RESEARCH ARTICLE

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Syndrome-Specific Growth Charts for 22q11.2 Deletion Syndrome in Caucasian Children

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Growth faltering occurs frequently in infancy in the 22q11 Deletion syndrome (22q11 DS). The subsequent course of growth in childhood and outcome for final adult height lacks consensus. We analyzed 5,149 growth data points from 812 Caucasian subjects with 22q11 DS, from neonates to 37 years old. Charts were constructed for height, weight, body mass index, and head circumference (OFC) using the LMS Chart Maker program. These charts were compared with the WHO birth to 4 years growth standard and US CDC 2000 growth reference between 5 and 20 years. Starting from the 50th centile at birth, by 6–9 months of age boys mean height and weight had fallen to the 9th centile, as did girls height but their weight fell less markedly, to the 25th centile. Feeding difficulties were non-contributory. In children under 2 years old with congenital heart disease (CHD) mean weight was −0.5 SD lighter than no CHD. Catch up growth occurred, more rapid in weight than height in boys. Up to 10 years old both sexes tracked between the 9th and 25th centiles. In adolescence, the trend was to overweight rather than obesity. At 19 years mean height was −0.72 SD for boys, −0.89 SD girls. OFC was significantly smaller than the WHO standard in infancy, between the 9th and 25th centile, rising to the 25th centile by 5 years old. Thereafter the mean was close to the 9th centile of the OFC UK growth reference, more prolonged and marked than in previous studies.

Key words: 22q11 deletion syndrome; velocardiofacial syndrome; Di George syndrome; growth charts

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INTRODUCTION

The 22q11 deletion syndrome (22q11 DS) is the most common autosomal microdeletion syndrome in man with an incidence of one in 4,000 [Botto et al., 2003]. The prevalence of major cardiac anomalies requiring surgery (30–40%), developmental delay/learning disorders (90%), immune deficiency with recurrent infections (40%), hypoparathyroidism (60%), hypothyroidism and growth hormone insufficiency, and early feeding difficulties (70%) including forms of cleft palate, are individually and cumulatively potential causes of growth impairment [Bassett et al., 2011]. Additionally, a direct effect of the deleted DNA on growth cannot be discounted [Shprintzen and Golding-Kushner, 2008]. Individuals with 22q11 DS have an increased prevalence of impaired growth in childhood, with reports of variable degrees of recovery by adulthood [Ryan et al., 1997; Digilio et al., 2001; Bassett et al., 2005; Shprintzen and Golding-Kushner, 2008]. The present retrospective study of mixed cross-sectional and longitudinal growth data of a Caucasian population aims to provide reference growth charts showing how such children are growing.

PATIENTS AND METHODS

We studied 818 (412 boys, 52%) subjects, newborn to 37 years. Height, weight, and head circumference (OFC) measurements recorded during outpatient attendances in two tertiary children's hospitals, The Children's Hospital of Philadelphia (CHOP), Philadelphia, PA, USA, and Great Ormond Street Hospital for Children (GOSH) London, England, were retrospectively gleaned from the records of Caucasian individuals with 22q11.2 deletion confirmed by fluorescent in situ hybridization (FISH). None were characterized as having an atypical deletion. Exclusions comprised clinically significant scoliosis, hemiplegia, and genetic co-morbidities. Thyroid disorders and growth hormone deficiency were investigated

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and treated on an individual basis where clinically appropriate [Weinzimmer et al., 1998] and these subjects' measurements included. Observations were made and recorded by trained nursing staff. Ethical committee approved protocols were followed for data analysis by note case review as applied in each hospital.

The LMS statistical program was used to derive growth curves from the data. It summarizes the reference data in terms of three curves, the median (M), coefficient of variation (S), and skewness (L). Each of the latter two is expressed as a Box-Cox power transformation, with age the independent variable. These curves are fitted as cubic splines using penalised likelihood (a trade-off between roughness and goodness of fit) by non-linear regression and the extent of smoothing required can be expressed in terms of smoothing parameters or equivalent degrees of freedom (EDF). Raising and lowering the EDF changes the deviance. The LMS Chart Maker Light version 2.4 [Pan and Cole, 2007] program allows choice of the variables, and fit can be improved by rescaling the age.

The construction of a population growth reference, ± 2 SD in range, requires approximately 50 measurements per year [Cole, 002]. Where <50, constructing a chart using the 9th to 91st centiles, within the "tails" of the normal Gaussian distribution, ± 1.33 SD from the mean is robust [Cole et al., 2007]. It was therefore decided to produce charts with 5 centile lines, each 0.67 SD apart, the 9th, 25th, 50th, 75th, and 91st centiles (available from the authors). For illustrative purposes the 9th, 50th, and 91st centiles are shown. The international growth references for height, weight, body mass index (BMI) as weight/height^2, and OFC comparison were World Health Organization (WHO) charts from birth to 4 years [WHO, 2006], combined with the US Centres for Disease Control 2000 charts from 5 years upwards for height, weight and BMI [CDC, 2000]. Combining the WHO chart with the US CDC 2000 growth reference for comparison in older age groups has been reviewed [de Onis et al., 2007].

OFC was compared with the US reference which stops at 3 years, and the WHO-UK combined reference chart which covered the age range of the subjects. The combined reference charts were overlaid on the derived 22q11 DS curves to allow comparison with normal populations.

The Growth Comparator [Pan and Cole, 2007] was used to derive standard deviation scores (z scores) of the growth references, and values reported as z scores.

Numbers for each growth variable were: height in centimetres (cm) for boys 1,027, girls 1,138; weight in kilograms (kg) for boys 820, girls 966; BMI (kg/m^2) 828 boys, 825 girls; OFC in cm for boys 542, girls 627. 59% of data were of subjects attending CHOP, 41% GOSH. The proportion prematurely born was not accurately known, but is thought not to be significantly increased in 22q11 DS compared with the general population.

The number of measurements per year up to 5 years old ranged from 222 in the first year to 56 at 4 years for height and weight, 149–37 for OFC; from 5 to 10 years between 33 and 75 per year for all

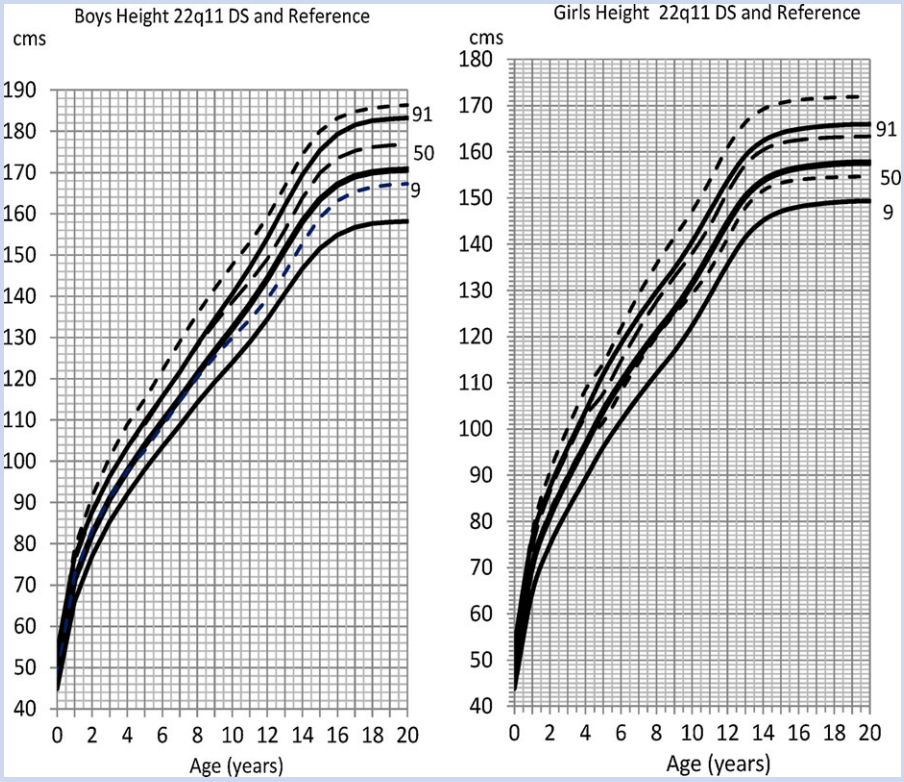

FIG. 1. Boys and girls height. Birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

parameters; from 11 to 20 years between 21 and 42 per year for height and weight, and 7 to 53 for OFC.

The proportion of subjects with one data set was 27%, 2–3 14%, and a maximum of 15 data sets in 1%. Of 818 (412 males, 52%) subjects, 38 (16 males) were over 19 years old, whose data were time frozen at 19.9 years. From 5,149 data, 29 (0.5%) were excluded after cleansing and modelling.

RESULTS

Height

Mean height for both sexes fell from the WHO 50th centile at birth to 9th centile by 9 months of age, and tracked the 9th centile up to 5 years old. Thereafter the 22q11 DS 50th centile lay between the US 9th and 25th centiles, approximately −1 SD (range −0.6 to −1.4 SD). The pubertal growth spurt was not delayed. Growth curves leveled out at 17 years for boys, mean height 172 ± 8 cm, (−0.72 SD), and 16 years for girls, mean height 158 ± 6 cm (−0.89 SD; Fig. 1).

Weight

In the first 2 years boys' mean weight fell from between the 25th and 50th centile at birth to below the 9th by 6 months, and returned towards the 25th by 2 years; girls showed less severe weight faltering, falling from the 50th to the 25th centile. The year of age mean z score between 3 and 10 years for both sexes averaged −0.65 SD (range −0.02 to −1.02), in adolescence the mean of −0.22 SD (−0.97 to 0.23) was closer to the reference population (Fig. 2).

In the first 2 years wide z score SD's in height (boys mean z score −1.82, SD 1.42; girls mean z score −1.66, SD 1.44) and weight (boys mean z score −1.63, SD 1.21; girls mean z score −1.34, SD 1.33) were consistent with a broad spectrum of growth or two populations. Comparison between the North American and British subjects identified only small mean z score differences of 0.05–0.27 SD, for height, weight, and OFC.

Growth impairment was then assessed applying WHO criteria for the prevalence of low height for age, underweight for age, and thinness as low weight for height expressed as BMI. Impairment was defined as present when −2 SD and severe if −3 SD. All data of those <5 years old were analyzed, comprising 226 boys and 207 girls. The prevalence of growth failure was highest under 2 years of age. Under a year, 39% were low height for age which was severe in 16%, underweight for age in 43% and severe in 14%. Thinness was less prevalent, total 24%, severe in 9%. By 5 years recovery was taking place, height lagging behind that of weight, with the prevalence of −2 SD for height 28% compared with weight at 16%. The severely

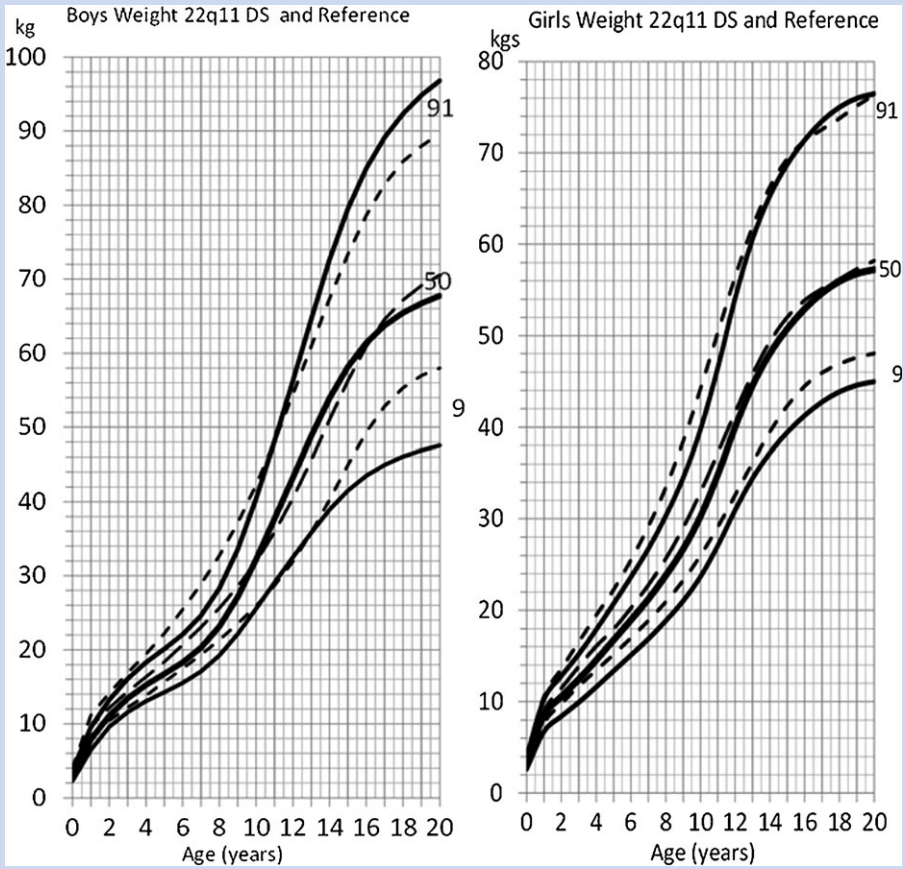

FIG. 2. Boys and girls weight. Birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

affected, as reflected in those below −3 SD, fell to 5% for height and 2% for weight; thinness below −2 SD fell to 4% in total, close to expected.

Factors potentially associated with undernutrition in under 2 years old, feeding difficulties and CHD, were scrutinized in a subgroup of GOSH subjects, by comparing mean weight z scores. Those with feeding problems (98 subjects) showed a small difference in mean weight z scores, −1.79, SD 1.13, from those without (35 subjects) −1.70, SD 0.95. In the presence of CHD (97 subjects), independent of whether cyanotic or non-cyanotic, there was a mean −0.55 SD difference in weight compared with no CHD (36 subjects), the mean z scores being −2.06 SD versus −1.51 SD. Above 2 years of age no differences in mean z scores were found between subjects with or without CHD.

BMI

In the first 1–2 years of life BMI showed a delayed peak compared with the normal population, with a staggered curve up to age 6 years. The maintenance of the mean BMI and range close to the reference population over 2 years old reflected the earlier recovery in weight than height. Between the ages of 10 and 19 years overweight, >85th centile, was 21% in boys, 27% in girls, and obesity >95th centile was 7% in boys, 8% in girls (Fig. 3).

Head Circumference (OFC)

Compared with the WHO standard the 50th centile was −1.21 SD below the mean in the first year, and remained a little less than −0.5 SD up to 5 years. The US CDC 2000 reference provided similar mean z scores, −1.39 SD in the first year, −0.65 SD second year, and −0.62 SD in the third year. The prevalence of microcephaly below the WHO −2 SD centile in boys was 30% (44/149), and girls 24% (27/114) in the first year. This prevalence persisted in both sexes up to 5 years old. The US CDC 2000 reference, restricted to the first 3 years of life, provided prevalence rates for −2 SD of 25% in the first year falling to 12% by 3 years. An increase in values at the interface between the composite WHO standard and UK reference at 5 years created a chart disjunction. This shifted the 22q11 DS 50th centile close to the WHO-UK Chart 9th centile, −1.33 SD below the mean, where it remained until late adolescence (Fig. 4).

Although the number of data over 10 years old were less than optimal, the plot of the growth curves and intercentile line distances were similar to the reference, except the outer centile lines for boys weight, which was reflected in the BMI curves, in late adolescence.

DISCUSSION

Growth faltering is a significant problem in 22q11 DS in infancy and the preschool years. Ryan et al. [1997] in a large multicenter European study of children found the weight to be below the 50th centile in 83%, and the 3rd centile in 36%. Similarly, Shprintzen and Golding-Kushner [2008] in a large study lacking standardized growth measurements and demographics found mean height and weight to be below the 10th centile under 1 year of age. They found mean height and weight rose to the 25th centile prior to the adolescent growth spurt. Subsequent mean height and

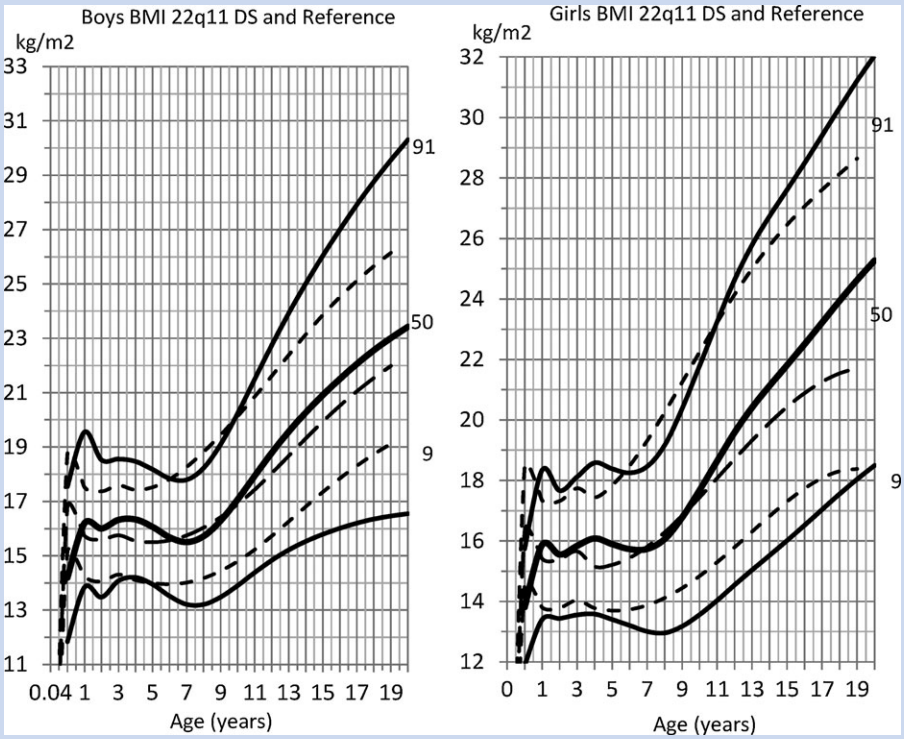

FIG. 3. Boys and girls BMI. Birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

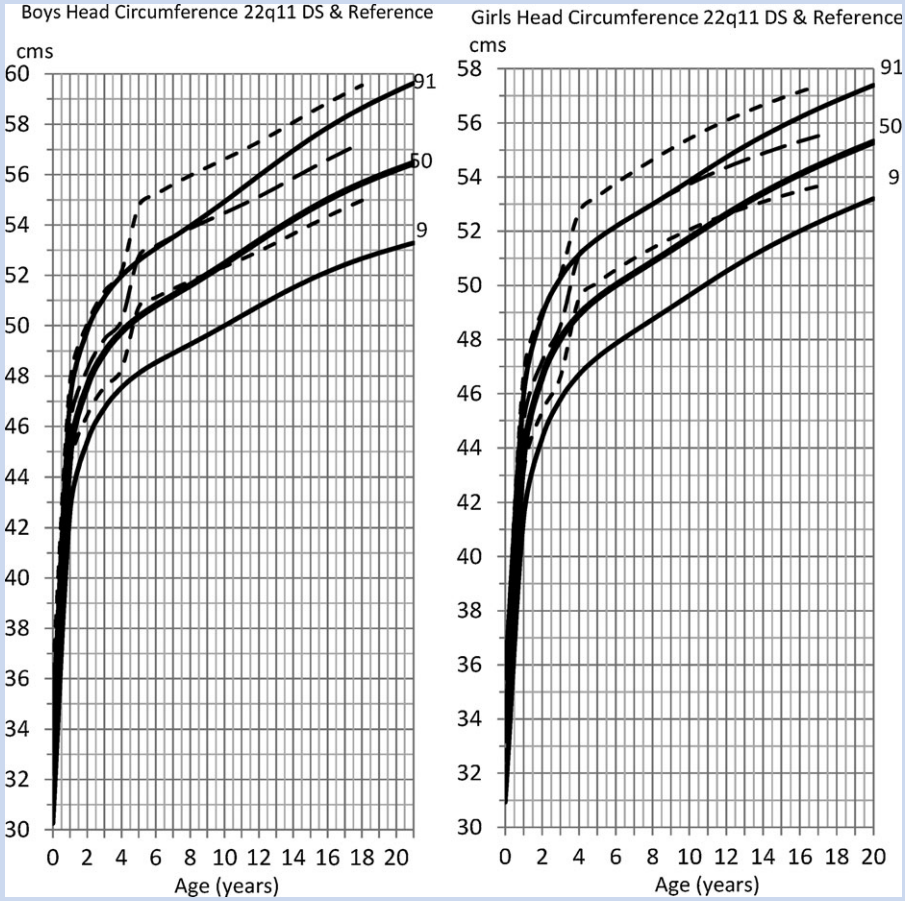

FIG. 4. Boys and girls head circumference birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

weight in adult females were on the 25th centile, and rose to the 50th centile in adult males. Digilio et al. [2001] found in 73 Italian children aged 0.3–16 years only 10% had short stature, all aged under 10 years old. The height distribution in 16 adolescents was within the normal range, with 31% obese. Among 78 Canadian adults Bassett et al. [2005] found a 20% prevalence of short stature below the 3rd centile, and obesity in 35%. The present study confirms the marked growth faltering in the first 6–9 months of age. Weight recovered more quickly than height, especially in girls. Height velocity continued to be reduced up to adult life, which resulted in below average final height.

The infant growth data are consistent with early undernutrition, of high (30–39%) to very high >40% prevalence [Golden, 1994]. The subsequent growth is characteristic of catch up [Prader et al., 1963]. Investigating this phenomenon, Costello [1989] found that the nutritional impact on long-term growth was limited to those aged <2 years old at the time of restricted food intake. When undernutrition is followed into adult life, 65–70% of the difference in height is linked to being −2 SD in height under 18 months old [Waterlow, 1988], the remainder due to continued impaired growth in later phases [Luo and Karlberg, 2000].

The cause of the early period of growth failure is uncertain at present. If it were attributable to reduced muscle mass [Shprintzen and Golding-Kushner, 2008] then one would not anticipate height to be affected. Feeding difficulties and CHD appear to play relatively little part, though optimising treatment to minimize the effects of incoordinate feeding, gastroesophageal reflux, gut dysmotility, and maximize cardiac function remains paramount An under researched factor in this context could be recurrent infection in altered immune states impacting on intestinal function. From the present study 12 symptomatic children were investigated [Tomar et al., 2010]. Low total immunoglobulins were found in 73%, one needing IgG and IgM supplementation, and 11 had normal lymphocyte counts. T cells were absent in one and slightly low in two. The most common features on gut biopsy microscopy were plasma cell and lymphocyte infiltration in nine, ranging from gastritis to pan enteric inflammation, and one had eosinophilic esophagitis. These findings support the possibility that they represent the more severe end of a spectrum of gastrointestinal dysfunction which may be common. Further, the reduction in frequency and severity of infections with age which occur in 22q11 DS children may facilitate the catch up growth.

The prevalence of thyroid and growth hormone deficiency is increased [Weinzimmer et al., 1998]. However the onset of growth faltering we observed is earlier than the usual presentation of growth hormone deficiency, which occurs after the age of 1 year.

Although the prevalence of hypothyroidism is increased it is routinely screened for and treated in our patients and would not have contributed in a major way.

Some report the prevalence of microcephaly is increased [Digilio et al., 2001; Bassett et al., 2005; Shprintzen and Golding-Kushner, 2008], others do not [Ryan et al., 1997]. Its prevalence of −2 SD (3rd centile) was 10% in Italian subjects, and 6% in Canadian adults. The WHO-UK OFC growth standard in the present study found a higher proportion; 30% were −2 SD, up to 5 years of age, and the mean was significantly below the reference population. The US CDC 2000 OFC reference prevalence of microcephaly was a half that of the WHO growth standard, a potentially significant underestimate for misclassified individuals. Disjunction about the age of 5 years between the WHO and UK head circumference references, combined in the WHO-UK chart, requires interpretation [Royal College of Paediatrics and Child Health, 2007]. In addition, variation in head measurement technique may account for some discrepancy between reference charts, and affect conclusions [Wright et al., 2011]. As craniosynostosis is increased in 22q11 DS [McDonald-McGinn et al., 2005] a considered approach to skull and brain imaging is appropriate when developmental and neurological symptoms or signs are present. The OFC findings in 22q11 DS reflect reduction in brain volume and neural connections [Barnea-Goraly et al., 2005; Campbell et al., 2006]. Although generally considered the consequence of the loss of genetic material in the deletion, early growth faltering may contribute.

The prevalence of obesity in the 22q11 DS adolescents in this study was 7–8%, half the present rate of non-Hispanic Caucasian American boys of 17% and girls 15% [Ogden et al., 2010]. However, their overall prevalence of 32% for overweight including obesity is similar to the study population of 28–35%. The trend towards overweight rather than obesity in 22q11 DS suggests early feeding difficulties may leave a legacy modifying dietary intake. This is beneficial as physical activity is limited in 22q11 DS by hypotonia, leg pains on exercise, and reduced exercise tolerance from heart or respiratory difficulties that the individual's clinical condition impose.

CONCLUSION

The 22q11 growth reference is representative of how such Caucasian children are growing compared with the WHO growth standard combined with the US CDC 2000 reference. Growth faltering is common in the first year of life and is most evident under 5 years of age. Recovery in height is incomplete, unlike weight gain. OFC is reduced from birth to 20 years compared with the WHO-UK growth reference. Investigation of microcephaly should be on a case by case basis. Further investigation of the period of early growth faltering may identify treatable causes.

Supplementary Growth Charts

22q11 DS five centile reference charts for height, weight, BMI, and head circumference overlaid with the WHO standard from birth to 5 years, or combined with the US CD 2000 reference birth to 20 years, can be downloaded: http://www.gosh.nhs.uk/medical-conditions/search-for-medical-conditions/digeorge-syndrome/di-george-syndrome-information/. The PDF can be found beneath the subheading "Glands, hormones and growth" and at the bottom of the "Useful documents" box on the right-hand of the webpage.

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