Prepubertal growth in congenital disorder of glycosylation type Ia (CDG-Ia)

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Aims: To delineate the pattern of growth in prepubertal children with congenital disorder of glycosylation type Ia (CDG-Ia) in order to identify critical period(s) and possible cause(s) of growth failure.

Methods: Longitudinal measurements of weight, length/height, and head circumference from birth to 10 years of age in 25 CDG-Ia patients with the R141H/F119L *PMM2* genotype were analysed. The data and derived body mass indices (BMI) were compared with standards and expressed as standard deviation scores (SDS). A linear mixed effects model was fitted to each set of data, and mean curves were estimated.

Results: The mean weight SDS decreased from -0.3 at birth to -3.0 at 7 months of age and remained low or increased slightly. The mean length SDS decreased from zero at birth to -2.4 at 7 months of age followed by a slight increase to a maximum of -1.8 SDS at the end of the second year of life. After age 2 the mean length/height SDS decreased again. The mean BMI SDS at birth was -0.7 and declined to a minimum of -2.8 at the end of the second year of life followed by a gradual increase. The mean head circumference SDS declined gradually from 0 at 3 months of age to -1.9 at age 5.

Conclusion: CDG-Ia patients with the R141H/F119L genotype have normal fetal growth and an immediate postnatal onset of severe growth failure. A notable decline in weight end length SDS takes place during the first seven months of life with no prepubertal catch up.

Congenital disorders of glycosylation (CDG), formerly known as carbohydrate deficient glycoprotein syndromes, are a rapidly growing group of disorders resulting from defects in the carbohydrate side chain (glycans) of proteins. The importance of glycans for the structure, function, and metabolism of glycoproteins is reflected by the severity of multisystem diseases resulting from defective N-glycan synthesis.

Congenital disorder of glycosylation type Ia (CDG-Ia, OMIM 212065), by far the most common type, is caused by deficiency of phosphomannomutase, an enzyme that converts mannose-6-phosphate to mannose-1-phosphate.¹ As a consequence the pool of GDP-mannose, which acts as a donor of mannose, is significantly reduced and leads to hypoglycosylation of proteins.

Phosphomannomutase is encoded by the *PMM2* gene, and CDG-Ia is inherited as an autosomal recessive trait.² 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.³

Clinical manifestations of CDG-Ia include psychomotor retardation, hypotonia, cerebellar ataxia, peripheral neuropathy, hepatic dysfunction, and dysmorphic features.⁴ Failure to thrive is a prominent feature, although its reported onset and degree have been variable.^{4–6} We have analysed longitudinal data of weight, length/height, and head circumference in our 25 patients with the R141H/F119L genotype in order to delineate the prepubertal growth pattern and to identify critical period(s) and possible cause(s) of growth failure.

PATIENTS AND METHODS

Patients

The 25 CDG-Ia patients (13 girls and 12 boys; mean age 7.6 years, range 0–19) with the R141H/F119L *PMM2* genotype came from 19 unrelated families of Danish origin. Two

patients had died as neonates, and four patients had died at 1.8, 4.3, 6, and 9.9 years of age, respectively. The patient population included two sets of monozygotic and one set of dizygotic twins. The diagnosis of CDG-Ia had been made by isoelectric focusing of serum transferrin, measurement of phosphomannomutase activity in cultured fibroblasts, and mutation analysis.⁷ Twelve patients had received supplemental feedings through nasogastric tube or gastrostomy for variable lengths of time during the first year(s) of life. No patient received mannose supplementation during the periods of growth evaluated.

Measurements

All available routine measurements of weight, length/height, and head circumference were collected from hospital records in our institution and in paediatric departments of other hospitals during a survey of all Danish patients with CDG-Ia. The patients' lengths were measured in the supine position at least until age 2–3; some patients were measured in the upright position beyond that age. Danish references allow for a change in position during measurement of height at age 2 years.⁸ The median numbers of observations per patient of weight and length/height were 13 (range 1–26) and nine (range 1–24), respectively. Only one set of measurements was available from each of the two children who died as neonates. A median number of four measurements (range 1–12) of head circumference were available on 22 patients.

Statistical analyses

Measurements of weight, length/height, and head circumference and calculated BMI (weight/height^2) were computed with standards for Danish children and expressed as SDS.^{8–10} A

Abbreviations: BMI, body mass index; CDG, congenital disorder of glycosylation; SDS, standard deviation score

Figure 1 Weight (A), length/height (B), BMI (C), and head circumference (D) SDS versus age (square root transformed age scale). Individual curves are shown as thin lines. The estimated mean curve is shown as a solid line, and the boundaries of the tolerance interval (95%) are shown as dashed lines.

linear mixed effects model was fitted to each set of data.¹¹ The model specifies a natural (cubic) regression spline for the mean process, and random effects comprise differences between individual patients' levels and rates of change. The model residuals were assumed to be correlated with a correlation coefficient exponentially decaying in time. A square root transformed age scale was chosen because of the dramatic failure to thrive in the first year of life. Cut offs were made at age 10 (age 6 for head circumference) as the number of observations beyond that age was too small. A likelihood ratio test was used to calculate *p* values for differences between females and males, and between patients who had or had not received supplemental tube feedings.

RESULTS

Of the 25 patients, 22 were delivered at term and had birth weights and lengths within ± 2 SD. The three preterm neonates (one patient with a gestational age of 36 weeks and a set of twins with a gestational age of 35 weeks) had birth weights which were appropriate for their gestational ages.

Weight

The mean weight SDS decreased during the first seven months of life from -0.3 to -3.0 followed by stabilisation or a

slight increase (fig 1A). Comparison of females and males showed that males had a lower mean curve ($p = 0.0016$, data not shown).

Length/height

The mean length SDS decreased during the first seven months of life from 0 to -2.4 followed by a slight increase to a maximum of -1.8 SDS at the end of the second year of life (fig 1B). After age 2 the mean length/height SDS decreased again. There was no difference between females and males.

BMI

The mean BMI SDS declined from -0.7 at birth to a minimum of -2.8 at the end of the second year of life followed by a gradual increase throughout the remainder of the period of observation (fig 1C).

Head circumference

The mean head circumference SDS declined gradually from 0 at 3 months of age to -1.9 at age 5 (fig 1D). All curves except two had a decreasing slope, and six patients became microcephalic as defined by a head circumference below -2 SDS. There was no difference between females and males.

Growth of patients receiving tube feedings

The mean weight and length/height SDS of children who received supplemental tube feedings decreased more rapidly, had lower minimum values, and remained lower during the period of observation than patients who did not receive such support ($p = 0.028$ and $p = 0.0007$, respectively; data not shown).

DISCUSSION

Although several previous publications have described failure to thrive, impaired linear growth, and acquired microcephaly in CDG-Ia,⁴⁻⁶ this report is the first analysis of longitudinal data on growth in a large and genotypically homogeneous group of patients. While there were differences in phenotypes within the group,¹² the anthropometric data showed remarkably similarity. Measurements of length, weight, and head circumference were within normal ranges at birth, but during the first seven months of life mean values of weight and length SDS declined dramatically. As reflected by decreasing BMI SDS, weight was affected more severely than length. Mean length/height, weight, and BMI SDS stabilised or increased slightly during late infancy and childhood, but they had not returned to normal ranges by age 10.

Some caution should be taken when interpreting our results. Limited range of joint mobility was reported in 50% of our patients, and kyphoscoliosis was present in 58% above age 3.¹² These skeletal problems may tend to overestimate the degree of linear growth failure. However, restricted joint mobility was most pronounced at birth when growth was normal, and kyphoscoliosis was mild below age 10.¹² The change of measurement from supine to upright position may contribute to the decrease in mean length/height SDS observed above age 2 years.

Failure to thrive is seen in many inborn errors of metabolism. Most children with enzymatic defects of intermediary metabolism, for example, branched chain amino acid catabolism, have normal weight and length at birth, and their postnatal growth failure is a result of the various consequences of amino acid intolerance. In contrast, several different mechanisms may contribute to the abnormal pattern of growth observed in patients with CDG-Ia.

Observations from unsuccessful attempts at prenatal diagnosis of CDG-Ia suggest that glycosylation of transferrin and α_1 antitrypsin is normal during most of gestation.^{13,14} A similarly undisturbed glycosylation of factors involved in growth may support normal intrauterine growth. On the other hand, the presence at birth of dysmorphic features and neurological dysfunction clearly shows the prenatal onset of CDG-Ia.^{4,5,12}

Nutrition is the prime determinant of growth early in life.¹⁵ Our patients were more or less anorectic, and the majority had frequent vomiting and diarrhoea during the first years of life. Data on our patients' protein and energy intake or gastrointestinal losses were not available. The feeding difficulties prompted feeding through nasogastric tube or gastrostomy in 12 children, who had more severe growth failure than patients not receiving this support. Our data do not allow us to determine the rate of growth these children would have had without nutritional support, but it is unlikely that this in itself was responsible for or contributing to their failure to thrive. Dysfunction of the small intestine and the liver may cause gastrointestinal symptoms in CDG-Ia,⁶ but the absorption of xylose, glucose, and triglycerides has been shown to be normal or close to normal.⁶

Adequate concentrations and function of growth hormone and thyroxine are necessary for normal growth during infancy and childhood. The influence of these hormones is considered to increase at the end of the first postnatal year,¹⁵ but previous studies have failed to hold them responsible for the growth failure of children with CDG-Ia.^{16,17}

Mean head circumference SDS of our patients was normal at age 3 months, but declined gradually during the subsequent years. This observation reflects our and others' previous findings of progressive cerebellar and cerebral atrophy.¹² The moderate to severe psychomotor retardation and ataxia associated with abnormal growth and development of the central nervous system may contribute importantly to the feeding difficulties of children with CDG-Ia.

Our data reveal a significant growth failure of immediate postnatal onset and no catch up during 10 years of observation. Inadequate nutrition caused by low energy intake and gastrointestinal losses is the most likely major explanation for the failure to thrive. So far, observations are too few to study the pubertal growth phase, and radiological evaluation of skeletal maturation is not available. We believe that the growth failure is most likely a result of loss of growth potential rather than delayed growth, but longer periods of observation are needed to confirm this hypothesis. Knowledge of the growth pattern of children with CDG-Ia should help in their management and provide a basis for interventional studies.

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Beyond Bristol: Improving Health Care - A Conference

Tragedies that expose the inadequacies of health care systems make the news and quite often a public inquiry follows but then they get forgotten by all but those affected. None, however, has gripped the British health care professions and the public quite as much as the unfolding of the events linking the performance of two cardiac surgeons and the paediatric cardiac surgical services at Bristol Royal Infirmary with the outcome for children entrusted to their care. The effect of this "local" difficulty on British health care in general and the medical profession in particular has been seismic. Perhaps the anger expressed over the avoidable deaths and disability of children looked after in Bristol has jolted us all to grasp the reality that this is not a "local" issue and that the underlying problems pervade the whole health service. The public inquiry, set up after it emerged that two surgeons had a much higher operative mortality than other paediatric cardiac surgeons and that problems with that unit had been "known about" for years, has been wide ranging. Although the terms of reference were "To look into the management of children receiving complex cardiac surgery services at the Bristol Royal Infirmary between 1984 and 1995", the inquiry team was also asked to conclude by making "recommendations that could help secure high quality care across the NHS". In the end there were 198 recommendations usefully categorised under seven headings to reflect the patient journey:

- Respect and honesty
- A health service which is well led
- Competent health care professionals
- The safety of care
- Care of an appropriate standard
- Public involvement through empowerment
- The care of children

These recommendations touch every aspect of the health care system and have relevance internationally. The events at Bristol may have started as a "local" issue but the problems and the solutions are to be found within the wider system of care. We all hold some responsibility for understanding what is needed and implementing the necessary changes. Action must replace anger and anguish as the motif of this tragedy. This is one inquiry whose end must not be a dusty footnote in the tired history of failures of health care. But taking it forward will not be easy. As noted in the introduction to the inquiry: "nothing can be done in the cheap"; "there are no quick fixes" and "change can only be brought about with the willing and active participation of those involved in health care". And as the inquiry also indicates, the most significant change called for is one that does not attract a heading of its own: "a change in the culture of the NHS".

A one day conference to explore some of the many tough but crucial areas for change articulated by the inquiry has been organised jointly by the BMA, the BMJ Publishing Group, the *Journal of Medical Ethics* and *Quality & Safety in Health Care*. The conference will take place on 18 November 2002 and aims to look forward and assess in the light of the report what needs to be done to: (1) improve the quality and safety of health care; (2) put the patient at the centre of health care; and (3) reduce errors. The conference will consider the lessons learnt from the Bristol Inquiry; discuss the practicality of implementing the recommended changes; and produce realistic action points that we hope will be the beginning of the long and difficult process of changing the culture of the NHS.

Venue: Queen Elizabeth II Conference Centre, Broad Sanctuary, Westminster, London SW1P 3EE.

Closing date: Monday 11 November 2002.

Further details and a brochure are available from: BMA/BMJ Conference Unit, PO Box 295, London WC1H 9TE. Telephone: + 44 (0) 207 383 6605; fax: + 44 (0) 207 383 6663; email: confunit@bma.org.uk; website: www.bma.org.uk

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