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Prevalence of low birth weight, short length, and body disproportion at birth in patients with skeletal dysplasias: A retrospective study

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ABSTRACT

Introduction. Skeletal dysplasias are rare genetic disorders that affect bone and cartilage development, with a prevalence of 3.2 cases per 10,000 newborns in South America. Neonatal auxologic evaluation enables the early detection of these conditions, serving as a cost-effective and accessible tool for early intervention. This study aims to determine the prevalence of low birth weight, short body length, and body disproportion at birth in patients with a molecular diagnosis of achondroplasia (ACH), hypochondroplasia (HCH), *SHOX* gene alterations (SHOX), and familial hypophosphatemic rickets (FHR).

Population and methods. Retrospective descriptive study based on medical records of patients evaluated between 2002 and 2023 in a high-complexity pediatric hospital. Patients with skeletal dysplasia and complete anthropometric data at birth were included in the study. Weight, body length, and head circumference were analyzed, with the calculation of Z-scores according to the INTERGROWTH-21st standards and the head circumference/body length index using Argentine references.

Results. Of the 581 patients, 453 were included (ACH 62%, HCH 12%, SHOX 8%, FHR 18%); 31% of the neonates with ACH and 12% with HCH had body length < -2 SD. True macrocephaly (>2 SD) was observed in 47% (ACH) and 32% (HCH), and relative macrocephaly in 57% and 28%, respectively.

Conclusion. Low body length at birth was more frequent in achondroplasia and hypochondroplasia. Relative macrocephaly, also prevalent in these groups, highlights the value of the head circumference/body length index as a neonatal screening tool.

Keywords: *osteochondrodysplasias; auxology; newborn; achondroplasia.*

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INTRODUCTION

Skeletal dysplasias are a heterogeneous group of rare genetic diseases that affect bone and cartilage development, with a prevalence of approximately 3.2 per 10,000 newborns in South America.[1] The most recent classification comprises 771 entities, divided into 41 groups, which reflect their clinical and genetic complexity.[2]

Some of these conditions can be detected prenatally by suggestive ultrasonographic findings, such as shortness of long bones, polyhydramnios, macrocephaly, and a narrow thorax.[3] After birth, physical examination, anthropometry, and radiology are fundamental tools for their diagnostic approach. The introduction of molecular studies has enabled precision diagnosis when the clinical suspicion is well-founded.[4]

In the neonatal period, assessing weight, body length, and head circumference is crucial for categorizing the newborn as small, adequate, or large for gestational age. These measurements are relevant due to their correlation with neonatal morbidity and mortality, and they influence the decision-making of health professionals during the first days of life. However, a detailed auxological evaluation should also include the measurement of vertex-buttock length and the calculation of body disproportion indices, such as vertex-buttock/body length and head circumference/body length ratios. The presence of short limbs, defined as a vertex-buttock/body length ratio greater than +2 SD, and relative macrocephaly, defined as a head circumference/body length ratio greater than +2 SD, both according to Argentine national references, will guide the diagnostic suspicion of skeletal dysplasia.[5-7]

Within these entities, those corresponding to the most frequent consultations in specialized centers include achondroplasia (ACH; *OMIM 100800*), hypochondroplasia (HCH; *OMIM 146000*), and *SHOX* gene alterations (SHOX; *OMIM 312865*), all characterized by short stature and body disproportion of variable severity, and detected at different times of life.[8]

There are also metabolic conditions, such as X-linked dominant hypophosphatemic rickets (FHR; *OMIM 307800*), which share skeletal features with these dysplasias.[9]

Knowing the prevalence of anthropometric alterations at birth in these rare conditions contributes to their early detection, facilitates a timely diagnosis, and enables adequate clinical follow-up from birth.

In the multidisciplinary clinics of skeletal dysplasias of the Hospital de Pediatría Prof. Dr. Juan P. Garrahan, around 2,000 children from all over Argentina and countries of the region have been evaluated with a registry of more than 20 years, which includes 517 children diagnosed with ACH, 80 with HCH, 67 with SHOX and 135 with FHR, among others.[10]

This work aims to establish the prevalence of low body weight and/or body length and body disproportion at birth according to the head circumference/body length index in patients with a molecular diagnosis of ACH, HCH, SHOX, and FHR in a population of patients under follow-up in the interdisciplinary skeletal dysplasia clinics of a referral hospital.

POPULATION AND METHODS

An observational, analytical, and retrospective study was carried out. We collected anthropometric data from the medical records of children with accurate diagnoses of ACH, HCH, SHOX, and FHR who were under follow-up in the interdisciplinary skeletal dysplasia clinics at the Hospital de Pediatría Prof. Dr. Juan P. Garrahan between 2002 and 2023.

Inclusion criteria: Children of both sexes with an accurate diagnosis of ACH, HCH, SHOX, and FHR were included, provided they had anthropometric data recorded at birth (weight, body length, head circumference, and gestational age) in their medical records or health booklet.

The Z-score was calculated based on gestational age and sex according to the INTERGROWTH-21st standards.[11,12] The head circumference/body length index and its standard deviation (SD) were calculated based on Argentinean references.[7] The Z-score was calculated based on gestational age and sex.

Sex and the presence or absence of a diagnosis of maternal skeletal dysplasia were also recorded.

Low body weight and low body length at birth were below -2 SD for age and sex.

Macrocephaly was defined when the head circumference at birth was greater than +2 SD for age, according to INTERGROWTH-21st standards. On the other hand, the relative macrocephaly corresponded to the head circumference/body length index above +2 SD, according to Argentine national references.

Statistical analysis

Descriptive statistics were performed, reporting the mean and standard deviation, median, and

interquartile range, as appropriate, according to the data distribution.

The data for each group were plotted on the INTERGROWTH-21st standards for weight, body length, and head circumference in both sexes, as well as the head circumference/body length index in the Argentine references.

The size at birth of the children was analyzed comparatively according to the presence or absence of maternal involvement.

A one-sample t-test was used to assess whether the mean values of each anthropometric measure (weight, height, and head circumference) differed significantly between each group of patients with skeletal dysplasia and the general population.

The protocol was approved by the Ethics and Research of the Institution under N.° 1578, on January 30, 2024. This work did not receive external funding.

RESULTS

Of 581 patients with a molecular diagnosis of skeletal dysplasia during the study period, 453 patients with complete anthropometric data at birth were included. The distribution by diagnosis was as follows: ACH, 62% (n = 280); HCH, 12% (n = 56); SHOX, 8% (n = 36); and FHR, 18% (n = 81). The median gestational age at birth was 38 weeks (range, 28-41 weeks) (*Table 1*).

The anthropometric analysis revealed that most newborns presented a birth weight within the normal range. However, a small percentage presented a weight of less than -2 SD compared to the general population (*Figure 1*), with the following values: ACH 1.42%, HCH 1.78%, SHOX 8.33%, and FHR 6.17%. The differences in mean weight between each group and the general population were not statistically significant (*Table 2*).

Regarding body length, significant differences were observed in the groups studied. All the groups studied presented a body length shorter than the general population, with an average of 45.54 cm (-1.43 SD; p <0.0001), 47.48 cm (-0.67 SD; p = 0.0031); 45.56 cm (-1.03 SD; p = 0.003) and 48.78 cm (-0.51 SD; p = 0.023) for ACH, HCH, SHOX and FHR, respectively (*Table 3, Figure 1*). In percentage terms, 31% of children with ACH and 12% with HCH had short stature at birth (< -2 SD).

Head circumference was significantly larger in children with ACH and HCH compared to baseline values. The mean in ACH was 36.23 cm (2.33 SD; p <0.0001) and in HCH, 35.96 cm (1.87 SD; p <0.0001). In the SHOX and FHR groups, the values did not show significant differences concerning the general population (*Figure 1, Table 4*).

When analyzing the proportion of children with macrocephaly, 47% (132) of those with ACH and 32% (18) with HCH were found to have true macrocephaly. Fifty-seven percent (162) of the former and 28% (16) of the latter had relative macrocephaly.

We found no significant differences in birth size (weight, body length, and head circumference) between children of affected and unaffected mothers in any of the groups studied.

DISCUSSION

This study provides a characterization of neonatal anthropometry in a cohort of newborns with precision-diagnosed skeletal dysplasias, including ACH, HCH, SHOX, and FHR.

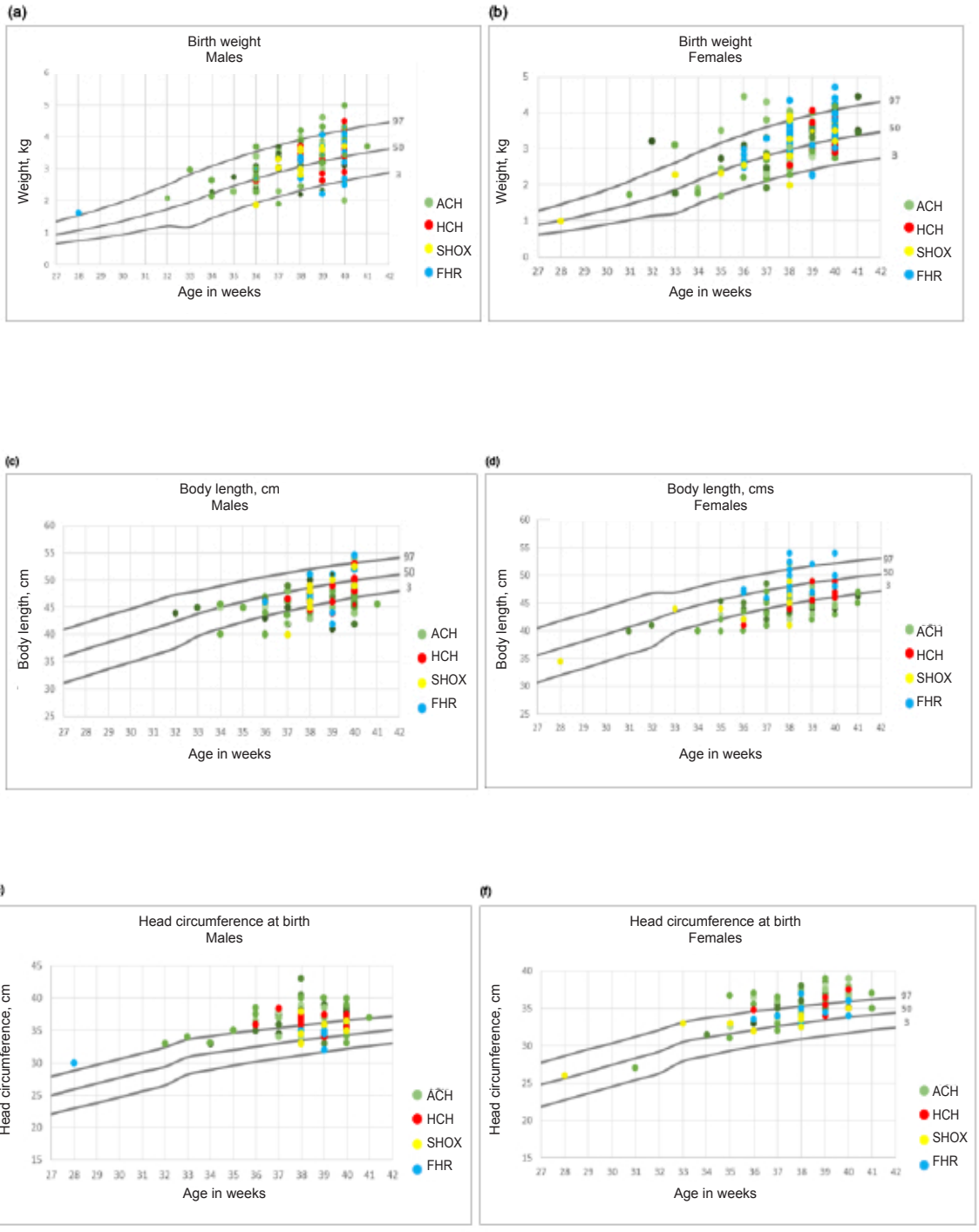
We found a high percentage of body length compromise and the presence of body disproportion secondary to relative and/or true macrocephaly, more frequent in ACH and HCH, belonging to the FGFR3 group (fibroblast growth factor receptor 3). These findings, which demonstrate the impact of skeletal conditions on neonatal anthropometry, highlight the importance of anthropometry as a key tool in early detection.

Achondroplasia and hypochondroplasia are caused by heterozygous variants in the *ACH* and *HCH* genes, which are part of the *FGFR3* gene group (*OMIM 134934*). Both are characterized auxologically by disproportionate short stature, although of variable severity; achondroplasia is the most common form and affects more than 360,000 people worldwide.[13-15] Hypochondroplasia, with a milder and more variable phenotype, can pose a diagnostic challenge in the first years of life. Although they have age-appropriate body length and head circumference at birth, a thorough auxologic evaluation reveals, in most cases, the presence of relative macrocephaly and body disproportion.[16]

The findings of our study indicate an increased prevalence of compromised body length at birth, with rates of 31% in ACH and 12% in HCH. These results are compatible with previous studies reporting reduced length at birth in individuals with ACH and HCH.[17,18]

The relatively elevated head circumference observed in 47% of neonates with ACH and 32% with HCH is consistent with the existing literature,

Figure 1. Curves of weight, body length, and head circumference at birth in males and females with skeletal dysplasias compared to the general population



In green, color patients with achondroplasia (ACH), red for hypochondroplasia (HCH), yellow for SHOX *gene alterations (SHOX), and light blue for X-linked dominant hypophosphatemic rickets (FHR).*
n = 453 (ACH: 280; HCH: 56; SHOX: 36; FHR: 81).
a, b: weight in kg; c, d: body length in cm; e, f: head circumference in cm.

Table 1. Characteristics of the sample according to diagnosis, sex, gestational age and presence of maternal diagnosis of skeletal dysplasia

Diagnosis	Patients (N)	Sex (F/M)	Gestational age (weeks) median and min/max ranges	Maternal diagnosis of skeletal dysplasia n (%)
Achondroplasia	280	142/138	38 (31-41)	16 (5.7)
Hypochondroplasia	56	5/31	39 (36-41)	7 (12.5)
SHOX gene disorder	36	17/19	38 (28-40)	21 (58.3
Hypophosphatemic rickets linked to dominant X	81	55/26	38 (28-41)	15 (18.5)
Total	**453**	**239/214**	**38 (28-41)**	**59 (13)**

F/M: female/male.

Table 2. Mean birth weight in patients with skeletal dysplasias

	Weight		
Diagnosis	**X (kg)**	**Z-score X (SD)**	**t-test**
ACH	3.217	0.47 (0,16)	NS
HCH	3.280	0.33 (0,15)	NS
SHOX	2.999	0.18 (0,17)	NS
FHR	3.206	0.62 (0,13)	NS

NS: not significant; SD: standard deviation.
ACH: achondroplasia, HCH: hypochondroplasia, SHOX: SHOX *gene disruption, FHR: X-linked dominant hypophosphatemic rickets.*

Table 3. Mean body length at birth in patients with skeletal dysplasias

	Body length		
Diagnosis	**X (kg)**	**Z-score X (SD)**	**t-test**
ACH	45.54	-1.43 (0.07)	$p = 0.0000$
HCH	47.48	-0.67 (0.23)	$p = 0.0031$
SHOX	45.56	-1.03 (0.24)	$p = 0.003$
FHR	48.78	-0.51 (0.21)	$p = 0.023$

ACH: achondroplasia; HCH: hypochondroplasia; SHOX: SHOX *gene disruption; FHR: hypochondroplasia-linked hypophosphatemic rickets; X dominant, SD: standard deviation.*

Table 4. Mean head circumference at birth in patients with skeletal dysplasias

	Head circumference		
Diagnosis	**X (kg)**	**Z-score X (SD)**	**t-test**
ACH	36.23	2.33 (0.10)	$p = 0.0000$
HCH	35.96	1.87 (0.20)	$p = 0.0000$
SHOX	33.75	0.73 (0.31)	NS
FHR	34.17	0.88 (0,19)	NS

NS: not significant; SD: standard deviation.
ACH: achondroplasia, HCH: hypochondroplasia, SHOX: SHOX *gene disruption, FHR: X-linked dominant hypophosphatemic rickets.*

which describes macrocephaly as a standard feature in these dysplasias. Macrocephaly is a valuable tool for selecting patients with HCH, even with subtle radiological signs. The introduction of the concept of "relative macrocephaly" may be a helpful tool for the early detection of skeletal dysplasias in the neonatal period.

SHOX gene alterations and X-linked dominant hypophosphatemic rickets pose diagnostic challenges in the newborn, particularly in the absence of a clear family

history. During childhood and adolescence, *SHOX* haploinsufficiency manifests with typical patterns of body disproportion and Madelung deformity.[19] X-linked dominant hypophosphatemic rickets is usually diagnosed after the second year of life due to lower limb axis disturbances and growth retardation. Affected children are born with normal body weight and length.[9]

As described in our work, neonates with FHR and *SHOX* gene deficiency did not exhibit an increased prevalence of low birth length. Therefore, a normal body length for gestational age does not exclude the diagnosis of skeletal dysplasia.

The lack of complete auxologic evaluation in the newborn could mean an underdiagnosis of skeletal dysplasias as a cause of fetal growth restriction and idiopathic short stature, as our findings show. In a previous study, the prevalence of skeletal dysplasias, such as those associated with FHR and *SHOX* gene alterations, was found to be 20% in children with a diagnosis of idiopathic short stature.[20] On the other hand, the vertex-buttock/body length ratio would provide more information about body proportions; however, it is not a common practice to measure the vertex-buttock length in the neonatal period.

The proportion of neonates weighing less than -2 SD was low in all groups studied, suggesting that birth weight may not be a sensitive indicator for detecting skeletal dysplasias. This finding is consistent with previous studies, indicating that birth weight in neonates with the conditions assessed in this study is usually within normal ranges.[21]

A notable limitation of our study is the lack of complete anthropometric data in 22% of the patients, which highlights the importance of systematically performing and recording neonatal anthropometry in the family health booklet. Additionally, we are unsure whether anthropometric measurements at birth were conducted according to established standards, which could impact the interpretation of growth data. This reinforces the need to promote strategies that ensure the application of uniform protocols already existing in neonatal evaluation, which allows an early approach to these patients.[22,23]

CONCLUSION

The prevalence of low body length at birth varied according to diagnosis, being more frequent in ACH and HCH. Relative macrocephaly was identified in a high percentage of patients with ACH and HCH, highlighting the usefulness of the head circumference/body length index as a tool for the neonatal detection of skeletal dysplasias. These findings underscore the importance of perinatal auxology as a practical, straightforward, and cost-effective tool for enhancing the early detection of these conditions. ■

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