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Growth Charts for Cri-Du-Chat Syndrome: An International Collaborative Study

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Low birth weight and slow growth are frequently observed in the patients with cri-du-chat syndrome. To provide a growth reference standard for children with cri-du-chat syndrome, syndrome-specific growth charts have been developed from a combination of cross-sectional and longitudinal measurements on 374 patients from North America, Italy, Australia, and the British Isles. The data were obtained from pediatric records, parent reporting, and personal examinations at national 5p- parent support group meetings in the U.S., Italy, U.K., and Australia. The growth curves include height and weight measurements for patients ages 0 to 18 years and head circumference measurements for patients ages 0 to 15 years. Birth weight was above the 5th percentile of general population in 50% of cases: mean weight 2.8 kg ± 1.85 SD for males and 2.6 kg ± 1.51 SD for females. Growth curve medians were usually at or below the 5th centile of reference populations throughout life. The median head circumference falls below the 2nd centile, and this change increases with age. The charts show that compared with the standard population, most children with cri-du-chat syndrome are small at birth and as they grow most, but not all, have significant microcephaly and compromised weight for age, and to a lesser extent, compromised height for age. Am. J. Med. Genet. 94:153–162, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: cri-du-chat syndrome; growth studies; chromosome 5

INTRODUCTION

Cri-du-chat syndrome (CDCS) is a segmental aneusomy syndrome that is associated with a deletion of the short arm of chromosome 5. The syndrome is one of the more common deletion syndromes with an incidence of 1:27,000 [Higurashi et al., 1990], but this may be an underestimate because the authors do not take into account patients with smaller deletions [Spinner and Emanuel, 1997]. The syndrome is usually suspected at birth on the basis of a characteristic monochromatic, high-pitched cry considered diagnostic of the syndrome. Other features noted at birth may include microcephaly, round face, hypertelorism, epicanthal folds, down-slanting palprebral fissures, low-set ears, and micrognathia [Lejeune et al., 1963; Niebuhr, 1978a, 1978b; Wilkins et al., 1980, 1983]. As the infant grows, moderate to severe learning difficulties and developmental delay are usually observed [Niebuhr, 1971, 1978b; Wilkins et al., 1980; Cerruti Mainardi, 1987; Cornish et al., 1999].

Growth delay is common in CDCS [Niebuhr, 1978b, Wilkins et al., 1983; Cerruti Mainardi, 1987; Cerruti Mainardi et al., 1994]. There may be evidence of intrauterine growth retardation. Most but not all infants

TABLE I. Birth Weights in CDCS (n = 280)

Birth weight (g)	Percentage of patients
Under 1,500	1.0
1,500–1,999	5.5
2,000–2,499	30.7
2,500–2,999	31.9
3,000 and over	30.9

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TABLE II. Birth Growth Parameters in CDCS

Parameters	Males	SD	Females	SD
Mean birth length (cm)	48.68	1.24	47.28	1.38
Mean birth weight (kg)	2.79	1.85	2.62	1.51
Mean head circumference (cm)	32.92	1.25	32.10	0.91

with CDCS are difficult to feed. Sucking problems and reflux vomiting can result in failure to thrive [Niebuhr, 1978b; Delozier-Blanchet et al., 1985; Collins and Livingstone, 1997]. Niebuhr [1978b] reported that in CDCS, height and weight nearly always remain below normal throughout life. This is in contrast with Prader-Willi syndrome and Downs syndrome, two conditions also characterized by relatively short stature in which early feeding difficulties are common, but prevention of obesity is a major problem later [Ehara et al., 1993; Collins, 1998].

A child's growth is affected by genetics, nutrition, and other factors such as disease and energy expenditure. The significant long-term consequences of undernutrition in the reference population have established the need for monitoring of growth to facilitate early identification of growth faltering [Gibson, 1990]. Growth can be assessed by comparison with reference values derived from children who are healthy and with good nutrition [Gibson, 1990]. However, this is more problematic in genetic syndromes in which children may not grow in the same way as normal, healthy, well-fed children in the general population.

Comparing the growth of a child with CDCS using reference values from a healthy normal population may suggest growth retardation. However, clinically it would be more useful to compare height (or length) and weight and head circumference of children with CDCS against CDCS-specific reference values. In CDCS, feeding problems can persist throughout childhood with a high risk of continuing under-nutrition [Collins and Livingstone, 1997]. Therefore, syndrome-specific reference data would be helpful to both clinicians and caregivers for monitoring growth of such children with the syndrome and for evaluating the impact of treatment interventions.

The aim of the present study was to compile growth charts for CDCS based on anthropometric measurements made by clinicians or other trained professionals in North America, Italy, the British Isles, and Australia.

PATIENTS AND METHODS

Subjects were recruited to the study through their parents who were members of syndrome support groups. These included the 5p- Society (U.S.) (167 cases), Italian Registry and Associazione Bambini Cri-Du-Chat (Italy) (150 cases), the Cri Du Chat Syndrome Support Group (U.K.) (47 cases), and the Australian Cri-Du-Chat Syndrome Support Group (10 cases). Informed consent was obtained for all individuals. Most but not all of the patients had been assessed at least once by a physician associated with one of the support groups. Serial photographs and medical records, which included the chromosome analysis, were also obtained from a majority of the participants to support the clinical diagnosis. Subjects from the U.S. included most ethnic origins (Caucasian, African-American, Asian, Hispanic), whereas the subjects from Italy, the British Isles, and Australia were of Caucasian origin.

TABLE III. Number of Data Points and Confidence Level For Each Growth Time Point

	Male			Female		
Age	Weight	Height	Head circumference	Weight	Height	Head circumference
Birth	113 (0.22)	77 (0.28)	65 (0.31)	168 (0.18)	130 (0.24)	117 (0.17)
3 months	52 (0.58)	48 (0.41)	46 (0.24)	108 (0.35)	97 (0.35)	89 (0.17)
6 months	48 (1.06)	43 (1.35)	38 (0.79)	94 (0.57)	91 (0.36)	80 (0.21)
9 months	43 (1.05)	42 (0.44)	38 (0.27)	72 (0.55)	67 (0.37)	59 (0.23)
12 months	43 (1.29)	38 (0.84)	28 (0.46)	77 (0.59)	74 (0.33)	62 (0.24)
15 months	30 (1.07)	26 (0.55)	19 (0.41)	57 (0.78)	53 (0.42)	46 (0.23)
18 months	25 (0.98)	19 (0.73)	12 (0.51)	62 (0.71)	57 (0.46)	43 (0.29)
21 months	14 (1.17)	12 (0.87)	9 (0.28)	30 (1.26)	19 (0.73)	10 (0.62)
24 months	41 (1.01)	38 (0.51)	23 (0.45)	65 (0.91)	58 (0.48)	39 (0.26)
3 years	38 (1.31)	33 (0.99)	19 (0.7)	71 (0.92)	65 (0.42)	41 (0.24)
4 years	41 (1.65)	34 (0.76)	19 (0.4)	52 (1.65)	40 (0.73)	15 (0.69)
5 years	38 (1.55)	33 (0.91)	14 (0.6)	43 (2.35)	38 (0.95)	16 (0.45)
6 years	29 (3.15)	24 (1.17)	12 (0.37)	39 (1.79)	34 (0.99)	18 (0.44)
7 years	31 (3.5)	24 (2.16)	9 (0.83)	28 (3.84)	25 (1.18)	8 (0.79)
8 years	23 (2.86)	18 (1.43)	7 (0.43)	23 (3.49)	24 (1.26)	9 (0.61)
9 years	19 (3.84)	13 (1.32)	6 (1.08)	29 (3.13)	22 (3.02)	7 (0.57)
10 years	18 (8.54)	16 (1.93)	8 (0.31)	20 (5.86)	18 (1.62)	5 (1.02)
11 years	12 (9.84)	8 (2.61)	4 (2.7)	18 (8.61)	17 (2.23)	4 (1.92)
12 years	11 (12.9)	9 (2.66)	6 (0.79)	19 (8.41)	17 (1.89)	6 (0.66)
13 years	15 (7.85)	10 (2.43)	5 (1.51)	11 (15.0)	10 (3.37)	3 (3.04)
14 years	13 (13.7)	10 (2.69)	7 (0.99)	14 (6.75)	9 (4.07)	6 (0.82)
15 years	14 (14.2)	9 (2.49)	7 (0.84)	11 (11.3)	8 (3.7)	4 (0.5)
16 years	7 (20.7)	6 (3.48)	—	6 (10.9)	4 (5.89)	—
17 years	5 (22.3)	5 (7.6)	—	7 (10.3)	6 (3.26)	—
18 years	4 (23.7)	3 (13.7)	—	8 (12.9)	12 (1.55)	—

The anthropometric data were obtained from pediatric records, assessment records held by parents, and measurements made by clinicians at national 5p- parent support group meetings in the U.S., U.K., and Italy. The measurements were placed in categories based on sex and age. All of the data were converted to kilograms and centimeters. Raw data were entered in 3-month increments for the first 2 years and every year up to age 18 years. Measurement recordings that fell between time points were assigned to the closest time point or randomly assigned to either the higher or lower age group. Only one measurement was used for each time point for each patient. The growth curves were developed using standard statistical methods and standard deviations described by others. Data points for the normal growth curves were obtained from Merenstein et al. [1994]. The curves were not smoothed using any statistical method.

RESULTS

Birth weight measurements for 280 infants were obtained. The ranges of birth weights are shown in Table I as well as the percentage of patients that fell into each group. At total of 104 infants (37.2%) had a birth weight of less than 2.5 kg and would be considered underweight. The mean birth measurements and the standard deviation (SD) are shown in Table II and are indicative of prenatal growth delay in a majority of the probands.

The number of data points that were used to derive each growth curve as well as the confidence level are shown in Table III. The growth curves were not smoothed but accurately reflect the fluctuation in the data that were compiled.

Serial growth records were available on 152 males and 222 females clinically diagnosed with CDCS. The ages of the patients ranged from birth to age 25 years. Growth information past age 19 years was not used. A total of 4,759 measurements were obtained. For females, 1,053 height measurements, 1,197 weight measurements, and 701 head-circumference measurements were obtained. For males, 636 height measurements, 768 weight measurements, and 404 head-circumference measurements were obtained (the males are measured statistically significant less than the females, $P < 0.01$). Table III shows the number of data points that were available for each time point and the confidence level.

Figures 1 and 2 show the growth curves, weight for age, of females from birth to age 24 months and age 2 to 18 years, respectively. At birth, the 50th centile for the female infants with CDCS was between the 5th and 50th centiles in the reference population, but by age 9 months, the CDCS median curve had fallen below the 5th centile for the reference population and stayed close to that centile until the 14th year after which it dropped below the 5th centile for the general population. The 95th centile for female infants with CDCS was above median weight for age growth curve for female infants in the general population until age 9 months and at or above the median curve until age 13 years after which it was below the median growth curve of the reference population.

Figures 3 and 4 show the growth curves, weight for age, for males from birth to age 24 months and age 2 to 18 years, respectively. The 50th centile for birth weight for males with CDCS was between the 5th and 50th centiles for the reference population, but by age 9 months the CDCS median curve had fallen below the 5th centile for the reference population and remained below it, the gap progressively widening with age. The CDCS 95th centile was above the median weight for age for males in the general population until age 9 months, then stayed close to the 50th centile for males in the general population until the 10th year after which the gap progressively widened. The CDCS 95th centile fell below the general population 5th centile in the 16th year.

Figures 5 and 6 show the height for age growth curves of females from birth to age 24 months and age 2 to 18 years, respectively. The 50th centile for height was between the 5th and 50th centiles for the reference population until the 7th year and remained close to the 5th until the 11th year after which the gap widened. The CDCS 95th centile was close to the reference population 95th centile until after age 18 months and remained above the reference population median growth curve for height until the 12th year.

Figures 7 and 8 show the height for age growth curves for males from birth to age 24 months and 2 to 18 years, respectively. From birth until age 18 months, the CDCS median curve remained between the 5th and 50th centiles for the reference population and continued close to the 5th centile until the 10th year, after which the gap widened. The CDCS 95th centile for length was at or close to the reference population 95th centile for the first year and stayed above the reference population median curve until the 12th year.

Figures 9 and 10 show the head circumference curves for age for females and males, respectively. By the end of the 3rd month in females and the 9th month in males, the median CDCS growth curve for head circumference was below the 2nd centile for the reference population. By 15 months, the CDCS 98th centile for females had fallen below the median growth curve for head circumference for the reference population, whereas in males the CDCS 98th centile fell below the median growth curve for the reference population at 7 years and remained below it.

DISCUSSION

Standard growth curves have been developed for head circumference for age, weight for age, and height for age for both males and females with CDCS. In general, there is consistent prenatal growth retardation and for the postnatal growth, the median is often near the 5th centile of the normal growth curve. The median head circumference and weight are consistently near or below, respectively, to the 2nd centile and to the 5th centile for all ages. The 50th centile for height from birth to age 2 years fell within normal parameters but then tracked at the 5th centile after age 2 years. How-

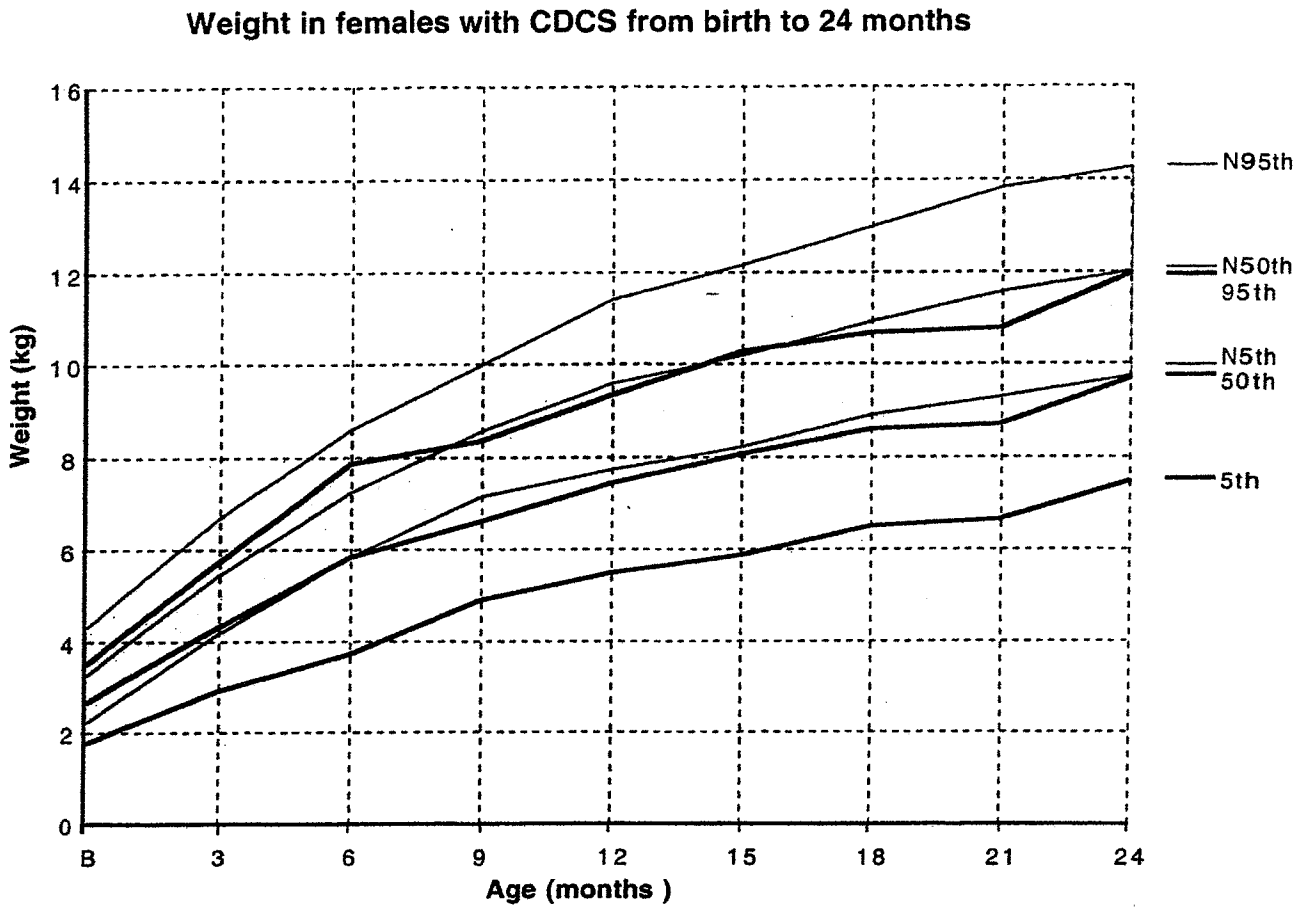

Fig. 1. Weight in females with CDCS from birth to age 24 months (**thick lines**). The normal growth curve (**thin lines**) is shaded.

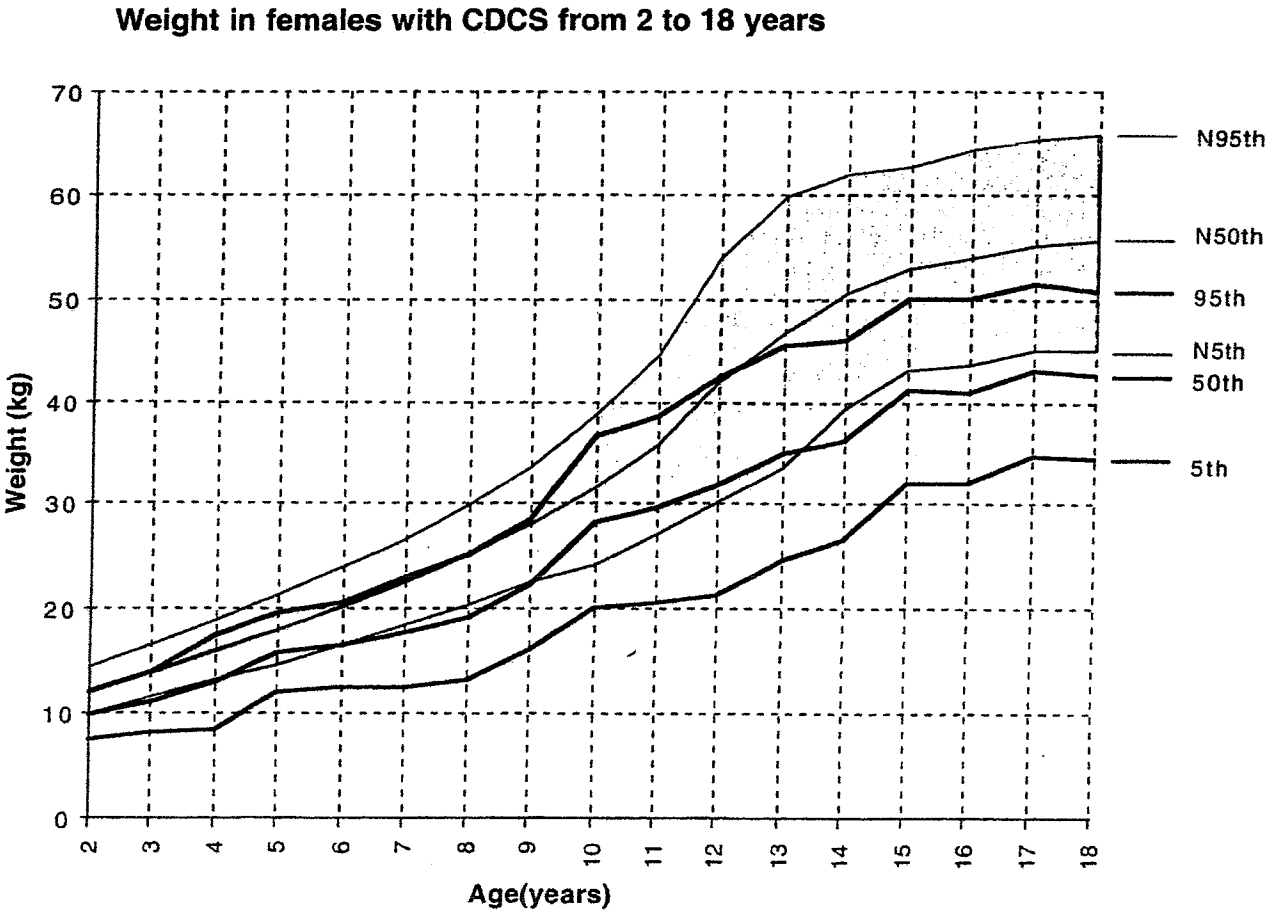

Fig. 2. Weight in females with CDCS from age 2 to 18 years (**thick lines**). The normal growth curve (**thin lines**) is shaded.

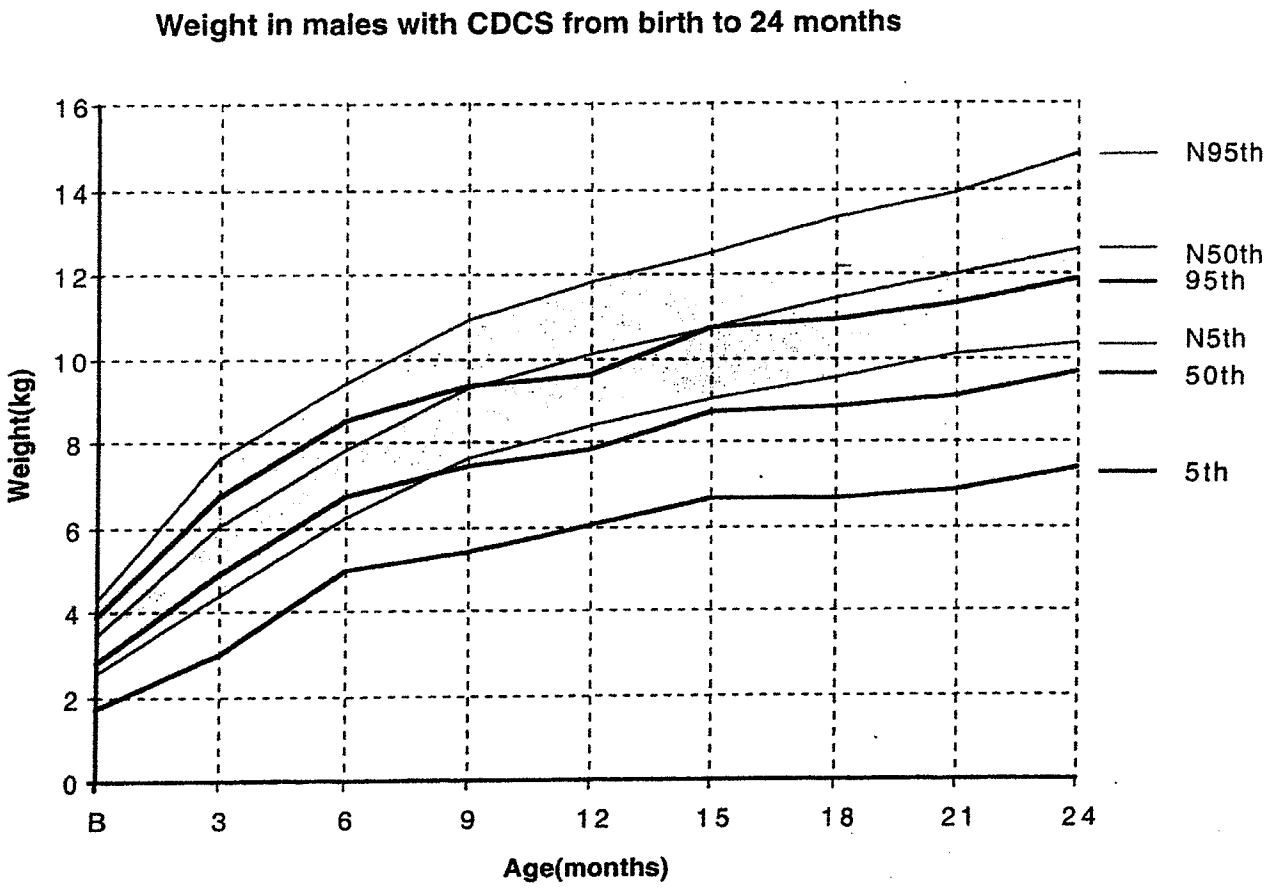

Fig. 3. Weight in males with CDCS from birth to age 24 months (**thick lines**). The normal growth curve (**thin lines**) is shaded.

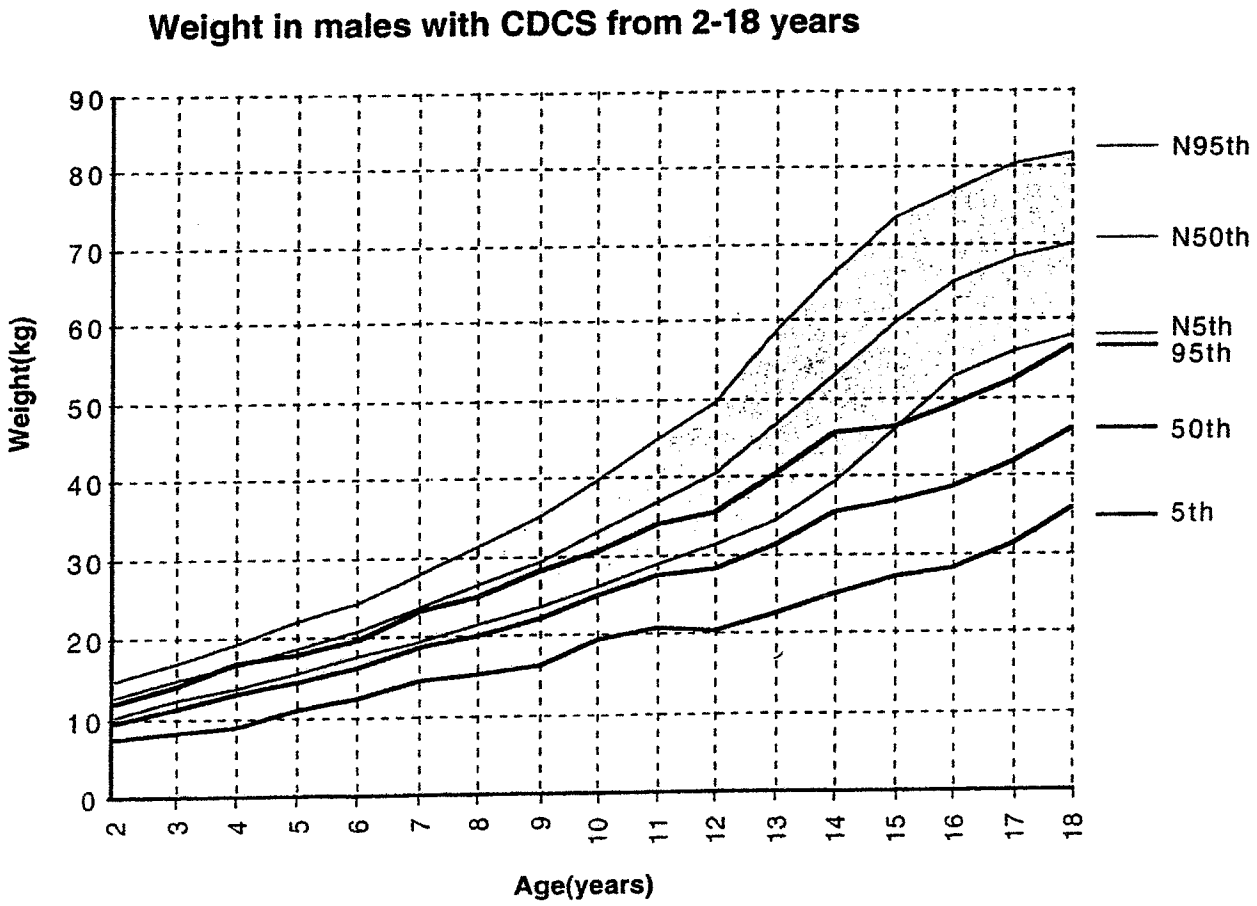

Fig. 4. Weight in males with CDCS from age 2 to 18 years (**thick lines**). The normal growth curve (**thin lines**) is shaded.

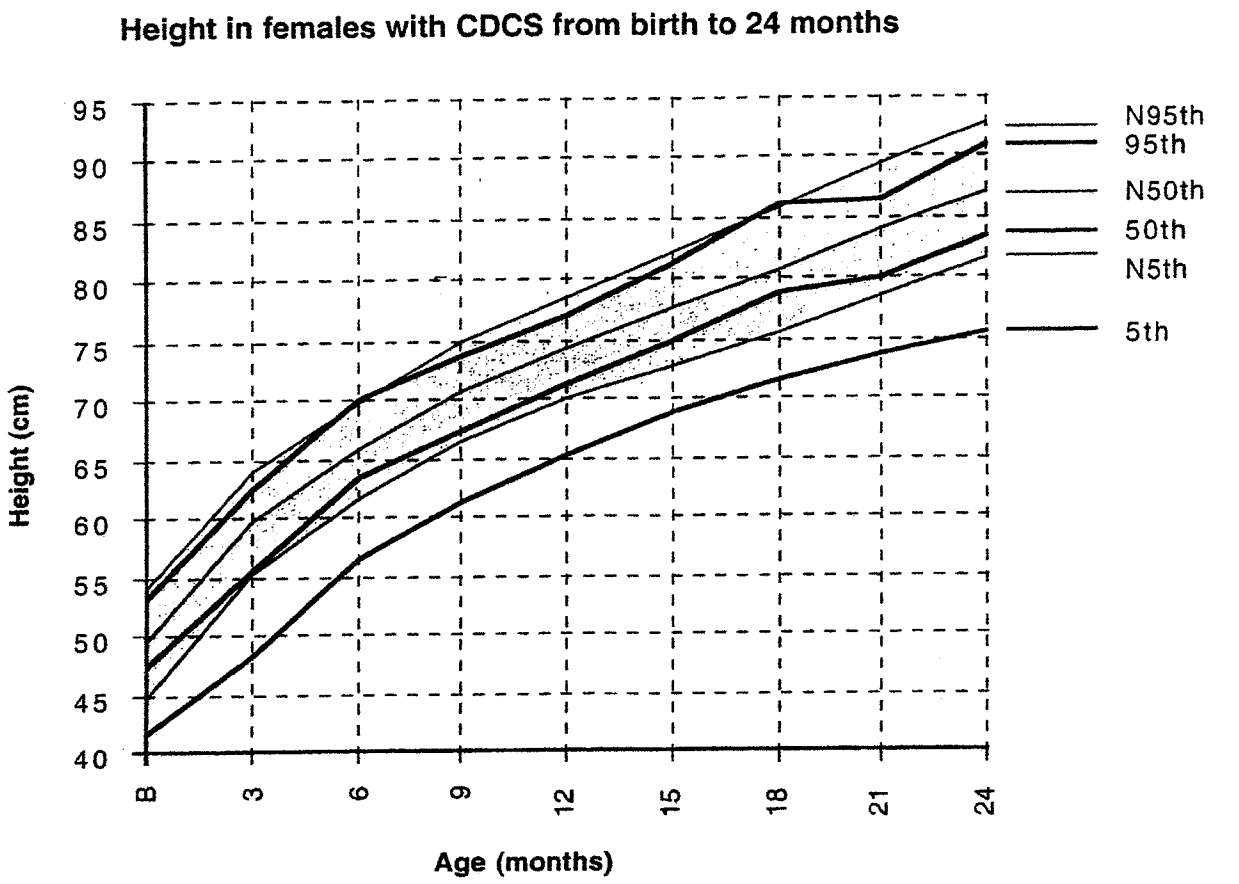

Fig. 5. Height in females with CDCS from birth to age 24 months (**thick lines**). The normal growth curve (**thin lines**) is shaded.

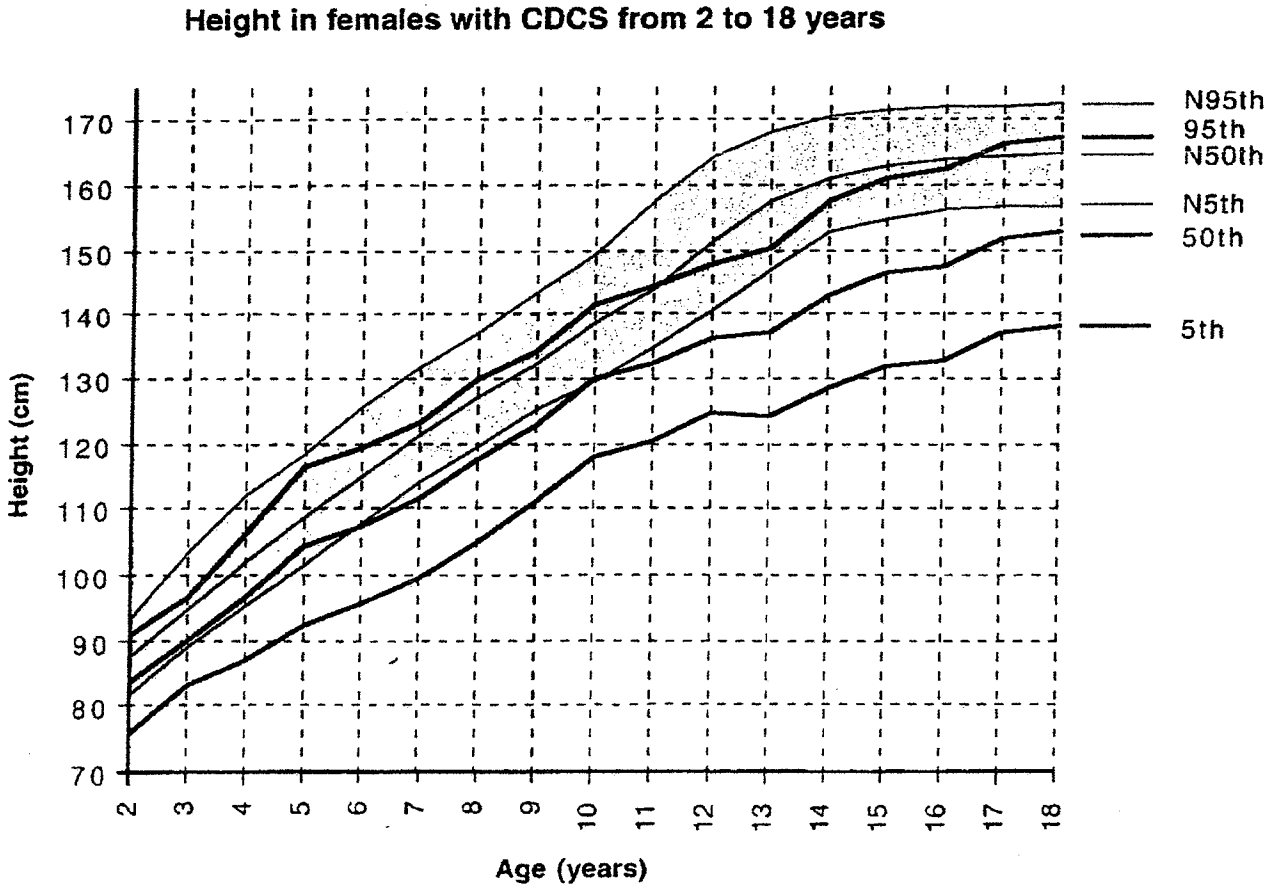

Fig. 6. Height in females with CDCS from age 2 to 18 years (**thick lines**). The normal growth curve (**thin lines**) is shaded.

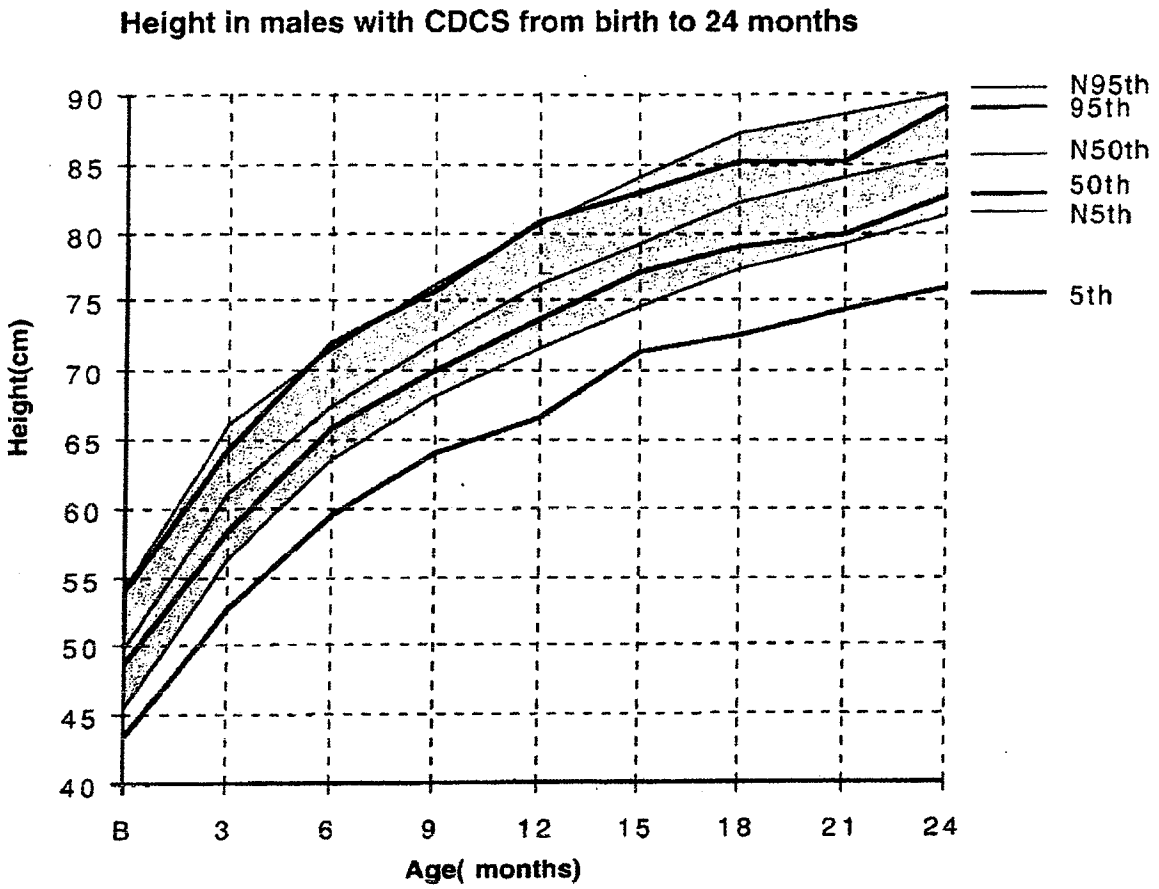

Fig. 7. Height in males with CDCS from birth to age 24 months (**thick lines**). The normal growth curve (**thin lines**) is shaded.

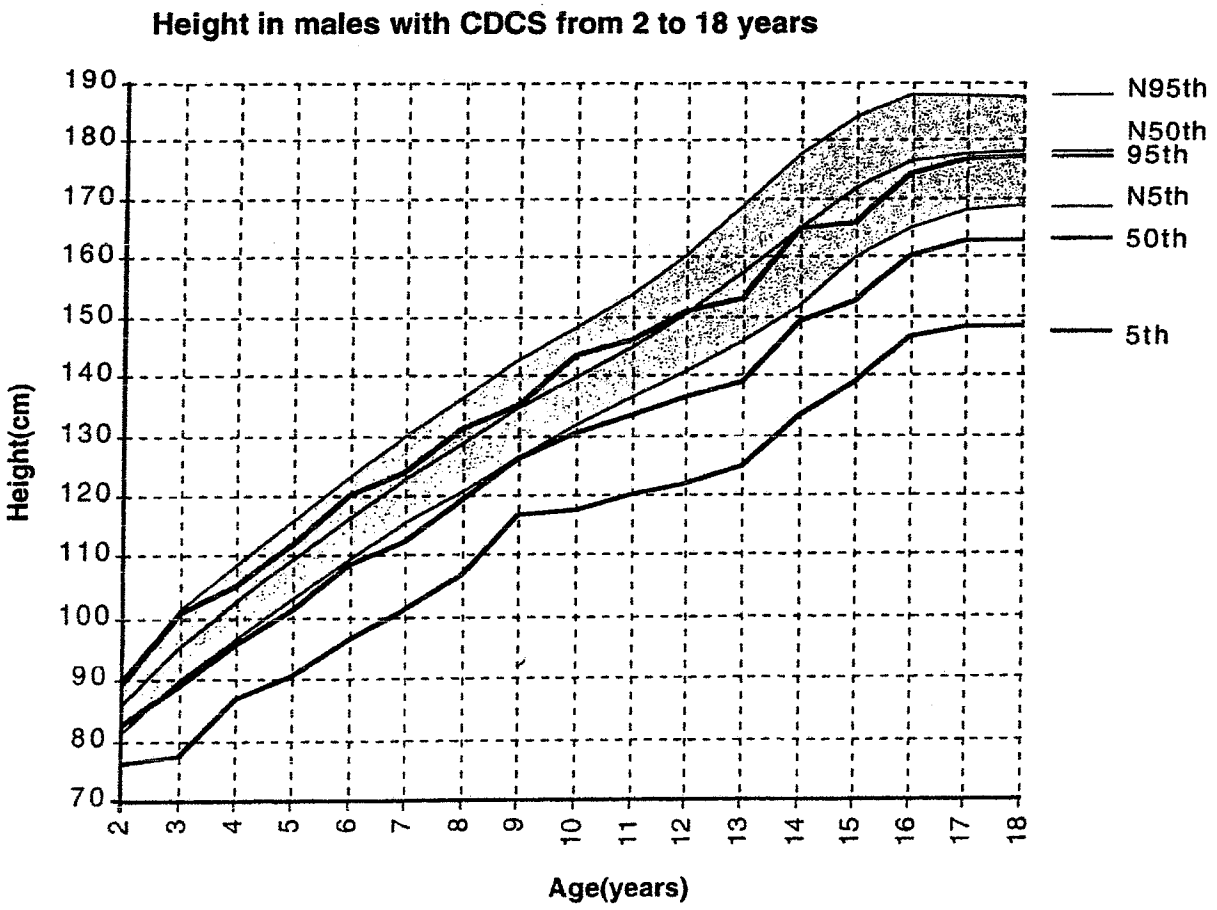

Fig. 8. Height in males with CDCS from age 2 to 18 years (**thick lines**). The normal growth curve (**thin lines**) is shaded.

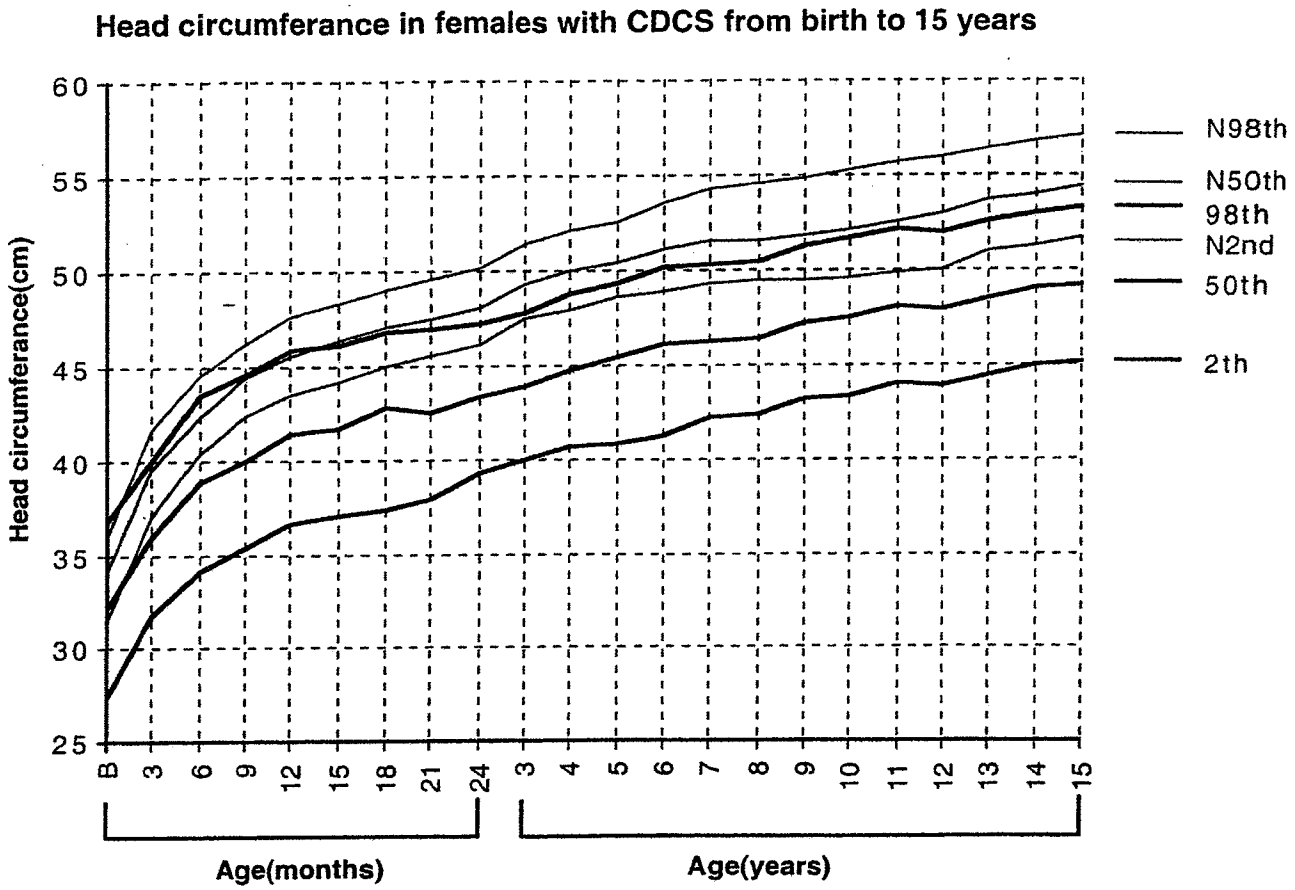

Fig. 9. Head circumference in females with CDCS from birth to age 15 years (**thick lines**). The normal growth curve (**thin lines**) is shaded.

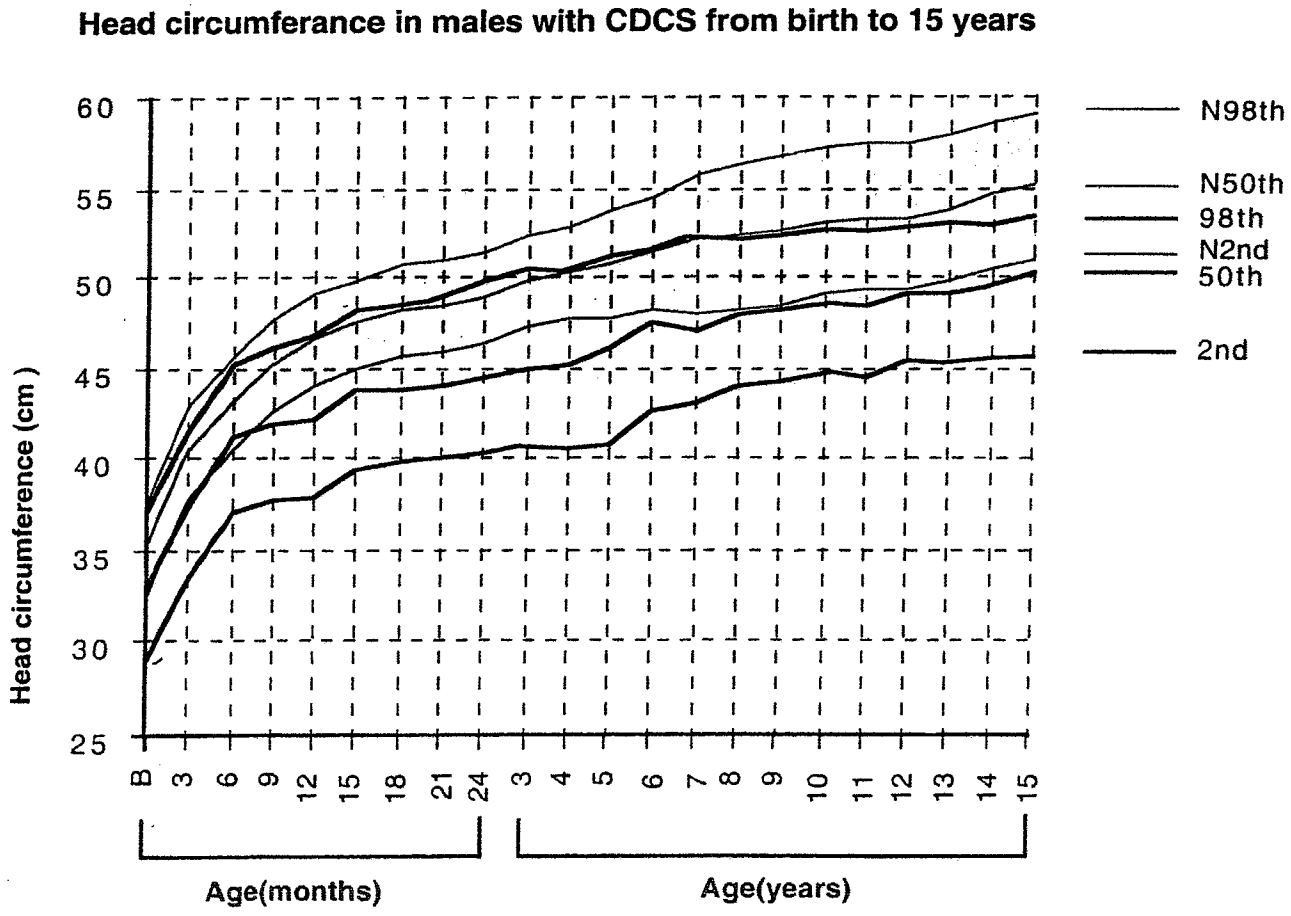

Fig. 10. Head circumference in females with CDCS from birth to age 15 years (**thcik lines**). The normal growth curve (**thin lines**) is shaded.

ever the height, especially in the males, is less compromised than the weight compared with the reference population. This observation is consistent with the reports by others that noted that patients with CDCS have a slender shape [Niebuhr, 1979; Cerruti Mainardi, 1987]. Therefore, during the first two years of life, poor growth is usually diagnosed since the height and weight parameters are not consistent with each other. Poor feeding and gastroesophageal reflux, which is a common complaint by parents during the early years, may be contributing factors to the low weight compared to height. That slender shape continues with age, particularly for the male, and might also be explained with constitutional factors related to the syndrome. However, after age 2 years, the slowed growth in height usually results in a small stature at adulthood with microcephaly as compared with the entire size of the body.

The apparently better figures for length in infants with CDCS compared with the figures for height for older children may be an artifact of sampling, but it could also reflect an increase in active treatment of failure to thrive and feeding difficulties. During the 1980s and 1990s, several papers have stressed the importance of intervention to prevent additional impairment due to malnutrition in the developmentally delayed [Wodarski, 1985; Simila and Niskanen, 1991; Amundson et al., 1994]. However, the observed reduced growth in children over 10 years may have been exaggerated because they were few in numbers.

Although there is a skewed distribution of age (more time points for younger ages than older ages), these charts are still informative for clinicians and parents who wish to compare the growth of a child with CDCS with the growth of others with the syndrome. The skewed distribution of weight in children with CDCS toward low weight must be considered when assessing an individual using these reference charts. A child's weight may be within normal limits for CDCS but below the general population weight for height or above the normal range for CDCS but not above the general population weight for height. Therefore, it is important that the CDCS-specific charts are used in conjunction with reference data for the general population.

Anthropometric data has been reported previously by others. Niebuhr [1979] determined growth parameters of 35 individuals with a 5p- karyotype. Data from patients of different ages were combined, and different statistical methods were used making comparisons difficult with the data presented here. Nevertheless, weight seemed to be more affected than height with the head circumference being the most significantly affected with respect to the norm. Z-scores for height and weight were around −2, whereas Z-scores for head circumference were between −3 and −4. Collins and Livingstone [1997] determined growth parameters of 40 individuals with CDCS, and they stated that most but not all of their probands were small in stature and of low weight. However, no specific data were provided. The data presented here provide a significant improvement in the number of patients and time points that are described by others [Niebuhr, 1979; Collins and Livingstone, 1997].

These international CDCS growth curves, taken in conjunction with other normative data, will be helpful to physicians as well as caregivers and parents who are monitoring their child's growth. From the growth curves, it is clear that although CDCS infants are smaller than normal at birth, there is slow but consistent growth throughout childhood. Knowledge that children with CDCS will usually be small and focusing on the proportional nature of the height and weight may minimize unnecessary interventions. This growth information should allow physicians to make more informed recommendations about treatments.

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