Eur J Pediatr (2003) 162: 710–713
DOI 10.1007/s00431-003-1278-8

ORIGINAL PAPER

**Luitgard M. Neumann · Arpad von Moers
Jürgen Kunze · Oliver Blankenstein
Thorsten Marquardt**

Congenital disorder of glycosylation type 1a in a macrosomic 16-month-old boy with an atypical phenotype and homozygosity of the N216I mutation

Received: 13 March 2003 / Revised: 18 June 2003 / Accepted: 20 June 2003 / Published online: 2 August 2003

Abstract We report on a 16-month-old boy with congenital disorder of glycosylation type 1a (CDG-1a; OMIM 212065) showing an atypical phenotype. Whereas failure to thrive is known to be a prominent feature in this condition, our patient developed postnatal macrosomia with increase of weight, length and occipitofrontal circumference (OFC) above the 95th percentile within his 1st year of life. Thereafter, weight and length were close to the 90th and OFC at the 50th percentiles. In contrast to other CDG-1a patients, the child did not have abnormal fat pads or inverted nipples; but unusual eyebrows were present. CDG-1a was confirmed by isoelectric focusing of serum transferrin and measurement of phosphomannomutase activity in leucocytes and cultured fibroblasts (residual activity < 5% of controls). Mutation analysis of the phosphomannomutase 2 gene (*PMM2*) revealed homozygosity for a 647A > T (N216I) mutation in our patient and heterozygosity in his consanguineous parents. *Conclusion*: This is the first report of macrosomia and of homozygosity for the 647A > T (N216I) mutation in a patient with congenital disorder of glycosylation type 1a which may allow further phenotype/genotype comparisons.

Keywords Carbohydrate deficient glycoprotein syndrome · Cerebellar hypoplasia · Congenital disorders of glycosylation · Macrosomia · Neuropathy

Abbreviations *BMI* body mass index · *CDG* congenital disorder of glycosylation · *OFC* occipitofrontal circumference · *PMM2* phosphomannomutase 2 gene

Introduction

Congenital disorders of glycosylation (CDG) are a group of metabolic disorders with multisystemic involvement caused by defects in the synthesis and processing of the asparagine-linked oligosaccharides of glycoproteins [9]. The most common form is CDG-1a caused by a defective phosphomannomutase 2, an enzyme that converts mannose-6-phosphate to mannose-1-phosphate. The enzyme is encoded by the *PMM2*gene, and CDG-1a is inherited as an autosomal recessive trait [11]. In a recent mutation update, compound heterozygosity for the R141H and the F119L mutation was the most frequent genotype, accounting for 27% of 249 patients from 23 countries [2, 12].

Since the first report of a patient with CDG syndrome by Jaeken et al. [6], about 500 patients have been identified worldwide. The patients are characterised by psychomotor retardation, failure to thrive, abnormal subcutaneous fat distribution, strabismus, inverted nipples, renal involvement, cerebellar hypoplasia and peripheral neuropathy. There is a substantial childhood mortality of approximately 25%, owing to severe infections or organ failure [5, 6].

The diagnosis of CDG-1a had been suspected in our patient based on his developmental delay and cerebellar hypoplasia, despite the fact that the phenotype did not seem typical for the disease.

L. M. Neumann (✉) · J. Kunze
Institute of Human Genetics,
Charité Campus Virchow-Klinikum,
Augustenburger Platz 1, 13353 Berlin, Germany
E-mail: luitgard.neumann@charite.de
Tel.: +49-30-450566042/450566083
Fax: +49-30-450566961

A. von Moers
Department of Neuropaediatrics,
University Children's Hospital Charité,
Berlin, Germany

O. Blankenstein
Department of Paediatric Endocrinology,
University Children's Hospital Charité,
Berlin, Germany

T. Marquardt
University Children's Hospital,
Münster, Germany

Case report

The patient, a 16-month-old boy, is the third child of healthy Turkish parents who are first cousins. The family history was unremarkable. No miscarriages occurred. Two older sisters were reported to enjoy good health. Length and occipitofrontal circumference (OFC) of both parents were at the 10th percentile, and a normal growth pattern during their infancy and childhood was reported. The boy was delivered at term after an uneventful pregnancy without gestational diabetes. Birth weight 4,250 g (90th percentile), birth length 52 cm (75th percentile), (length-SDS +0.3, body mass index (BMI-SDS +2.5), OFC 33 cm (25th percentile). His Apgar scores were 9 at 1 and 5 min. The neonatal period was uneventful. He was breast-fed during the first 8 weeks and thereafter bottle-fed without problems. During the first months of life he had several upper airways infections. At the age of 4 months, he was admitted to hospital with bronchopneumonia. At that time, general muscular hypotonia with impaired head control was obvious. His crying was weak. At the age of 11 months, magnetic resonance imaging of his brain showed cerebellar hypoplasia of the vermis and the hemispheres, dilatation of the infratentorial cisternae and moderate dilatation of 4th ventricle (Fig. 1). At the age of 12 and 18 months he experienced febrile convulsions.

At 12 months of age, his body length (85 cm; +2.5 SDS) and weight (14 kg) were above the 97th percentile with a BMI-SDS of +1.7 and his OFC was at the 97th percentile (49.5 cm). At the age of 16 months, his length (86 cm) and weight (14 kg) were at the 97th percentile and his OFC (49.2 cm) at the 75th percentile. The boy has shown a convergent squint present since birth. He had neither an abnormal subcutaneous fat distribution nor inverted nipples. No genital abnormalities were observed. Muscular hypotonia was general, talipes equinus being present. At the lower extremities the deep tendon reflexes were weak but present. There was no Babinski sign. He could not sit unsupported.

Due to macrosomia, a bone age calculation was performed which was appropriate for his chronological age. Serum levels of insulin-like growth factor-1, insulin-like growth factor binding protein-3, testosterone, TSH and thyroid hormones were within the expected normal ranges for his age. Plasma glucose levels after a fasting period of at least 7 h at the age of 4 and 12 months were within the normal range (3 months: 6.3 mmol/l, 12 months: 6.2 mmol/l) as well as C-peptide levels at the age of 18 months and 3 years. Serum transaminases were in the upper normal range (AST 24 U/l, ALT 28 U/l), alkaline phosphatase, GGT, serum cholinesterase, GLDH, bilirubin, protein and serum albumin concentrations were also normal. As expected for CDG-1a, coagulation parameters were abnormal due to hypoglycosylation of the proteins involved: factor XI activity was 39% (normal above 70%). AT III showed reduced activity with 50% (normal 70%–90%) but was higher than in most CDG-1a patients who have values between 20% and 30%. Activities of protein C (44%, normal 64%–140%) and protein S (55%, normal 60%–140%) were slightly reduced. Prothrombin time with 94%, PTT with 33.5 s and fibrinogen with 325 mg/dl were within the respective normal ranges. APC resistance was negative. Chromosome analysis showed a normal 46/XY karyotype.

EEG recordings revealed no abnormalities. In contrast to other CDG-1a patients, motor nerve conduction velocity of the N. tibialis posteriores of the lower limbs was normal. Sensory nerve conduction velocity of the nervi suralis was slower than normal, but the child was restless during the examination. Ophthalmological examination indicated bilateral hyperopia of 2 dioptrin and a normal retina. Screening for hearing impairment was normal.

The isoelectric focusing of serum transferrin disclosed hypoglycosylation being consistent with the pattern of CDG-1. Enzyme analysis verified deficient phosphomannomutase (PMM) activities in leukocytes and fibroblasts (residual activities <5%). Molecular studies revealed a homozygous mutation in the phosphomannomutase 2 gene (PMM2) on chromosome 16p13.3-p13.2 at the beginning of exon 8 (647A > T, N216I). Heterozygosity of the parents was proven by DNA analysis and by a reduction of the PMM enzymatic activity in their leukocytes to approximately 50% of normal.

When the child was re-evaluated at the age of 2 years (Fig. 2a and Fig. 2b) we saw a happy, co-operative boy whose body length (100 cm, +2.52 SDS) continued to be at the 97th percentile; his weight was 16 kg (90th percentile) (BMI-SDS +0.2), OFC was 50 cm (50th percentile). He had truncal floppiness and was still unable to sit unsupported. He could not yet eat by himself. At the age of 3 years (see Fig. 2c and Fig. 2d), at his most recent assessment, the body length had dropped to the 90th percentile (102 cm, +1.84 SDS), while weight (17 kg), BMI-SDS (+0.5) and OFC (51 cm) were still in the former range. He showed general muscular hypotonia and a dystonic ataxic movement disorder. His deep tendon reflexes were reduced but present. Occasionally, a dorsal plantar response of the big toes but no complete Babinski reflexes were observed. Valgopronation position in the ankle joints was present. At this time, the eyebrows appeared bushy, the right one with an unusual upward-growth in the middle. His mouth was

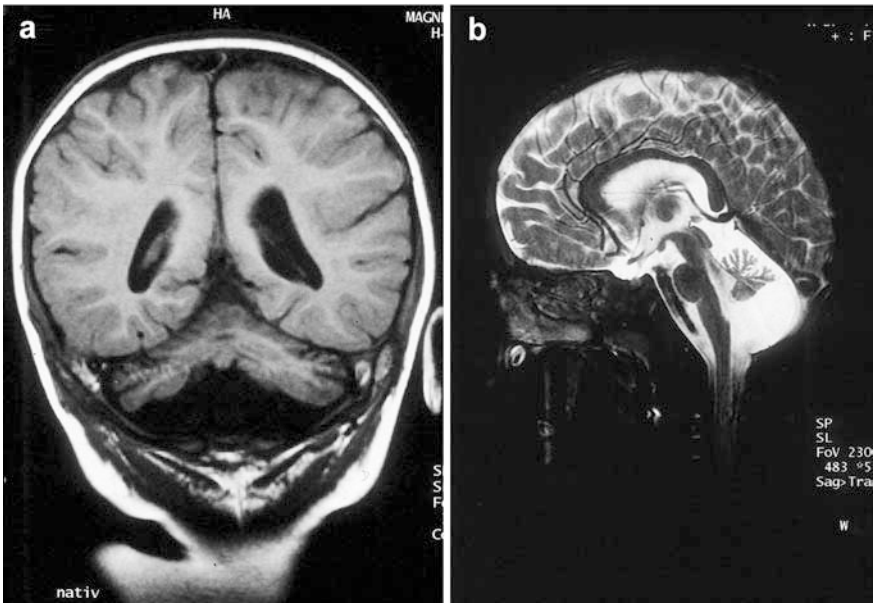

Fig. 1 **a** T1-weighted coronal and **b** T2-weighted sagittal magnetic resonance imaging section of brain demonstrating pancerebellar hypoplasia, consecutive dilatation of the infratentorial cisternae and moderate dilatation of the 4th ventricle

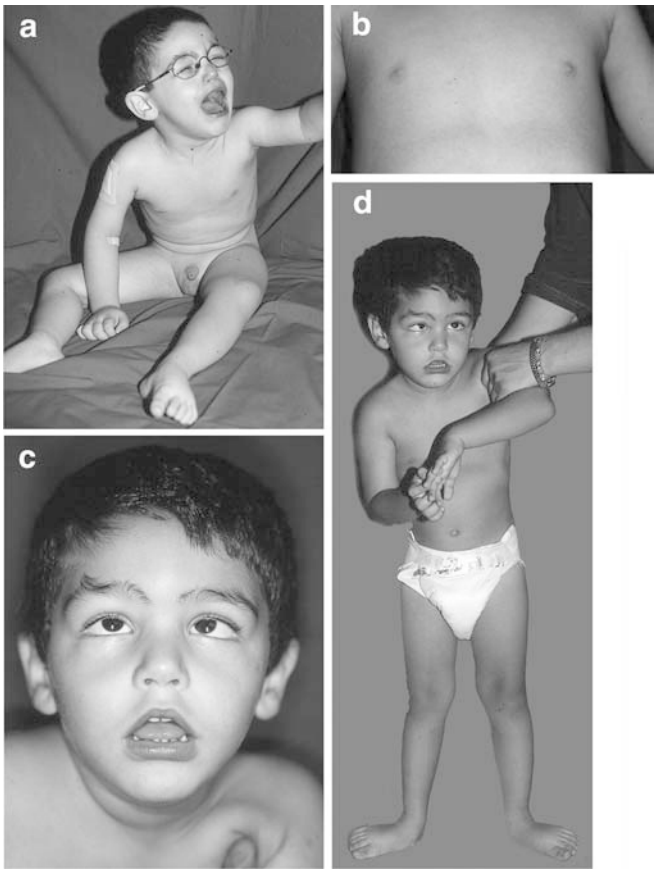

Fig. 2 **a** Patient at the age of 2.5 years with obvious muscular hypotonia and macrosomia. **b** The nipples are not inverted. **c** Patient at the age of 3 years with hypotonia of the tongue and a bizarre eyebrow on the right side. **d** Generalised muscular hypotonia and valgopronation position in the ankle joints

mostly held open and hypersalivation was present. He could now sit unsupported; he could crawl and pull himself into standing position. Motor skills of the hands were limited by dystonic movements. Social contact was good. He was able to distinguish between familiar and unfamiliar people. He could pronounce some double syllables and his receptive language was better.

Discussion

We present an unusual patient with CDG-1a. Diagnosis was proven by enzyme and molecular analysis. Out of more than 500 CDG-1a patients known today, only in four was the same mutation present as in our patient (for reference see the CDG mutation database at http://www.med.kuleuven.ac.be/cdg/). To our knowledge, our patient is the first described CDG-1a patient homozygous for the 647A > T mutation, making it possible to compare the clinical phenotype of this genotype with the classical presentation of CDG-1a.

In CDG-1a, neuroradiological imaging usually shows cerebellar hypoplasia [4] which was also present in our patient. Psychomotor impairment in our child was comparatively mild although he was clearly delayed in all his aspects of development. Whereas deep tendon reflexes of the lower limbs are usually absent at his present age and nerve conduction velocities at the lower limbs are reduced, our patient had a normal nerve conduction velocity and deep tendon reflexes were present.

Other features that can be present in CDG-1a are slight facial dysmorphic signs (as epicanthus, prognathism, elongated face) [4]. Our patient exhibited bushy eyebrows and a bizarre form of the right eyebrow not noted in other reported patients. There have been no further signs of multisystem involvement such as pericardial effusions or cardiomyopathy that are commonly observed in this disorder [10]. Distinct from the classical CDG-1a phenotype are in particular the missing characteristic inverted nipples and abnormal subcutaneous fat distribution as well as the macrosomia in the 1st year of life which has until now not been reported in CDG-1a patients. Recently Enns et al. [3] reported failure to thrive being present in all of their nine patients. Postnatal onset of growth failure has also been reported [7]. In 25 children with CDG-1a, measurements of length, weight, and OFC were within normal ranges at birth, but during the first months of life, mean values of weight and length SDS declined dramatically. In contrast, our patient manifested weight and length gain after birth. The growth during the first 12 months was accelerated with adequate OFC and length/weight relationship. His macrosomia was only present at the age of 1 year. During the subsequent 2 years of life the growth velocity diminished and stabilised to growth and length at the 90th percentile while OFC stabilised on the 50th percentile until the age of 3 years (Fig. 3).

Kjaergaard et al. [7] discussed malnutrition as the major cause of growth failure in patients with CDG-1a during the first 12 months of life. Our patient, however, showed increased growth and weight gain under a normal feeding regime. There were no feeding problems in this boy, and he never vomited nor had diarrhoea. There was no history of hypoglycaemia and the measured blood sugar values were within the normal range which gave no clue to any hyperinsulinaemic periods as a possible cause of overgrowth; later on the measured C-peptide levels were normal which makes hyperinsulinism also unlikely. As indicated by the increase in length-SDS and the decrease in BMI-SDS during the 1st year of life, overfeeding as a possible cause of the growth acceleration can be excluded. Previous studies have failed to hold growth hormone and thyroxine deficiency responsible for the growth failure of children with CDG-1a [1,8]. While the endocrine evaluation of our patient was unremarkable, there is no explanation at the moment for the overgrowth during the 1st year of life. It remains uncertain if the macrosomia in this child of consanguineous parents is due to homozygosity of infant alleles other than the PMM2. Further assessment will show his definite development of growth. We emphasise that macrosomia during the 1st year of life should not be considered as an exclusion criterion for CDG syndrome. The atypical clinical presentation of

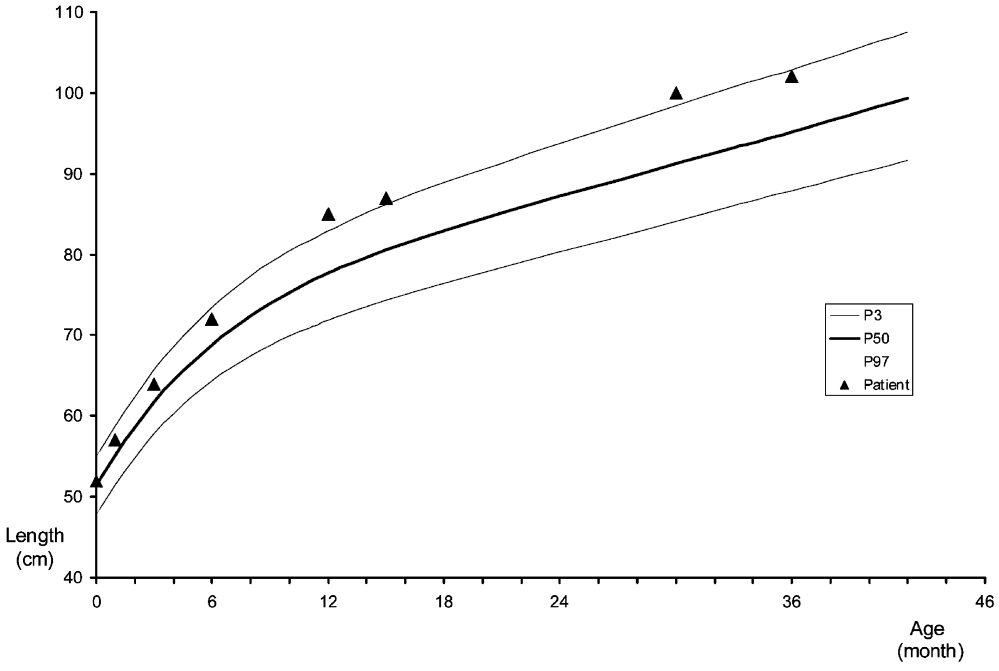

Fig. 3 Longitudinal growth curve of the patient. The curve relates height and age. Note increased longitudinal growth up to the age of 2.5 years and a decline at the age of 3 years

our patient supports the suggestion that CDG-1a is probably still underdiagnosed.

Acknowledgements The authors thank Julia von Heppe for helpful discussions concerning the growth parameters in our patient, Lydia Vogelpohl for mutation analysis, and Katrin Wardecki for the PMM assay. T.M. was supported by DFG grant MA 1229/3. For further information on CDG please see our web site: http://cdg.uni-muenster.de/

References

1. De Zegher F, Jaeken J (1995) Endocrinology of the carbohydrate-deficient glycoprotein syndrome type 1 from birth through adolescence. Pediatr Res 37: 395–401
2. Erlandson A, Bjursell C, Stibler H, Kristiansson B, Wahlstrom J, Martinsson T (2001) Scandinavian CDG-Ia patients: genotype/phenotype correlation and geographic origin of founder mutation. Hum Genet 108: 359–367
3. Enns GM, Steiner RD, Buist N, Cowan C, Leppig KA, McCracken MF, Westphal V, Freeze HH, O'Brien JF, Jaeken J, Matthijs G, Behera S, Hudgins L (2002) Clinical and molecular features of congenital disorders of glycosylation in patients with type 1 sialotransferrin pattern and diverse ethnic origins. J Pediatr 141: 695–700
4. Grunewald S, Matthijs G, Jaeken J (2002) Congenital disorders of glycosylation: a review. Pediatr Res 52: 618–624
5. Jaeken J, Matthijs G (2001) Congenital disorders of glycosylation. Annu Rev Genomics Hum Genet 2: 139–152
6. Jaeken J, Stibler H, Hagberg B (1991) The carbohydrate-deficient glycoprotein syndrome. A new inherited multisystemic disease with severe nervous system involvement. Acta Paediatr Scand Suppl 375: 1–71
7. Kjaergaard S, Muller J, Skovby F (2002) Prepubertal growth in congenital disorder of glycosylation type Ia (CDG-Ia). Arch Dis Child 87: 324–327
8. Macchia PE, Harrison HH, Scherberg NH, Sunthornthepfvarakul T, Jaeken J, Refetoff S (1995) Thyroid function tests and characterization of thyroxine-binding globulin in the carbohydrate-deficient glycoprotein syndrome type I. J Clin Endocrinol Metab 80: 3744–3749
9. Marquardt T, Denecke J (2003) Congenital disorders of glycosylation: review of their molecular bases, clinical presentations and specific therapies. Eur J Pediatr 162: 359–379
10. Marquardt T, Hulskamp G, Gehrmann J, Debus V, Harms E, Kehl HG (2000) Severe transient myocardial ischaemia caused by hypertrophic cardiomyopathy in a patient with congenital disorder of glycosylation type Ia. Eur J Pediatr 161: 524–527
11. Matthijs G, Schollen E, Pardon E, Veiga-Da-Cunha M, Jaeken J, Cassiman JJ, Van Schaftingen E (1997) Mutations in PMM2, a phosphomannomutase gene on chromosome 16p13, in carbohydrate-deficient glycoprotein type I syndrome (Jaeken syndrome). Nat Genet 16: 88–92
12. Matthijs G, Schollen E, Bjursell C, Erlandson A, Freeze H, Imtiaz F, Kjaergaard S, Martinsson T, Schwartz M, Seta N, Vuillaumier-Barrot S, Westphal V, Winchester B (2000) Mutations in PMM2 that cause congenital disorders of glycosylation, type Ia (CDG-Ia). Hum Mutat 16: 386–394