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Canalization of growth between 2 and 5 years of age in apparently healthy children with short stature at age 2 years

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ABSTRACT

Introduction. Newborn size is associated with intrauterine conditions. Genetic potential is expressed later; the canalization of growth is typically described up to 24 months of age.

Objective. To describe the canalization of growth between 2 and 5 years of age in apparently healthy children with short stature at age 2 years.

Population and methods. Retrospective, cohort study. Children seen at a community teaching hospital between 2003 and 2019, who had a Z-score for height below -2 SDs for age and sex at age 2 years were included. Infants born preterm, with a low birth weight, and chronic conditions were excluded. Growth patterns were assessed. Canalization was defined as reaching a normal stature for the general population.

Results. Sixty-four children were included; 37 (58%) showed canalization of growth at 5 years old (20 at 3 years, 8 at 4 years, and 9 at 5 years). The growth rate at 3 and 5 years of age was significantly higher among those who showed canalization compared to those who did not; a similar trend was observed at 4 years of age. Among 27 children with short stature at 5 years of age, 25 had at least 1 annual growth velocity below the 25th centile.

Conclusions. Most apparently healthy children with short stature at 2 years old reached a normal stature at 5 years old. The annual growth velocity allows to detect children at risk of not showing canalization.

Key words: *canalization, growth and development, growth failure, growth charts.*

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INTRODUCTION

Growth during childhood is regulated by multiple factors that interrelate in an intricate manner. Newborn size is mainly a reflection of intrauterine conditions. The genetic potential for growth begins to be expressed in the postnatal life. At around 2 years of age, most children are positioned in a growth channel in accordance with their genetic potential, a phenomenon known as canalization.[2,3] The classic concept of canalization of growth at 2 years of age is based on studies showing very low concordance between child and parent size at birth, and substantial change during childhood, with a correlation coefficient of approximately 0.5 at 2–3 years.[4] After this period, it is expected that the child's growth curve will remain within this growth channel if the child's health status is adequate.[5,6]

However, according to observations from clinical practice in our setting, some children mayreach their genetic channel at a later age. Demonstrating the canalization of growth in children between 2 and 5 years of age would reduce family concerns and costs associated with unnecessary ancillary tests and consultations. To date, we have not found any study that addresses this phenomenon.

The objective of this study was to describe the canalization of growth between 2 and 5 years of age in apparently healthy children with short stature at age 2 years.

POPULATION AND METHODS

This was a retrospective cohort study in children younger than 5 years of age followed-up in a community teaching hospital between January 1st, 2003 and December 31st, 2019. In this hospital, pediatricians and subspecialists care for children whose families have health coverage through a private or a social heath care insurance.

Children with short stature at age 2 years, defined as a height Z-score below -2 standard deviations (SDs) for age and sex, were included using the growth standards established by the World Health Organization (WHO) and the WHO Anthro Software®, an anthropometric calculator.[7,8]

The following exclusion criteria were defined: lack of clinical follow-up (less than 1 assessment per year during the first 5 years of life); prematurity (less than 37 weeks of gestation); fetal growth restriction (birth weight of less than 2500 grams or below the 3rd percentile for gestational age);[9] low weight (weight-for-height Z-score below -2 SDs), and chronic diseases (celiac disease, hypothyroidism, chronic kidney disease, recurrent bronchospasm requiring inhaled corticosteroids, liver disease, heart disease, genetic syndromes, cancer, and neurological or metabolic diseases) at 2 years old.

Data were collected from electronic medical records (EMRs), which includes an electronic repository of controlled data based on the SNOMED clinical terms. The completeness of weight and height data in this registry is 72%, which indicates a high quality registry.

In the absence of reliable data on parental height, canalization was defined as reaching a normal stature for the general population (Z-score ≥ -2 SDs) during the follow-up period. Height data were considered at 2, 3, and 4 years ± 6 months, and at 5 years ± 12 months, according to the usual frequency of health checkups for healthy children. For those with more than 1 annual height measurement, the value obtained closest to 2, 3, 4, and 5 years of age was taken into account. The annual growth velocity was assessed; a growth velocity below the 25th centile for age and sex, was considered suboptimal.[10,11]

The number of ancillary tests performed was analyzed: general (hemoglobin, urea, creatinine, alkaline phosphatase, calcium, phosphorus, gamma globulin, urinary density, thyrotropin, anti-transglutaminase and anti-gliadin antibodies), specific (insulin-like growth factor-1 and karyotype), stimulation tests (growth hormone after stimulation tests), and imaging tests (X-ray of the left hand and wrist, and computed tomography and magnetic resonance imaging of the brain), and the number of consultations with pediatric subspecialties (endocrinology, genetics, nutrition, and others related to the condition). The presence of chronic diseases diagnosed between 2 and 5 years of age was assessed.

Categorical variables were expressed as absolute values and percentage, and continuous variables, as mean and SD. The 95% confidence interval (CI) was calculated when applicable. The χ^2 test was used for the analysis of categorical variables and the Wilcoxon test, for continuous variables. A value of $p < 0.05$ was considered significant. The statistical software package used was Stata® 15.

The study was approved by the Ethics Committee for Research Protocols of the institution (no. 5125).

RESULTS

A total of 231 children with short stature at 2 years of age were identified; 94 had been born preterm or had fetal growth restriction, 69 had been diagnosed with a chronic disease, and 4 had a record of low weight for height; they were all excluded. A total of 64 apparently healthy children with a height Z-score below -2 SDs at 2 years of age were included; 38 were males.

Table 1 and *Figure 1* show the annual height measurements beween 2 and 5 years of age. Canalization was observed between 2 and 5 years of age in 37/64 children (58%, 95% CI: 43-70). The difference in the Z-score between the measurement at 2 and 5 years was 0.68 SD (95% CI: 0.5-0.9, $p < 0.01$). No significant differences were observed in terms of sex. The median time until canalization was reached was 36 months (95% CI: 23-43). Out of 37 children who canalized, 20 did at 3 years; 8, at 4 years; and 9, at 5 years.

The annual growth velocity (mean ± SD) in the group with and without canalization was 9.7 ± 3 and 7.4 ± 1.1 cm/year at 3 years ($p < 0.01$), 7 ± 2.2 and 6.7 ± 1.9 cm/year at 4 years ($p = 0.4$), and 7.5 ± 1.7 and 5.7 ± 0.9 cm/year at 5 years ($p < 0.01$), respectively. Out of 27 children who did not reach canalization, 25 had at least a period of suboptimal growth rate during the study. The analysis of the growth pattern of the 2 remaining children showed that the height Z-score in 1 of them was -3.6 SDs at the beginning of the study, and height at 5 years of age showed a 1.4-point gain (Z-score: -2.2 SDs); the other child reached a height Z-score of -2.03 SDs, and this was not considered canalization as per the study definitions.

In relation to clinical course, 1 of the children was diagnosed with growth hormone deficiency at 5 years of age and showed abnormal growth rates and a short stature at 5 years. No other endocrine or general conditions were observed in either group (short stature at 5 years and late canalization) during the study period.

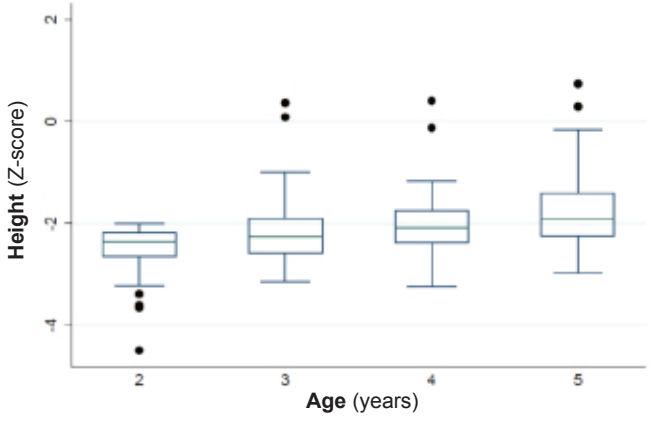
Table 2 shows the number of consultations and tests performed. Among children with short stature at age 5 years, a higher number of general tests and consultations with subspecialists were carried out than among those with canalization of growth.

Table 1. Height (mean ± SD) and height trajectory in apparently healthy children at 2 years of age (n = 64)

Parameters	2 years	3 years	4 years	5 years
Age (months), mean ± SD	24.3 ± 2.5	36.3 ± 2.4	47.5 ± 2.7	59.7 ± 5.1
Height (Z-score), mean ± SD	-2.48 ± 0.4	-2.12 ± 0.6	-2 ± 0.6	-1.79 ± 0.7
Short stature, n (%)	64 (100)	44 (69)	36 (56)	27 (42)

SD: standard deviation.

Figure 1. Height in apparently healthy children at 2 years of age (n = 64). Height Z-score as per annual measurements



DISCUSSION

In this study, more than half of the children with short stature at 2 years of age showed growth canalization and reached a standard stature for their age and sex at age 5 years. Short stature is often a cause for concern for families and pediatricians. However, some healthy children may require a few months or years longer than what has been typically described to achieve a normal stature, without intervention.

In a cohort of more than 10 000 healthy children, it was observed that 2% to 10% of them had crossed 2 or more height percentiles between 24 and 60 months of age; this finding may be due, at least in part, to the canalization of growth at a later age.[12] It would be very useful to have further studies looking at factors that may predict this phenomenon. According to the results of this study, the lack of canalization at 4 years of age could be considered a risk factor. In a recent article, Lejarraga described that girls have a greater tendency to remain in the same growth channel compared to boys.[5] In our sample, no differences were observed between sexes in terms of canalization of growth.

There is a group of children who experience a delay in the transition from growth during infancy to childhood in association with circumstances such as malnutrition, chronic diseases or unfavorable socioeconomic conditions.[13–15] Unlike what occurs at other ages, this phenomenon is not followed by a phase of catch-up growth and could have an irreversible impact on final stature.[16] The identification of factors that allow differentiating children with canalization of growth between 2 and 5 years of age from those with other conditions with potential impact on their final stature would allow designing strategies to prevent this consequence. In this regard, the findings of this study continue to underscore the importance of growth velocity as a key guide to differentiate normal from pathological growth.[17] The vast majority of children with short stature at 5 years of age had at least a suboptimal growth velocity between 2 and 5 years old. The analysis of the 2 cases with an adequate growth rate revealed that these children showed a clinically substantial catch-up growth (not suggestive of underlying diseases), although their height was not sufficient to consider canalization of growth. As noted in the medical literature, children with height Z-scores below -3 SDs may require a more comprehensive initial assessment.[18,19]

When seeing a child with short stature, pediatricians face the challenge of establishing whether this is a normal variant or a sign of a disease, which in many cases requires ordering other tests and subspecialty consultations.[20,21] Not surprisingly, this study showed a wide variety of ancillary tests performed and a significant number of children were assessed by pediatric subspecialists. It is interesting to note that children who did not canalize underwent a higher number of tests than those who did. This is consistent with pediatricians' interest in trying to findx for underlying diseases, with greater emphasis on those who did not exhibit the expected growth. However, despite these efforts, the cause of short stature and lack of canalization of growth has not been elucidated. Most likely, some cases may be explained by entities that are not observed in laboratory tests, such as psychosocial growth retardation.[22,23] It would be important to generate a multidisciplinary discussion to review the approach to the assessment of growth in these children in their prenatal stage and their first 2 years of life.

Table 2. Number of tests and consultations carried out in apparently health children with short stature

Tests and consultations	Children with short stature at 5 years of age (n = 27) Mean ± SD	Children with canalization of growth at 5 years of age (n = 37) Mean ± SD	*p* value*
General tests	7.7 ± 6.7	4.2 ± 5.8	< 0.01
Specific tests	0.1 ± 0.4	0.08 ± 0.3	0.6
Function tests	0.1 ± 0.4	0.05 ± 0.3	0.3
Imaging tests	0.4 ± 0.6	0.1 ± 0.3	0.02
Subspecialty consultations	3.4 ± 3.5	1.4 ± 2.5	< 0.01

** χ^2 test.*

In addition, the systematic request of specific ancillary tests or consultations in children with short stature may not be justified. A retrospective analysis of more than 1300 children with short stature showed a 1.3% incidence of disease in children whose history and physical examination did not show any findings.[24] This study found a high percentage of children who showed canalization of growth between the ages of 2 and 5 and also the absence of new diagnoses of underlying diseases in children with a normal growth velocity. Based on these findings and on similar studies in other populations, it would be possible to consider a change in the assessment of children with short stature. When a comprehensive history taking and clinical assessment at 2 years of age rule out the presence of disease indicators, it would be reasonable to continue clinical follow-up for a few years, with potential positive consequences in relation to health care system access and costs, and less stress for children and their families.

It should be noted that this study excluded children who had been born preterm, had a low birth weight or chronic diseases at 2 years of age. These groups are at increased risk for a dexlay in the transition from growth during infancy to childhood.[14] When indicators of underlying disease are present, an early diagnosis and intervention are necessary to prevent consequences in final stature.[25] In addition, it is also worth considering that the population of this community teaching hospital has favorable socioeconomic characteristics, and that food insecurity and adverse socioeconomic conditions are also risk factors for growth retardation.[15]

Catch-up growth in children with fetal growth restriction has been extensively studied. Although it is usually described up to 2 years of age, as in the general population, a percentage of these children canalize at 3 years, and a smaller proportion do so even later.[26-28] In this study, exclusion criteria were based on birth weight –regardless of knowledge of intrauterine growth trajectories–. Therefore, some patients with a birth weight in the normal range and growth disorders in the last trimester could have been included, which may account for the postnatal catch-up growth observed in some children. Likewise, although the presence of diseases or low weight at 2 years of age in these children undergoing pediatric follow-up were considered exclusion criteria, it is possible that some of these apparently healthy children had short stature due to growth retardation in the first 2 years of life of unknown cause. If such unapparent damage had subsequently resolved, reaching a normal stature between 2 and 5 years old in these children could be due to catch-up growth following a period of growth retardation.[29]

This study has a series of limitations. First of all, due to its retrospective nature and the fact that analyzed data were obtained from an EMR, it was not possible to study parental height—key for interpreting children's growth. Secondly, the growth curve of these children during the first 2 years of life, which could provide information on the cause of lack of canalization, was not analyzed. In addition, although our sample reflects the pediatric population receiving care in a community teaching hospital, it was relatively small. Lastly, long-term studies are required to demonstrate if children reached a normal final height. However, this study may provide valuable information to consider the timing of canalization of growth in apparently healthy children.

CONCLUSIONS

Most apparently healthy children with short stature at 2 years old reach canalization of growth before 5 years old. The annual growth velocity allows to identify children at risk of not showing canalization. ■

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