDG-Id), due to a defect in endoplasmic reticulum (ER) mannosyltransferase VI, is one of the less common types of CDG-I.

We describe two Vietnamese siblings with confirmed ALG3-CDG (CDG-Id) by molecular testing. As far as we are aware, they are the oldest reported patients in the literature at 15 and 21 years. They share similar clinical features with previously reported patients including facial dysmorphism, severe psychomotor retardation, microcephaly, seizures, and gastrointestinal symptoms. Furthermore, our sibling pair highlights the intrafamilial variability, the natural clinical course of ALG3-CDG (CDG-Id) and the benefit of reassessing patients with undiagnosed and complex syndromes, particularly when they present with neurological deterioration.

1. Introduction

Congenital disorders of glycosylation (CDG) are a rapidly growing group of genetic defects in protein N-glycosylation, O-glycosylation, combined N- and O-glycosylation, and lipid glycosylation. Most CDG are protein hypoglycosylation diseases and most of these are due to defects in the N-glycosylation pathway. During the past 30 years since the first clinical description of CDG in 1980, more than 60 members of this pleiotropic disease family have been identified [1].

CDG are mostly multisystem disorders with a broad clinical spectrum, and usually a significant neurological component. Screening for congenital disorders of protein N-glycosylation is generally made by serum transferrin isoelectrofocusing (IEF), but other screening techniques are used as well such as capillary zone electrophoresis and high performance liquid chromatography (HPLC).

PMM2-CDG (CDG-Ia) is by far the most common CDG-I [2]. The other CDG-I subtypes are much less common. There are only seven patients with ALG3-CDG (CDG-Id) described in the literature. We report two siblings, and compare their clinical and molecular findings with the previously reported patients.

2. Patients

2.1. Patient 1

AD was born at 39 weeks gestation by assisted delivery due to breech presentation. Pregnancy history was unremarkable. She was the fourth child of non-consanguineous Vietnamese parents. At delivery, she had a cord coiled around her neck and meconium liqueur. Her Apgar scores were 5 and 8 at 1 and 5 min respectively, birth weight was 2920 g, birth length 47 cm and head circumference 33 cm, all between the 10th and 25th centiles. She was slow to feed, was hypotonic and showed facial dysmorphism including hypertelorism, a flat nasal bridge and large ears as shown at an older age (Fig. 1).

At 3 months, she presented with focal seizures. Her developmental milestones were appropriate for her age at this stage. AD's epilepsy later evolved into a symptomatic, generalized epilepsy with tonic and myoclonic seizures, the latter often triggered by startle.

EEG at four months of age captured a focal seizure arising from the right hemisphere, clinically associated with behavioural arrest and eye deviation to the right. Video-EEG monitoring at two years showed an absence of normal dominant rhythms and a slow background for

* Corresponding author at: Metabolic Genetics, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne, ViC 3052, Australia. Fax: +61 3 83416390.
E-mail address: joy.yaplito-lee@vcgs.org.au (J. Yaplito-Lee).

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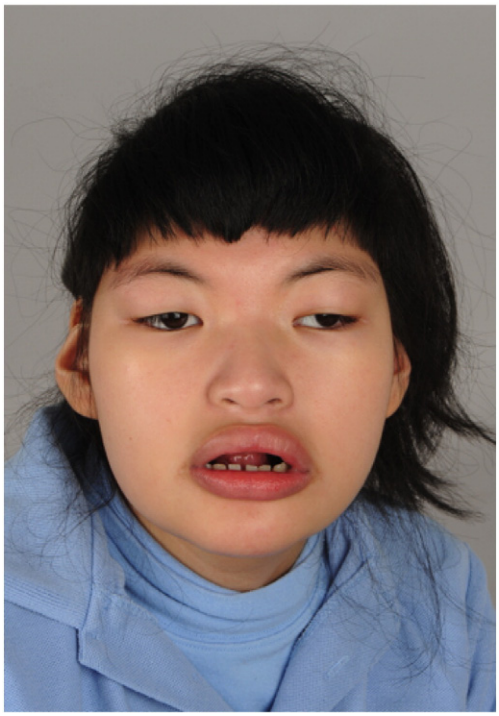

Fig. 1. Facial features of patient 1.

age. Prominent high amplitude rhythmic slowing was seen frequently over bilateral frontal regions. Focal interictal epileptiform discharges were present in wake and sleep, particularly over the left temporal, right temporal and right frontal regions. Three tonic seizures were recorded, associated with generalized ictal rhythms.

Over the years, AD made little developmental progress. Severe psychomotor retardation was apparent. She also had deceleration of head growth by 4 months of age. Seizures were refractory to anticonvulsant medication and occurred multiple times per day at their peak. EEG at age 12 years showed similar patterns to the earlier video-EEG, as well as bilaterally synchronous spike-wave activity and electrodecrements. Seizure control improved following the introduction of sodium valproate, in combination with lamotrigine, at age 12 years.

At 13 years of age, she was admitted with a six-week history of excessive sleeping, up to 14 to 16 h per day. Even during periods of wakefulness, she remained relatively drowsy. Accompanying this, she had minimal oral intake and lost seven kilograms in weight. She missed most of her usual medications and consequently had more frequent seizures, though they remained unchanged in form. There was a noticeable regression in overall functioning, particularly evident in her motor abilities. Where she had previously been able to walk with assistance, AD was now wheelchair bound and was unsteady when stood and with transfers. Deterioration was presumed secondary to evolution of her underlying condition, which remained undiagnosed at that time. Subsequent reduced feeding capacity had lead to poor nutrition and dehydration, somnolence and noncompliance with anticonvulsant therapy. This clinical decline prompted further investigations. Electrocardiogram and echocardiography were normal.

MRI scan performed at 13 years age demonstrated volume loss involving the cerebrum as well as the cerebellum, with parenchymal thinning, generalised ex-vacuo ventricular dilatation, increase in prominence of sulci and overlying extra-axial CSF spaces when compared to an earlier normal MRI scan performed at 7 months age (Figs. 2a and b).

Metabolic investigations were normal except for serum transferrin isoforms that showed a type 1 pattern [disialotransferrin level was 20% ($N < 3$) and tetrasialotransferrin 66% ($N = 71–84$)]. Genetic testing showed two mutations: c.206T > C (p.169 T) and c.626T > C (p.M209T) in the ALG3 gene confirming ALG3-CDG (CDG Id).

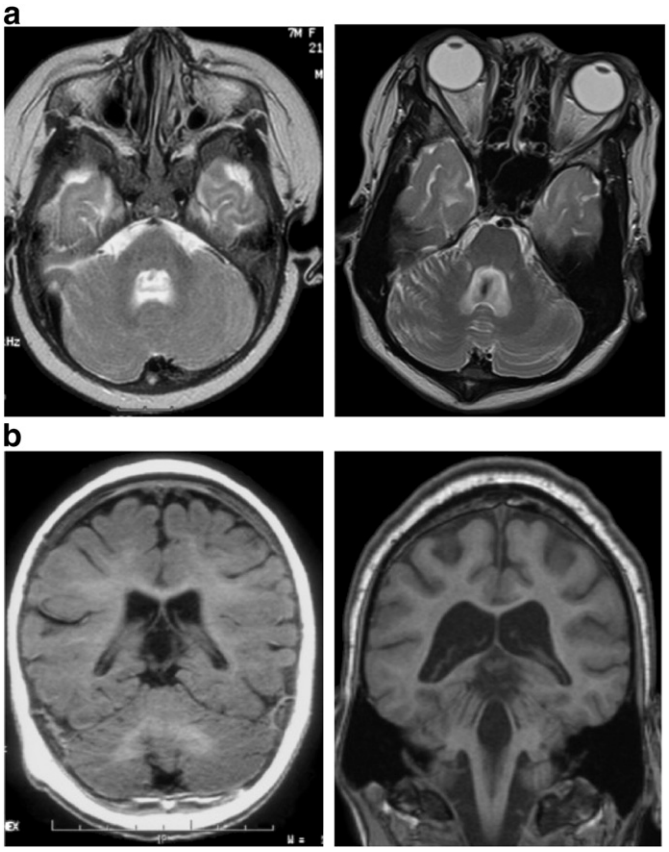

Fig. 2. a: Axial T2 weighted MRI images of patient 1(AD), from scans performed at 7 months and 13 years respectively, demonstrate interval volume loss involving the cerebellar hemispheres and vermis with prominent folia and ex-vacuo dilatation of the fourth ventricle. b: Coronal T1 weighted MRI images of patient 1(AD), from serial scans performed at 7 months and 13 years. Compared to the normal initial MRI scan, on the subsequent study there is volume loss involving the cerebral hemispheres with reduced parenchymal mantle, prominent sulci and overlying extra-axial CSF spaces, as well as ex-vacuo dilatation of the lateral ventricles.

At 15 years of age, AD is receiving most of her nutrition via gastrostomy tube. She continues to have 2–3 seizures monthly despite her anticonvulsants. She has developed small breast buds and pubic hair but is yet to go through menarche. AD is fully dependent on her parents for her daily activities. She is wheelchair bound. She has no expressive language skills. She is able to smile, reach out and put objects into her mouth. She is able to respond to loud noise and name calling. On ophthalmologic assessment, she was found to have a cortical visual impairment with divergent strabismus, myopia and mild optic atrophy. She has normal retina, no cataracts and no clear nystagmus.

2.2. Patient 2

JD was born at term by normal delivery. Pregnancy history was unremarkable. His birth weight was 2760 g. JD also had initial feeding difficulties. At 6 months of age, he had delayed development. Deceleration in head growth was noted at around 10 months of age. He presented to medical attention in his first year of life due to poor feeding and developmental delay. At 12 months of age, he developed intractable seizures. At 17 months, his psychomotor level was delayed. At that time, no cause for his presentation was found. Chromosomal analysis and a metabolic screen were normal.

Brain MRI at 6 years of age showed generalized cerebral volume loss with prominence of sulci, overlying extra-axial spaces and increase in lateral ventricular sizes when compared to earlier CT scans performed at 9 and 20 months of age.