

Analysis of Neurofibromatosis Type 1 (NF1) Children and Adolescents' Weight, Length and Head Circumference - A Cross-Sectional Study

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Abstract

Objective: The main purpose of this study was to carry out a clinical evaluation about anthropometric measurements (weight, length and head circumference) of a group of Brazilian Neurofibromatosis type 1 (NF1) children and adolescent individuals.

Patients and Methods: This was an observational and cross-sectional study. The patient sample included 146 children and adolescents of both sexes; aged zero to 19 years and each individual was measured just once. The dispersion of the anthropometric measurements was evaluated and their position in relation to the percentiles of standard WHO growth charts were used as a reference in pediatric practice.

Results: Short stature was present in 17.1% of the subjects; the higher frequency was observed in males aged 5-19 years (20.4%). The heritability of NF1 in patients with short stature was not statistically significant (p value >0.05) when we compared the individuals that presented short stature or not and positive or negative familial history of NF1 using a 2x2 Table (χ^2 analysis). In males, the percentage of low birth weight was 5.5% while in females it was 1.4%. The percentage of underweight individuals was 3.7%. Macrocephaly was observed in 25.0% of boys and girls aged 0-5 years.

Conclusions: In a group of Brazilian NF1 patients, we found cases of short stature even in the first five years of life. Weight below percentile 50 was predominant in girls aged 0-5 years (72.2%) and head circumference above percentile 50 with macrocephaly was also present. Birth's mean weight and length below average apparently are not general characteristics of NF1 individuals from Brazil.

Keywords: Neurofibromatosis; Children; Adolescent; Body weight; Body length; Cephalometry

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting approximately 1 in every 3000 people and is mainly characterized by "café au lait spots", ephelides, Lisch nodules and neurofibromas as well as other signs and symptoms. It is mainly caused by heterozygous mutations in the *NF1* gene located on chromosome 17q11.2. Almost 50% of affected individuals have *de novo* mutations [1,2]. There are only a few reports in the literature about anthropometric data of NF1 patients [3-8]. Short stature and macrocephaly have been commonly observed in these studies. Accordingly, Spiegel et al. [9] reported overgrowth on NF1 children that presented microdeletions in the *NF1* gene.

During clinical follow-up of NF1 patients registered in the National Center for Neurofibromatosis (CNNF), we observed that many of them were slim and shorter than non-NF1 pediatric patients. Our study was designed to better understand part of the anthropometric profile (weight, length/stature and head circumference) of Brazilian NF1 child and adolescent patients' from CNNF.

Patients and Methods

An observational, cross-sectional study was carried out with a sample of children and adolescents of both sexes, aged zero to 19 years, registered in the CNNF database (www.cnnf.org.br) and followed-up on the Medical Genetics Service of Martagão Gesteira Pediatric Institute (IPPMG), at the Federal University of Rio de Janeiro (UFRJ). The patients that participated in this study were all included in the database and platform that we have been developing named DataGenno [10].

The clinical investigation was conducted according to the principles described in the Resolution 196/96 of the National Health Council (Ministry of Health, Brazil) and in The Code of Medical Ethics (1988;

articles 122-130). The study was also approved by the institution's Ethics and Research Committee. Patients were aware of the study objectives and their legal guardians signed an informed consent form.

Young patients who did not meet the diagnostic criteria for NF1, patients with incomplete data in the CNNF database and patients with acute or chronic illness at the moment of clinical examination, because of the possibility of weight change, were excluded from this study.

Each patient was measured just once and this one measurement is what appeared on the standard growth charts from the WHO [11]. Measurements of each patient were taken by only one healthcare professional and repeated in order to check the intra-observer reliability. The instruments used were a 1mm resolution stadiometer (Sanny), a 50 g resolution digital scale (Filizola) and a 1 mm resolution metal tape measure flexible and extendable, suitable for anthropometric measurements. The results were analyzed by measurements of central tendency (mean and median) and dispersion (standard deviation; SD).

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Received March 27, 2015; **Accepted** April 09, 2015; **Published** April 15, 2015

Citation: Ribeiro MG, Coutinho MP (2015) Analysis of Neurofibromatosis Type 1 (NF1) Children and Adolescents' Weight, Length and Head Circumference - A Cross-Sectional Study. *Pigmentary Disorders* 2: 182. doi:10.4172/2376-0427.1000182

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Frequency measures were used to categorize variable's analysis. The nonparametric χ^2 test and Fisher Exact test were used for exploratory analyses and significance level was considered for p value <0.05.

Weight, length/stature and head circumference measurements were plotted on standard growth charts from the WHO Multicentre Growth Reference Study [11] to observe dispersion and positioning of the values in relation to the standard chart percentiles. We considered short stature when stature was below 3rd percentile; overweight when weight was above 97th percentile and macrocephaly when head circumference was above 97th percentile. The measurements were not serial of the same patient in different periods of time but rather a compilation of cross-sectional measures taken at various time points. Birth growth parameters were obtained from the medical records of each patient.

A total of 184 patients were initially selected to participate in the study. We excluded 17 patients (infants) who still did not meet the diagnostic criteria for NF1, 16 patients (non infants) who had incomplete data in the database and did not return for clinical follow-up, three patients because of chronic diseases (one patient with multidrug-resistant tuberculosis, who remained in treatment, and two patients with a history of severe asthma and multiple episodes of hospitalization, including in intensive care unit) and two other patients because of acute disease at the moment of examination.

Results

A total of 146 patients were evaluated; 85 males and 61 females. The patients' mean age was 7.9 years (0-19 years, SD $\pm$ 4.8); 8.5 years for females and 7.5 years for males. Sixty-eight subjects had positive NF1 familial history (68/145; 46.9%) based on tracking the family for NF cases. We have identified two patients with a severe outcome, one with a dorsal plexiform neurofibroma tumor and another with a plexiform neurofibroma tumor in the right lower limbs.

The statistical analysis of weight, length/stature and head circumference measurements taken on male and female NF1 patients aged 0-5 years and 5-19 years are shown on Tables 1 and 2. Individual measurements as well as mean weight, length/stature and head circumference of both age groups were plotted on standard WHO growth charts [11]. Figure 1 shows the data (weight, length and head circumference) of boys and girls aged 0-5 years, and Figure 2 shows the data (weight and stature) of male and female patients aged 5-19 years.

Among the 146 individuals studied, we observed short stature in 25 subjects (25/146, 17.1%). Short stature as observed in 17.6% of the boys (15/85) and in 16.4% of the girls (10/61). There was no significant difference between boys and girls related to the presence of short stature (p value >0.05). We compared the individuals that presented short stature or not and positive or negative familial history of NF1; the heritability of NF1 in patients with short stature was not statistically significant (p value >0.05). A total of eight patients presented tall stature.

	0 to 5 years					
	Boys			Girls		
	Mean	Median	SD	Mean	Median	SD
Age (months)	31.0	27.5	$\pm$ 16.37	30.41	31.0	$\pm$ 16.92
Weight (Kg)	13.96	13.0	$\pm$ 4.48	12.21	11.25	$\pm$ 4.63
Length (cm)	81.20	92.0	$\pm$ 10.87	86.05	87.0	$\pm$ 11.21
Head Circumference (cm)	48.48	50.5	$\pm$ 4.52	48.2	49.25	$\pm$ 3.14

Table 1: Weight, length and head circumference measurements from male and female NF1 patients aged 0-5 years.

	5 to 19 years					
	Male			Female		
	Mean	Median	SD	Mean	Median	SD
Age (years)	10.96	10.14	$\pm$ 3.08	10.42	10.95	$\pm$ 4.12
Weight (Kg)	25.22	25.0	$\pm$ 4.02	26.27	26.0	$\pm$ 4.25
Length (cm)	132.1	127.0	$\pm$ 15.95	135.20	133.0	$\pm$ 17.76

*The WHO growth charts for Head Circumference aren't available for this age group

Table 2: Weight and length measurements from male and female NF1 patients aged 5-19 years.

In the present study, there was a predominance of weight measures under percentile 50% in girls aged 0-5 years (p value=0.03). It was of non-significance the predominance of weight measures under percentile 50% in individuals for both sexes considering the whole sample (p value >0.05). The total of overweight cases considering 0-19 years was six (6/81; 7.4%) and of underweight, three (3/81; 3.7%).

The male group's mean birth weight was 3.180 g (2.300 to 4.330 g; SD $\pm$ 0.430 g) and mean birth length was 50.7 cm (46.0 to 56.0 cm, SD $\pm$ 2.3 cm). The female group's mean birth weight was 2.920 g (2.040 to 4.400 g, SD $\pm$ 0.340 g) and the mean birth length was 47.1 cm (36.0 to 52.0 cm, SD $\pm$ 2.7 cm). The frequency of low birth weight was 5.8% (5/85) in the male group and 2.3% (1/61) in the female group.

Macrocephaly was present in the first five years of life in 29.6% (8/27) of male patients and in 17.6% (3/17) of female patients. Macrocephaly seemed to be more frequent after the fifth year of life (p value=0.0002).

Discussion

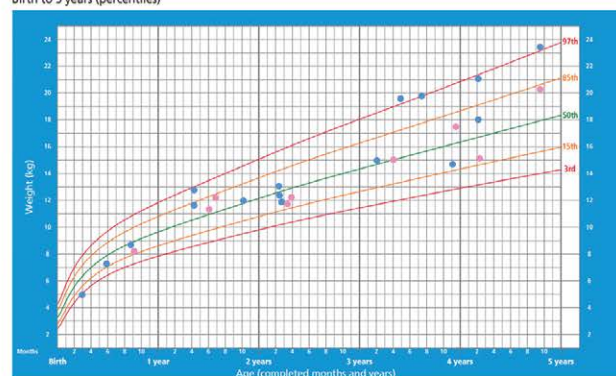
As far as we know, this is the second study of Brazilian NF1 patients related to weight, length/stature and head circumference. The first study was carried out by Viana et al. [7] and 23 individuals were investigated. In our study, we have a higher cohort of patients compared to the previous study and this might enhance the knowledge on Brazilian NF1 characteristics. Even with sample size differences, the findings of high average weight in males (Tables 1 and 2) are different from the findings of Clementi et al. [3], who observed a slight weight increase in females compared to males, mostly in adulthood, independent of the disease severity.

Some authors have shown that short stature is a common finding in NF1 [3-8]. The percentage of short stature reported in the present study (17.1%) was lower than in other studies, such as 25.5% reported by Carmi et al [4], 24.4% reported by Viana et al. [7] and from 20% to almost 50% reported by Clementi et al. [3]; but closer to Suzudek et al. [5] who observed a percentage of 13%. The reported variation of short stature frequency in several studies may be explained by the difference between the populations' ethnical origin: Clementi et al. [3] evaluated Italian patients, Rafia et al. [6], Spanish patients and Szudek et al. [5], Caucasian patients from North America. Unlike Raffia et al. [6], who observed short stature in girls after 10 years, we observed the occurrence of short stature since the first five years of life (Figure 1). However, given the fact that same cases of NF1 cannot be diagnosed in very young children by standard clinical diagnostic criteria [12], it is possible that the young children who are included in the study are more severely affected than the older children. On the other hand, Boulanger and Larbrisseau [13] reported 3.4 years as the mean age diagnosis of Neurofibromatosis type 1. Other factors such as diet and environmental changes could also be affecting the patient's weight [1].

Carmi et al. [4] observed that short stature was more frequent

Weight-for-age BOYS

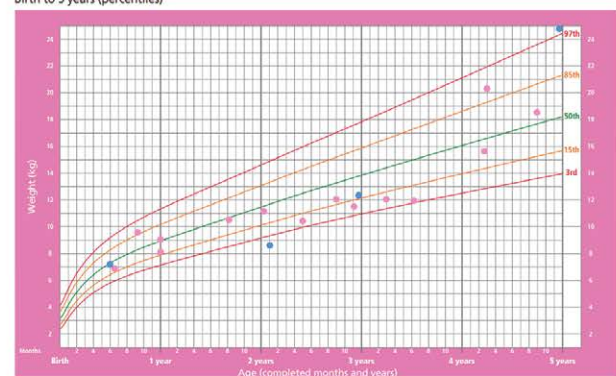
Birth to 5 years (percentiles)



A

Weight-for-age GIRLS

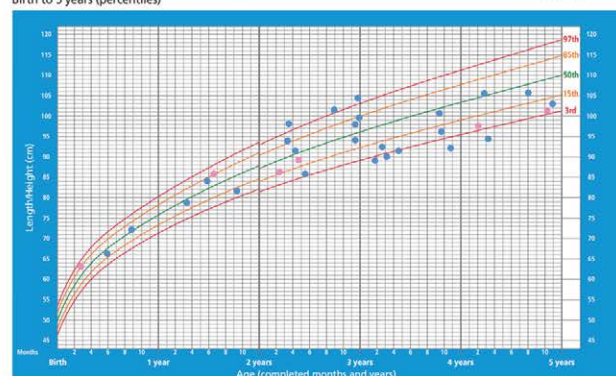
Birth to 5 years (percentiles)



B

Length/height-for-age BOYS

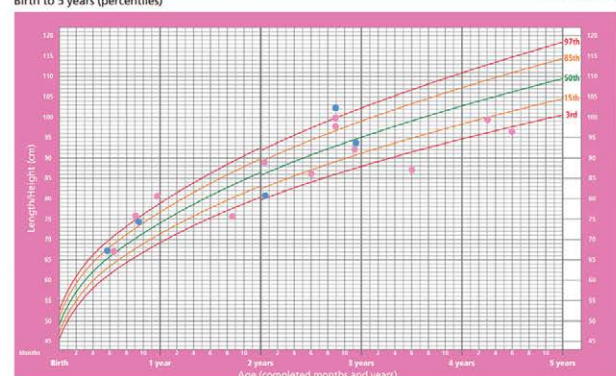
Birth to 5 years (percentiles)



C

Length/height-for-age GIRLS

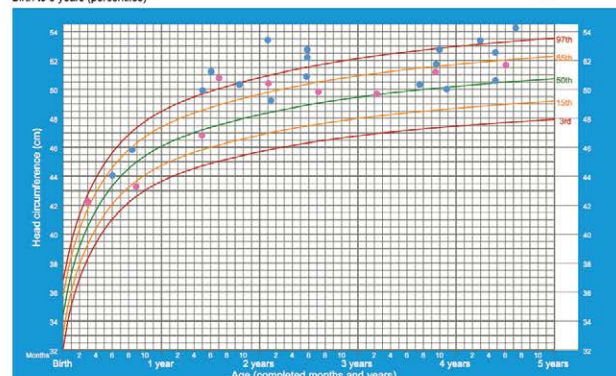
Birth to 5 years (percentiles)



D

Head circumference-for-age BOYS

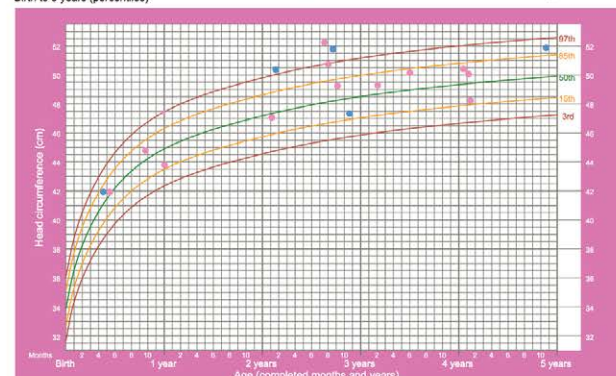
Birth to 5 years (percentiles)



E

Head circumference-for-age GIRLS

Birth to 5 years (percentiles)



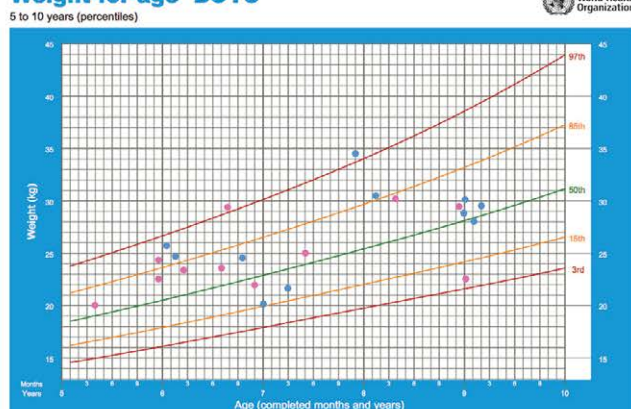
F

Figure 1: Weight, length and head circumference percentiles of NF1 patients of both sexes aged 0-5 years. Weight for boys (A) and girls (B), height for boys (C) and girls (D) and head circumference for boys (E) and girls (F). Blue circle, familial cases; pink circle, index cases. The 3rd, 15th, 50th, 85th and 97th percentiles are represented with lines of different colors in the graphs.

in individuals with familial history of NF1. However, according to statistical analysis, the cases of short stature reported in our study were not related to positive familial history of NF1. We should stress

that neither Carmi et al. [4] nor our group had evaluated parents height, in order to see if short stature could be inherited only by the genetics related to parental contribution. Despite the possibility of

Weight-for-age BOYS



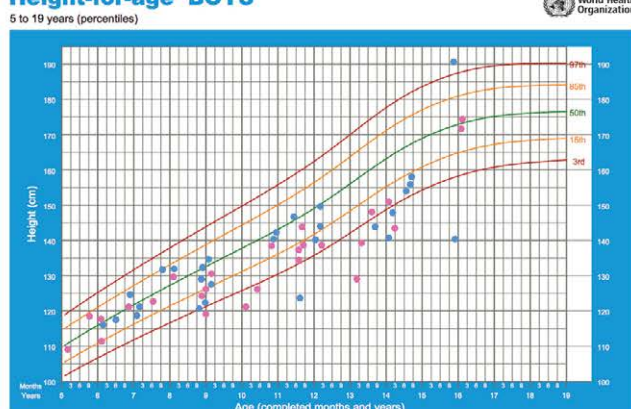
A

Weight-for-age GIRLS



B

Height-for-age BOYS



C

Height-for-age GIRLS



D

Figure 2: Weight, length and head circumference percentiles of NF1 patients of both sexes aged 5-19 years. Weight for males (A) and females (B), height for males (C) and females (D). Blue circle, familial cases; pink circle, index cases. The 3rd, 15th, 50th, 85th and 97th percentiles are represented with lines of different colors in the graphs.

hormonal change episodes, about one third of NF1 patients present short stature without evidence of hormone deficiency or any endocrine disorder [1,8]. Several endocrine abnormalities have been described in NF1, such as precocious puberty, acromegaly, pheochromocytoma, hyperparathyroidism, hyperthyroidism and multiple endocrine types of cancer. However, short stature is the most common endocrine disorder reported [1,8]. It was thought that all NF1 endocrine changes would be assigned to central nervous system (CNS) tumors affecting both hypothalamic and pituitary functions. However, other causes have been described, among them, slowly growing hamartomas and cellular mechanisms where neurofibromin, the protein encoded by *NF1* gene, could interfere in transcription regulation affecting signalling pathways that could finally cause endocrine alterations. However, the molecular mechanisms associated to this event are not very clear [1].

As observed in previous studies, we reported cases of tall stature in the group of NF1 patients analyzed. According to Spiegel et al (2005), this finding might be related to 1.4/1.2 Mb microdeletions in the *NF1* gene. Unfortunately, our patients were not molecularly tested for microdeletions.

In our study, we also reported a significant predominance of weight

measurements under percentile 50% for females aged 0-5 years, but when we compared females and males in general, it was not significant. Clementi et al. [3], in a study where adult NF1 patients from Northeast Italy were evaluated, reported a slight weight increase (especially in females) compared to normal individuals, regardless of disease severity. NF1 patients with below average weight were not reported on previous studies.

In the present study, we identified only a few NF1 patients who presented below average birth weight and length. According to this finding, we suggest that the distribution of birth weight and birth length for both males and females was not significantly different from that of the general Brazilian population. We found no study that had described birth weight and length of NF1 patients in the literature. Patients analyzed in this study showed no complications or health problems throughout life that could hinder growth and weight gain. Other authors had not mentioned the existence of disease recurrence in their studies [3-8].

The macrocephaly incidence reported in this study is in accordance with what has already been described in the literature for both sexes [3,5,6,14]. However, unlike Ricardi [15] who reported head

circumference increase only after age 5, we verified a mean frequency of macrocephaly of 25.0% in patients of both sexes who presented it during the first five years of life. Although it may be a result of the presence of tumors, some authors described macrocephaly as a result of brain size enlargement [1,15].

Some study limitations, such a small number of patients aged 0-5 years (49/146, 33.5% of the sample), lack of information on the socio-economic status of the patients in the CNNF database, and retrospective data related to birth measures could have influenced the results observed in our study. Even with some limitations, the anthropometric data obtained from 146 patients will stimulate the production of specific NF1 Brazilian population growth charts, throughout a multicentre study carried on collaboration with several specialized health services from different Brazilian regions. Such charts will be useful to establish a profile of NF1 patients and proper weight, length/stature and head circumference monitoring during their lives.

Conclusion

In our study with NF1 patients, we identified the presence of short stature; weight below percentile 50 predominant in girls aged 0-5 years and head circumference above percentile 50. Based on our results, birth's mean weight and length below average are not general characteristics of NF1 patients. Finally, we believe that our study can shed some light in the morphological analyses of NF1 patients helping in their care and follow-up.

Acknowledgements

We are thankful to the National Center for Neurofibromatosis (CNNF), the Medical Genetics Service of Martagão Gesteira Pediatric Institute (IPPMG) from Federal University of Rio de Janeiro (UFRJ) and to the NF1 patients. We also thank Eduardo Braga Ferreira Junior and Júlio Betta for helping with the design of standardized WHO graphs for this study. FFC is supported by the Maeve McNicholas Memorial Foundation.

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