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Association between Head Circumference and Body Size

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Key Words
Head circumference · Cranial growth · Growth disorders · Sotos syndrome · IGF1R defect

Abstract
Background/Aims: Studies on the association between head circumference (HC) and height or weight have shown variable results. ***Methods:*** Using data from the Dutch nationwide survey performed in 1997 (n = 14,500), we calculated correlations for different ages, and fitted a regression model for the estimation of HC. HC versus height charts were created for different age groups. Data from children from other ethnic groups and children with various growth disorders were plotted on the charts and compared with reference data. ***Results:*** Correlations between HC and height or weight showed similar patterns: highest at birth, followed by a rapid decline to a stable level and a peak in adolescence. On charts containing the regression line ±2 standard deviations for subjects aged 0–2 months and 2 months to 21 years, Turkish and Moroccan children, as well as children with idiopathic short stature and small for gestational age, had a normal HC for height, whereas children with an insulin-like growth factor 1 receptor defect or Sotos syndrome showed trends towards a smaller or larger HC for height, respectively. ***Conclusion:*** HC correlates strongly with height and weight. The charts of HC for height may serve as an additional tool to interpret HC in short or tall children.

Introduction

Head circumference (HC) is one of the anthropometric parameters included in the physical examination of the infant and toddler. This measure of cranial growth gives a global indication of the growth and development of the brain. Growth charts of HC for age are available for different ethnicities [1–5], and usually an HC of more than 2 standard deviation scores (SDS) above or below the mean of the reference population at a given age and sex is considered abnormal (macrocephaly or microcephaly, respectively). A clear positive or negative change in the HC percentile position (or SDS) over time suggests hydrocephalus or craniostenosis, respectively.

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In the clinical assessment of a child with short or tall stature, it is important to include a measurement of HC. For example, a short child born small for gestational age (SGA) with a small HC has an increased risk of a defect in the insulin-like growth factor 1 *(IGF1)* or the insulin-like growth factor 1 receptor *(IGF1R)* genes [6, 7]. At the other end of the spectrum, Sotos syndrome should be considered in a tall and macrocephalic child with a large birth length, especially in the presence of typical dysmorphic features [8]. Short children with growth hormone (GH) deficiency may present with a normal HC, which is sometimes called 'relative macrocephaly'.

It is generally assumed that HC and height are related to each other. However, only few studies have investigated this association [9–16], with widely variable and even conflicting results. In addition, there are very scarce data on possible associations with other anthropometric measures, such as body weight. If there were a strong correlation of HC with height or weight, reference charts for HC for height or weight could provide a tool to better interpret HC in short or tall children, and possibly enable earlier diagnosis of growth disorders.

We therefore studied the association between HC and height or weight for both sexes in various age groups (0–21 years) of children of Dutch ancestry who participated in a large nationwide growth study [1], and investigated whether this association also existed for other ethnicities and for various patient groups with growth disorders.

Subjects and Methods

Subjects

All children of Dutch descent participating in the Fourth Dutch Growth Study were included to assess the correlation between HC versus length (if age <2 years) or height (if age ≥2 years) and weight (n = 14,500) [1]. Furthermore, data from 2,904 children of Turkish origin and a sample of 2,855 Moroccan children were used from this nationwide growth study [2, 3].

In addition, height, weight and HC data were used from a group of 151 children (99 boys and 52 girls) with idiopathic short stature (ISS) and 66 children (44 boys and 22 girls) born SGA, diagnosed in the growth clinic in Tübingen, Germany. Gestational age ranged from 30 to 42 weeks, with a mean of 38.9 weeks. The SGA group was further divided into an SGA group showing catch-up growth (20 subjects) and an SGA group with persistent short stature (46 subjects), using the Swiss references [17] for cut-off points [18, 19]. Of these children, two measurements of height, weight and HC were used: one measurement at birth and a measurement at a mean age of 9.81 years (range 3.35–16.89) in the ISS group and 11.11 years (range 3.59–26.35) in the SGA group.

A further sample consisted of 15 patients (4 male, 11 female) with a mutation or deletion of the *IGF1R* gene. This group contained cases from the literature [7, 20–28], some of whom were diagnosed at the Leiden University Medical Center [7, 28] and 2 novel cases from a German population [unpubl. data]. Nine subjects had measurements of length, weight and HC at birth, and measurements of height, weight and HC later in life were present in 9 cases, with a mean age of 7.00 years (range 0.17–35.00).

Finally, a group of 40 persons with Sotos syndrome was included (20 males, 20 females), all confirmed by a mutation of the *NSD1* gene. Measurements at birth of length, weight and HC were present in only 4 cases. Later in life, at a mean age of 3.31 years (range 0.06–20.25), measurements of height, weight and HC were documented for all patients. Twenty-four of these patients were described previously [29].

Statistical Analysis

In all groups, HC was measured with a non-extensible measuring tape to the nearest 0.1 cm according to the standard technique (www.growthanalyser.org). In this study, no measurement errors were calculated. In other growth studies, the technical error of measurement is 0.9–3.0 mm (www.growthanalyser.org).

SDS for length/height, weight and HC were calculated with respect to the current Dutch references [1] for all Caucasian subjects, using the LMS model [30]. For the Turkish and Moroccan sample, SDS were calculated based on references of the Turkish and Moroccan population living in the Netherlands [2, 3]. Since the first measurements in the Dutch reference sample were taken at 2 weeks of age, SDS of birth data in the ISS and SGA groups as well as from the cases with IGF1R defects and Sotos syndrome were calculated using the Swedish references [31], taking gestational age into account. HC in the ISS and SGA groups aged between 2 months and 21 years were converted to SDS using the Dutch references.

In the reference population, correlations between HC SDS and height SDS or weight SDS were calculated separately for various age groups: six age groups in year one (2-month periods), four in year 2 (3-month periods), groups aged 2–4 and 4–8 years, a group aged 8–11 for girls and age 8–12 for boys, a group aged 11–14 for girls and age 12–16 for boys, and a last group aged 14–21 for girls and age 16–21 for boys. Smoothed correlation coefficients (cubic B spline) and their 95% confidence intervals were plotted for each age group. We labeled each age group in the plot as 1, 3, 5, 7, 9 and 11 months (six age groups in year one), 13.5, 16.5, 19.5, and 22.5 months (four age groups in year 2), 3, 6, 10 years (8–11 years for girls and 8–12 for boys), 14 years (11–14 years for girls and 12–16 for boys) and 18 years (14–21 years for girls and 16–21 years for boys).

Regression analyses were performed with HC SDS as the dependent variable. First, height SDS and weight SDS were added to the model, both separately as well as together. The effect of age was assessed using an interaction term (age × height SDS and age × weight SDS). Thereafter, the influence of other parameters, including sex, birth rank, number of children in the family, geographical region and height of both parents, was assessed by adding these parameters to the model. Separate equations were developed for the age groups where age had shown to be an important factor. Charts of HC SDS versus height SDS and of HC SDS versus weight SDS were created showing a regression line ±2 SD.

For the other groups of children, a regression model was used including patient group and an interaction term height SDS × patient group to assess the differences in HC SDS of these groups in comparison to the Dutch reference population for any given

height SDS. Residuals were calculated in order to assess the mean deviation from the normal distribution. Data were plotted on the reference charts for visual comparison.

All statistical analyses were performed using SPSS version 14.0 and S-plus version 7.03.

Results

In the Dutch reference group, correlations between HC SDS and height SDS ranged between 0.324 and 0.519 in the various age groups. Correlations between HC SDS and weight SDS varied between 0.401 and 0.628 (see fig. 1 for observed and smoothed correlations and their 95% confidence intervals). The pattern of the correlations between HC SDS and both height SDS and weight SDS by age was similar, but correlations between weight SDS and HC SDS were significantly higher. Correlations were highest at birth, followed by a rapid decline to a stable level and a peak in adolescence. There was a significant influence of age in the first 2 months ($p < 0.001$), no significant influence from that moment onward until adolescence (cutoff 11 years), and again a significant influence of age in adolescence (11–16 years; $p < 0.001$). Therefore, four different correlation coefficients were calculated, namely for 0–2 months, 2 months to 11 years, from 11–16 years and from 16 years until 21 years (table 1).

In order to promote readability and usability, we decided to analyze all data in two different groups. One group consists of all subjects aged 0–2 months, and the other group comprises all subjects from 2 months until 21 years.

Regression analysis revealed that both height SDS and weight SDS were significantly associated with HC in all age groups. When height SDS and weight SDS were jointly added to the model, weight SDS was a stronger predictor of HC. Regression equations were established for the estimation of HC using either height, weight or both variables (table 2). The explained variance is highest in the first 2 months ($R^2 = 0.401$), but is still 0.237 in the period from 2 months onward. The mean residual was 0.0034 with a standard deviation of 0.87, confirming a near-normal distribution.

The influence of sex, birth rank, number of children in the family, geographical region and height of both parents was assessed in the same way, but yielded no statistically significant associations.

Charts for HC SDS versus height SDS were created (fig. 2–4), as well as charts for HC SDS versus weight SDS (data not shown). Although HC SDS correlated better with weight SDS than with height SDS, we reasoned that for clinical purposes a chart of HC SDS versus length/height SDS would be more useful. Regression lines ±2 SD were plotted on the graph.

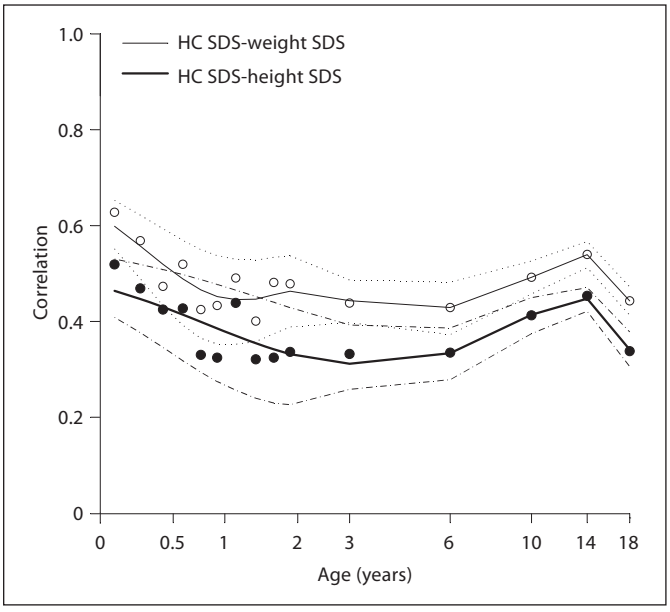

Fig. 1. Correlations between length SDS/height SDS and HC SDS and between weight SDS and HC SDS versus age (0–21 years, logarithmic scale), including 95% CI (dotted lines).

Table 1. Correlations per age range between HC SDS and height SDS or weight SDS

Age	HC SDS and height SDS	HC SDS and weight SDS
0–2 months	0.519	0.628
2 months to 11 years	0.370	0.464
11–16 years	0.436	0.526
16–21 years	0.339	0.441

In order to see whether these charts would also be suitable for other ethnicities, data from Turkish and Moroccan children were plotted on these charts (fig. 2). Table 3 shows the percentage of measurements from Turkish and Moroccan children found within the ±2 SD regression lines and the results of the regression equation, including the calculated mean and standard deviation (SD) of the residuals.

Figure 3 shows data from children with ISS or SGA plotted on the same chart. Since almost all children in

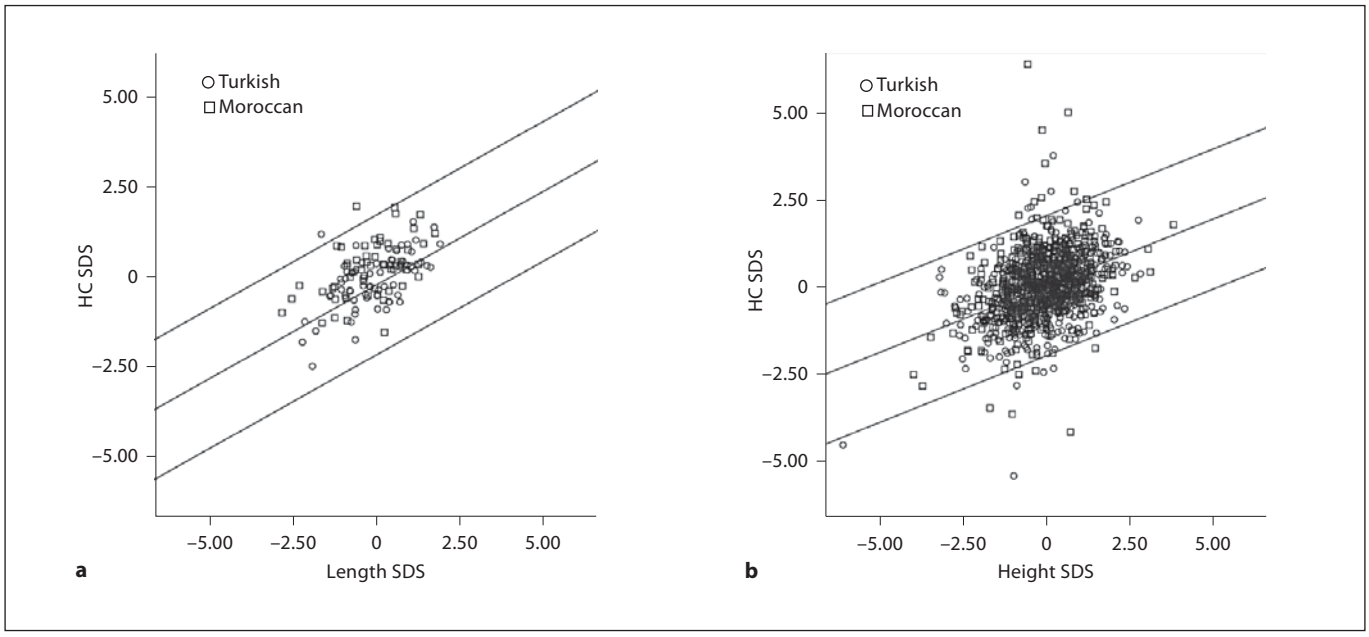

Fig. 2. HC SDS versus length SDS or height SDS for Turkish and Moroccan children versus the regression line ±2 SD for Dutch children. **a** Age range 0–2 months. **b** Age range 2 months to 21 years.

Table 2. Regression formulas for HC SDS as dependent variable and length or height SDS and weight SDS as independent variables

Age	Predictors	Regression formula	R^2	n
0–2 months	Length SDS	HC SDS = 0.540 (0.469–0.611) × length SDS	0.270	606
	Weight SDS	HC SDS = 0.604 (0.545–0.663) × weight SDS	0.394	627
	Length SDS and weight SDS	HC SDS = 0.518 (0.430–0.607) × weight SDS + 0.129 (0.034–0.225) × length SDS	0.401	605
2 months to 21 years	Height SDS	HC SDS = 0.381 (0.365–0.397) × height SDS	0.148	12,580
	Weight SDS	HC SDS = 0.479 (0.463–0.494) × weight SDS	0.228	12,829
	Height SDS and weight SDS	HC SDS = 0.399 (0.378–0.419) × weight SDS + 0.120 (0.100–0.140) × height SDS	0.237	12,568

Unstandardized coefficients are given, with their 95% confidence intervals.

these groups are found between the regression lines ±2 SD (fig. 3; table 3), we conclude that the short stature in these children is mainly proportionate with regard to HC versus height. In the children born SGA who showed catch up growth, HC SDS for height SDS was in the lower range, and after 2 months the relation between HC SDS and height SDS tends to become negative (not significant). Similar results were found for HC SDS for weight SDS (data not shown).

In figure 4, data from short patients with *IGF1R* mutations or deletions, tall patients with Sotos syndrome and a patient with an *IGF1R* duplication [32] are plotted on the chart, and numerical data are provided in table 3. Although proportions seem to be normal around birth, several patients with an *IGF1R* mutation have a substantially smaller HC for their height. With respect to Sotos syndrome, one third of these patients had a very large HC for height (>+2 SD line). The only case with tall stature due to *IGF1R* duplication showed an HC in the expected range.

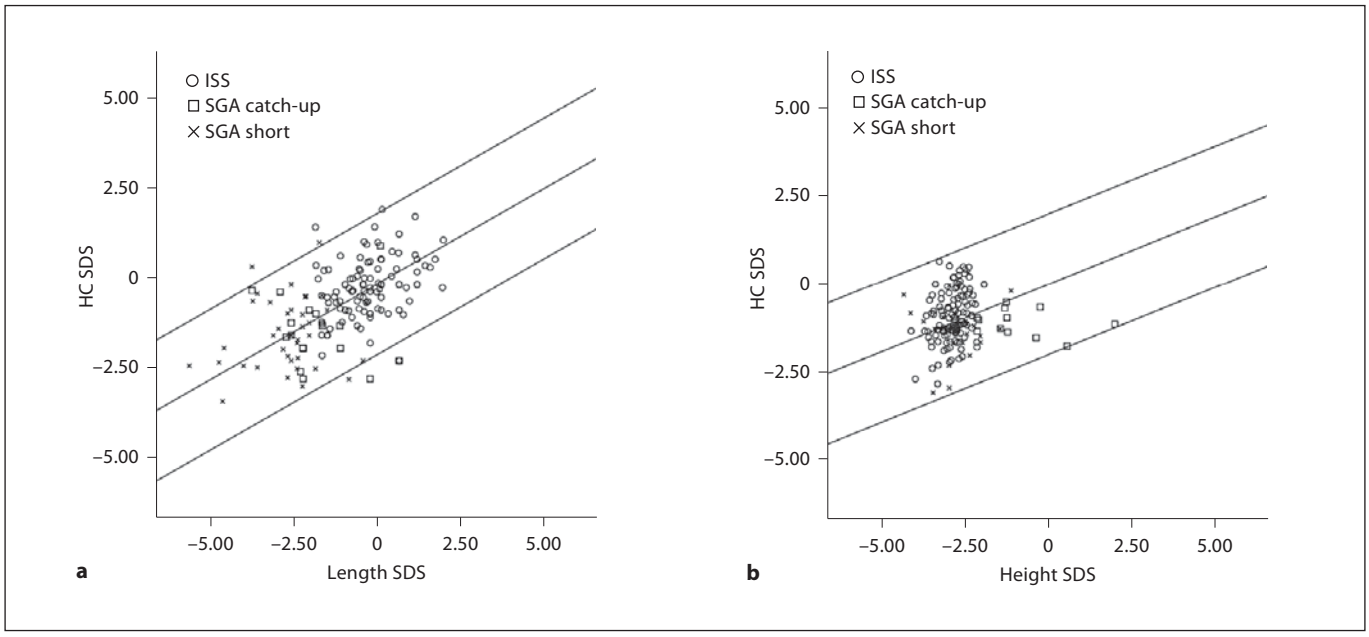

Fig. 3. HC SDS versus length SDS or height SDS for children with ISS/SGA children versus the regression line ±2 SD for Dutch children. **a** Age range 0–2 months. **b** Age range 2 months to 21 years.

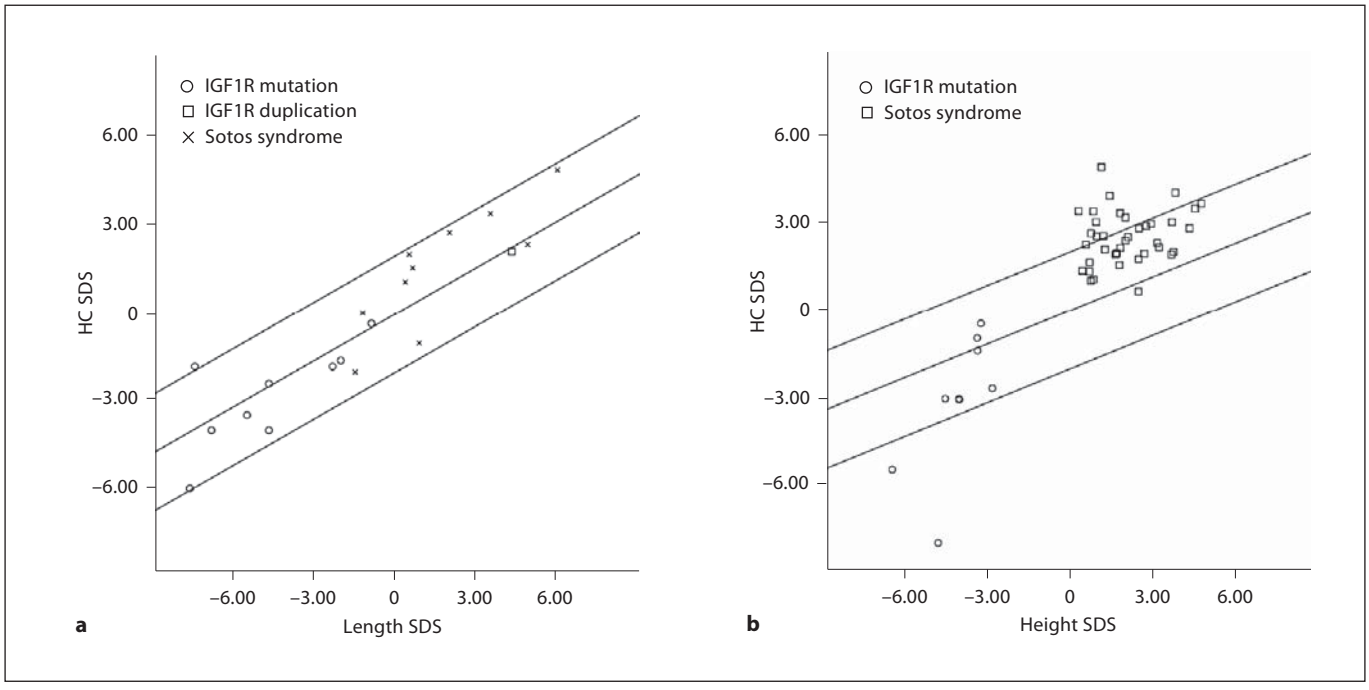

Fig. 4. HC SDS versus length SDS or height SDS for children with an IGF1R mutation or Sotos syndrome children versus the regression line ±2 SD for Dutch children. **a** Age range 0–2 months. **b** Age range 2 months to 21 years.

Table 3. Analyses of the differences between groups (Turkish, Moroccan, ISS, SGA, IGF1R and Sotos) and the Dutch references (HC for height)

Age	Group	n	Percent outside ±2 SD lines	Mean residual	SD residual
0–2 months	Dutch	606	2.1	0.00	0.91
	Turkish	70	1.4	0.18*	0.62
	Moroccan	56	1.8	0.57**	0.73
	ISS	98	3.1	0.06	0.80
	SGA catch-up	17	11.8	–0.37	1.22
	SGA short	39	7.7	0.04	1.06
	IGF1R	9	11.1	–0.34	1.15
	Sotos	10	0	0.68	1.23
2 months to 21 years	Dutch	12,580	3.0	0.00	0.92
	Turkish	575	2.1	–0.11**	0.84
	Moroccan	465	3.7	0.22**	0.98
	ISS	125	1.6	0.10	0.87
	SGA catch-up	17	0	–0.47*	0.90
	SGA short	30	0	–0.14	0.89
	IGF1R	9	22.2	–1.54	2.05
	Sotos	39	33.3	1.74**	0.95

* $p < 0.05$; ** $p < 0.01$.

Discussion

This study shows that HC SDS is highly correlated with height SDS and even stronger with weight SDS, irrespective of ethnicity. On average, children with *IGF1R* mutations have a significantly smaller HC for height than controls, but still in many of them HC for height is normal. Similarly, mean HC for height is high in Sotos syndrome, but still most values are within the normal range.

Our results on the correlation between HC SDS and height SDS confirm an earlier study (n = 3,600) [15] in children aged 0–6, where a correlation coefficient adjusted for age of 0.30–0.35 was found, and a slightly higher correlation with weight (0.37). Other studies on this topic were based on small patient groups, and yielded highly variable correlation coefficients, ranging from 0.26 to 0.98. In all these studies, measurements were not standardized for age and sex. In postmortem studies, the relationship between HC and height (not standardized for age and sex) was 0.98 in newborn children [16] and between 0.32 and 0.38 in adults [10]. Two studies confined to very young children up to 1.5 years of age [12, 14] reported age dependency similar to the one we found. In both studies, absolute correlations were higher. Another study with children around this age even found a correlation of 0.94 [11]. In young adults, results range from 0.26 [9] to 0.77 [13].

This study shows that height and weight both have a high correlation with HC in the first 2 months, followed by stabilization and a small peak in adolescence. Interestingly, these three stages roughly overlap with the three components of the ICP- model (Infancy, Childhood and Puberty) proposed by Karlberg [33]. According to that model, growth in infancy represents the postnatal contribution of fetal growth, which is mainly regulated by IGFs and insulin, while GH and genetic factors are the main contributors to growth in the childhood phase [6]. Growth in puberty is mainly regulated by sex steroids, partially through an increased GH and IGF-I secretion. We speculate that genetic and hormonal factors associated with growth in early infancy and puberty may also play a role in the regulation of head growth. The observation that HC for height is relatively low in SGA who show catch-up in height may be caused by the difference in timing of cranial and longitudinal growth: at birth HC is already 62% of its adult size, while length at birth is only 28% of adult stature [1]. Why the correlations between HC and weight are higher than the correlations between HC and height is yet to be explained. This observation would suggest that the number of common genes involved in cranial growth and weight may be greater than the number of common genes involved in head growth and height.

Plotting the data of HC for height of patients with ISS or SGA on the new charts indicated that these children had grown proportionately. Data from another group of SGA reported in the literature [34] also fit well between the reference lines. In contrast, patients with an *IGF1R* mutation had a relatively small head for their height, and patients with Sotos syndrome had relatively large heads. However, in both groups most of the data still fitted within the ±2 SD reference lines. As there was only one child out of 40 who had an HC for height <0 SDS, such cutoff has a high sensitivity for Sotos syndrome. Published data from patients with GH deficiency [35] fit well between the reference lines, with mean values around the 0 SD line. We assume that for the detection of hydrocephalus or microcephaly the charts of HC for height are not suitable, as in these conditions it is the change of HC SDS for age that leads to the diagnosis, rather than HC SDS itself.

In conclusion, HC SDS correlates with weight SDS and height SDS. This signifies that in the interpretation of HC of a child not only age, gender, and parental HCs are to be taken into account, but also body size. However, the clinical value of charts of HC for height in short or tall children is limited.

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