Isolated lateralized overgrowth: clinical, radiological, and auxological characteristics of a single-site cohort of 76 cases

María J. Romaris[a], *Silvia Caino*[a], *Paula Adamo*[a], *Virginia Fano*[a]

ABSTRACT

Introduction. Isolated lateralized overgrowth (ILO), formerly referred to as hemihyperplasia/hemihypertrophy, is the overgrowth of one-half of the body to its contralateral in the absence of a recognizable pattern of malformations or genetic syndromes. Our objective was to analyze the growth clinical and radiological characteristics of patients with ILO under follow-up in a tertiary care hospital in Argentina between 1993 and 2020.

Population and methods. Retrospective, observational, single cohort study of patients with ILO.

Results. A total of 76 cases were included; 41 were males. Median years of follow-up: 5.85 (interquartile range [IQR]: 2.60–10.96), maximum: 15.76 years. Forty-eight of 76 patients had overgrowth compromising more than 1 body segment (complex ILO). The mean birth weight *Z*-score of term girls with complex ILO was +0.51 (standard deviation [SD]: 0.91) (p 0.022). Most children grew between the 50th and 97th centile of the Argentinian population height reference. The median leg length discrepancy was 1.5 cm (IQR: 1.01–2.2) in patients receiving medical treatment and 3.70 cm (IQR: 2.95–3.98 cm) in those who required epiphysiodesis. Progression of discrepancy ≤ 2 cm was observed in 75% of cases. Renal asymmetry ≥ 1 cm was observed in 8 cases; Wilms tumor was noted in 2 cases: mean age at diagnosis: 0.75 years.

Conclusions. Prenatal growth of children with ILO is normal, except in girls with complex ILO, in whom it tends to be increased. The average height of boys and girls tends to be located in high centiles with normal growth over time. Embryonal tumor screening is recommended in this group of children.

Key words: *isolated hemihyperplasia, limbs, germ and embryonal cell tumors, Wilms tumor.*

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a. Department of Growth and Development, Hospital de Pediatría S.A.M.I.C. "Prof. Dr. Juan P. Garrahan," City of Buenos Aires, Argentina.

E-mail address:
María J. Romaris: romarismariajose@gmail.com

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INTRODUCTION

Isolated lateralized overgrowth (ILO) refers to the increase in length and/or partial or total circumference of one side of the body compared to its contralateral, without a recognizable pattern of major or minor malformations, dysplasia or morphological variants.[1] Its diagnosis requires the exclusion of genetic syndromes associated with lateralized overgrowth, such as Beckwith-Wiedemann syndrome, Proteus syndrome, PROS (*PIK3CA*-related overgrowth spectrum), and hemihyperplasia-multiple lipomatosis syndrome. Approximately 30% of patients with ILO have methylation defects in *H19* and/or *KCNQ1OT1*.[2,3] The reported prevalence of ILO is 1:86 000,[4] although it has recently been described as 1:3000[5] in healthy adolescents.

An increased risk for embryonal tumors has been reported,[6] such as Wilms tumor and hepatoblastoma, with an incidence of 5.9% as indicated by Hoyme et al.[7] Therefore, screening for embryonal tumors with periodic abdominal ultrasounds is recommended until 7–8 years of age.[8]

To our knowledge, the natural history of this condition comes from case reports or small case series,[9–11] and and we did not find national or international studies describing the growth of these patients. For this reason, the primary outcome of this study was to assess the growth in height, trunk, and lower limbs of a cohort of patients with a clinical diagnosis of ILO who were receiving follow-up in our

hospital between 1993 and 2020 compared to the Argentine reference population.

The secondary outcomes were to analyze the clinical characteristics, complications, treatment, and radiological progression pattern in children with leg length discrepancy.

POPULATION AND METHODS

The medical records of patients with a clinical diagnosis of ILO assessed at the Department of Growth and Development of Hospital Garrahan (Buenos Aires, Argentina) between January 1st, 1993 and December 31st, 2020 were reviewed.

All children aged 0 to 18 years, diagnosed with ILO and who had a difference of ≥ 1 cm in length and/or circumference in 1 body segment compared to its contralateral side were included.[1] Simple ILO was defined as involvement of a single limb, whereas complex ILO was defined if at least 1 upper and 1 lower limb were affected, with the possibility of ipsilateral or crossed involvement.[7]

Cases with overgrowth associated with genetic syndromes, secondary to a congenital bone defect, without clinical records and/or without anthropometric data were excluded.

The following variables were included:

Demographic variables: sex, age, place of residence.

Auxological variables: gestational age, weight, body length, and head circumference at birth. Weight, height/body length, sitting height/length from the vertex to the buttocks, and head circumference. Length and circumference of the affected segment and the contralateral segment, calculating the difference (in cm); height of both parents.

In case of leg length discrepancy, all radiological measurements taken during follow-up were recorded.

The same observer (PA) conducted the anthropometric measurements every 6–12 months at the Department of Growth and Development using standardized techniques.[12] Height, supine length, and sitting height or length from the vertex to the buttocks were measured using Harpenden instruments (Crosswell, Crymych, Pembrokeshire, UK); head circumference was measured using a non-extensible tape measure. The long limb was considered for measuring body length. A lift was placed on the short limb to measure height until both iliac crests were level.[12] The intra-observer technical error of measurement for height, sitting height, and head circumference was 0.10 cm and 0.11 cm for supine length and sitting height.[13]

The radiological measurement was performed based on the telemetry of lower limbs with an error of measurement of 1.1 mm following the anatomic landmarks established by Sánchez.[14] The progress of discrepancy over time was analyzed following the five Shapiro growth patterns: type I, upward slope; type II, upward slope-deceleration; type III, upward slope-plateau; type IV, upward slope-plateau-upward slope; and type V, upward slope-plateau-downward.[15]

In cases with leg length discrepancy that required epiphysiodesis and had X-rays taken at adult bone age, the percentage of correction was calculated as follows: [(ID-FD)/ID] x 100, where ID means initial discrepancy and FD, final discrepancy.[16]

Clinical variables: number and location of involved segments, surgical treatment, and tumors.

Ancillary tests: laboratory results and imaging tests (ultrasound, computed tomography and magnetic resonance imaging) were recorded. In cases with renal asymmetry ≥ 1 cm by ultrasound, kidney size was compared with local references.[17]

Statistical analysis

Descriptive statistics were used, and categorical variables were expressed as absolute and relative frequency, while continuous variables were described with mean or median based on observed distribution. Standard deviation (SD) or interquartile range (IQR) were used as measures of dispersion, respectively.

Data on height, leg length (calculated as: height - sitting height) and trunk length (sitting height) were compared with Argentine references.[18,19] The Z-score of the anthropometric variables was calculated using LMS growth for the Argentine population, and the adjusted height Z-score for parents was calculated as the child's Z-score - (mother's Z-score + father's Z-score)/2. Birth weight was compared with the international references established by the World Health Organization[20] and Intergrowth[21] for term and preterm infants, respectively.

The sample was divided into children with complex and simple ILO, using an exploratory t test to analyze the difference between continuous auxological variables. The alpha level was established at 0.05. The R 4.1.0 software was used.

Data were dissociated to maintain

confidentiality as per the personal data protection law. The study was approved by the hospital's Ethics Committee.

RESULTS

A total of 114 medical records with a diagnosis of ILO were reviewed. Of these, 38 were excluded: 30 because overgrowth was associated with a genetic syndrome, 7 because of a difference < 1 cm in length and/or circumference of 1 limb compared with its contralateral, and 1 due to lack of auxological data. The final sample was made up of 76 cases: 35 girls and 41 boys.

The median age at the time of the first consultation was 1.13 years (IQR: 0.55–2.70). Forty-nine patients were 8 years or older at the time of the last consultation. The median duration of follow-up was 5.85 years (IQR: 2.60–10.96), with a maximum of 15.76 years. Eighty-one percent of cases lived in the City of Buenos Aires and Greater Buenos Aires.

Simple overgrowth was observed in 28 patients; 16/28 had right side involvement. Complex overgrowth was observed in 48 cases: 24 compromised the right side of the body, 15 the left side and 9 had cross compromise. Facial involvement was observed in 28 of the patients with complex overgrowth (*Table 1*).

Auxological characteristics

The median number of height/body length measurements per child was 7 (IQR: 4–11).

During the last consultation, based on clinical measurement, the median discrepancy in leg length was 1.90 cm (IQR: 1.24–2.55); in thigh circumference, 2.15 cm (IQR: 0.5–6); and in calves circumference, 2.0 cm (IQR: 0.5–5.1).

Also, 4/34 girls and 3/40 boys were born preterm. The average birth weight Z-score in term girls with complex overgrowth was +0.51 (SD: 0.91) (p 0.022); whereas in boys, it was +0.45 (SD: 1.05) (p 0.052); One girl and one boy had a high birth weight for gestational age. The average body length Z-score at birth was -0.18 (SD: 0.92) in girls (n = 9) and +0.34 (SD: 1.42) in boys (n = 14).

The median age at the time of the last consultation was 11.87 years (IQR: 7.75–14.77) in girls and 10.51 (IQR: 3.09–13.68) in boys. The average height Z-score was +0.75 (SD: 1.03) in girls and +0.27 (SD: 1.03) in boys. *Table 2* shows the anthropometric data by age group.

Figure 1 shows the height curves for girls and boys plotted on the Argentine reference populations. The average height curve of boys and girls was located between the 50th and 97th centiles, with an upward centile crossing in the first 2 years of life. The same was observed in the growth of the trunk and lower limbs (*Figure 2*). Eight cases (6 girls) showed a high height for the population at the time of the last consultation.

There was a tendency to a higher Z-score in the anthropometric measurements assessed in cases with complex overgrowth compared to simple overgrowth, without statistically significant differences (*Table 3*).

Clinical characteristics

Ultrasound abnormalities were observed

TABLE 1. *Characteristics of analyzed sample*

Sex (M:F)	1.17:1
Place of origin n (%)	
CABA and GBA	62 (81.6)
Other provinces	14 (18.4)
Age at first consultation (years) median (IQR)	1.13 (0.55–2.70)
Years of follow-up median (IQR)	5.85 (2.60–10.96)
Simple overgrowth n (%)	
Total	28 (36.8)
Right side	16 (57.1)
Left side	12 (42.9)
Isolated upper limbs	1 (3.6)
Isolated lower limbs	27 (96.4)
Complex overgrowth n (%)	
Total	48 (63.2)
Right side	24 (50)
Left side	15 (31.3)
Crossed	9 (18.7)

CABA: Autonomus City of Buenos Aires; GBA: Greater Buenos Aires; IQR: interquartile range.

in 8 cases: pyelocaliceal dilatation in 2, nephrocalcinosis in 1, bifid renal pelvis without urinary tract dilatation in 2, nephrolithiasis in 1, common bile duct dilatation in 1, and Wilms tumor in the left kidney in 2.

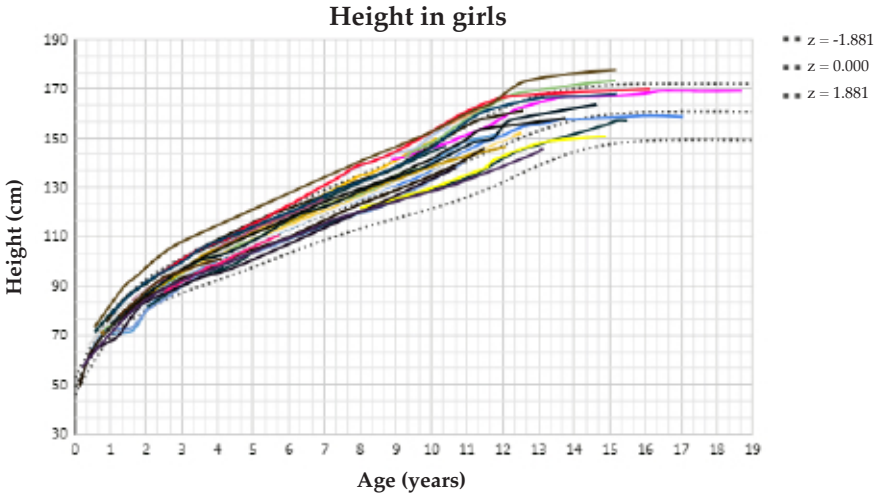
Of the patients with Wilms tumor, 1 was a

TABLE 2. *Height, leg length, and trunk length Z-scores by age group and sex*

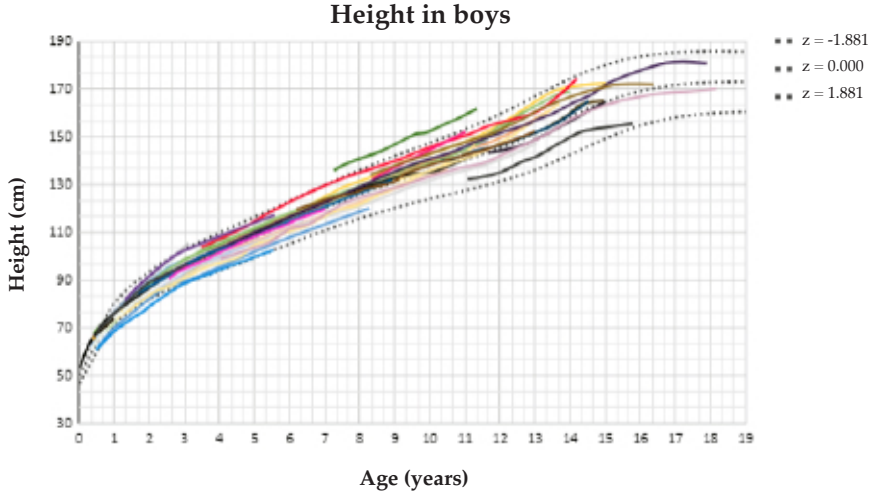
Age range	Height Z-score X (SD)		Leg length Z-score X (SD)		Trunk length Z-score X (SD)	
	Boys (n = 41)	**Girls (n = 35)**	**Boys (n = 40)**	**Girls (n = 30)**	**Boys (n = 38)**	**Girls (n = 29)**
0–2.0 years old	-0.10 (1.06) (n = 23)	+0.18 (1.48) (n = 24)	+1.10 (1.28) (n = 22)	+2.12 (1.23) (n = 22)	+1.09 (1.20) (n = 22)	+1.22 (1.26) (n = 22)
2.01–prepuberty	+0.40 (0.96) (n = 34)	+0.73 (1.10) (n = 37)	+0.23 (0.97) (n = 32)	+0.43 (1.09) (n = 33)	+0.27 (1.11) (n = 32)	+0.48 (0.92) (n = 34)
Last measurement on puberty	+0.72 (1.02) (n = 21)	+0.71 (1.11) (n = 24)	+0.41 (1.02) (n = 19)	+0.69 (1.05) (n = 20)	+0.38 (1.02) (n = 19)	+0.49 (1.16) (n = 20)

X: arithmetic mean; SD: standard deviation.

FIGURE 1. *Growth curves for height in girls and boys*



.....3rd, 50th, and 97th centile for the Argentine population.



.....3rd, 50th, and 97th centile for the Argentine population.

male with right complex overgrowth; diagnosis was made at 5 months of age by ultrasound screening. The second case was a female patient with left complex overgrowth whose diagnosis was made at 10 months of age by magnetic resonance imaging of the spine. Both patients were in stage I at the time of diagnosis; complete resection of the tumor was performed and they had a favorable course.

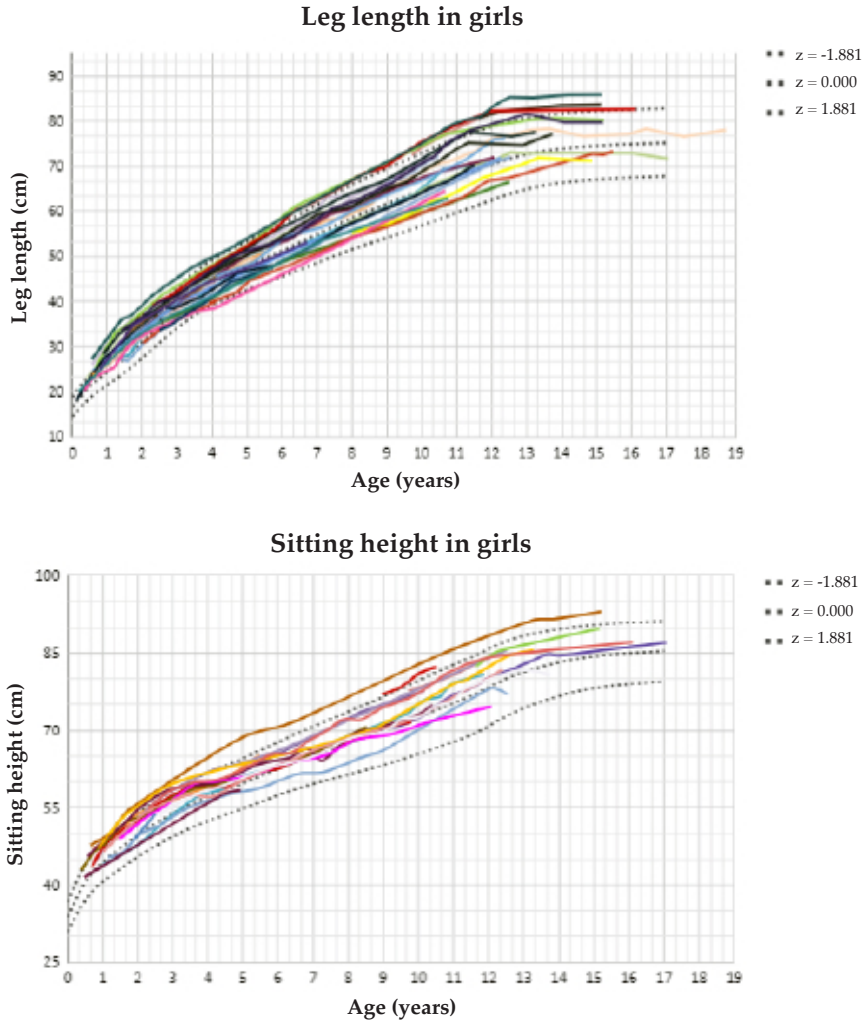
Eight of 76 cases showed renal asymmetry ≥ 1 cm. Four were girls, and 6 had complex overgrowth. The largest kidney was contralateral to the affected hemibody in 3 cases, ipsilateral in 4, and 1 crossed. The average Z-score of the largest kidney was +3.04 (SD: 1.41). All children showed normal renal function; 1 had microscopic hematuria, and none had proteinuria.

Radiological characteristics of lower limbs

Out of 76 children, 63 (82.9%) had leg length discrepancy.

Fourteen underwent surgery (epiphyseal closure or epiphysiodesis). Eight were males. The median discrepancy before surgery was 3.70 cm (IQR: 2.95–3.98), whereas the median discrepancy in children on medical treatment was 1.5 cm (IQR: 1.01–2.2). No patient had a discrepancy of more than 5 cm. The median age at the time of epiphysiodesis was 11.74 years (IQR: 11.42–12.08) in girls and 13.66 (IQR: 13.06–13.96) in boys. Four children had X-rays taken at adult bone age, which showed a correction percentage

FIGURE 2. *Curves for leg length and trunk length in girls*



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of 12.3%, 54.1%, 72.3%, and 93.3%, respectively. The epiphysiodesis procedure that achieved a 12.3% correction was performed at an advanced pubertal development. No patient required lengthening of the short limb.

An upward slope pattern (Shapiro I)[15] was observed in 9 out of 30 children (30%) (*Figure 3*). The median discrepancy at the time of the first consultation was 1.20 cm (IQR: 0.9–2.8) and at the time of the last consultation, 2.90 cm (IQR: 1.66–5.00), with a median progression of 1.40 cm (IQR: 0.90–2.80) per child.

In 28 children, the median duration of follow-up was 9.51 years (IQR: 8.32–10.43); 11 (39.3%) showed changes of less than 1 cm in lower limb length discrepancy during follow-up; 10/28, changes between 1 and 2 cm; and 7/28, changes between 2 and 5 cm. The median age at the time of follow-up initiation was 2.35 years (IQR: 1.19–4.05) and, at the end of follow-up, 11.9 (IQR: 11.20–13.38).

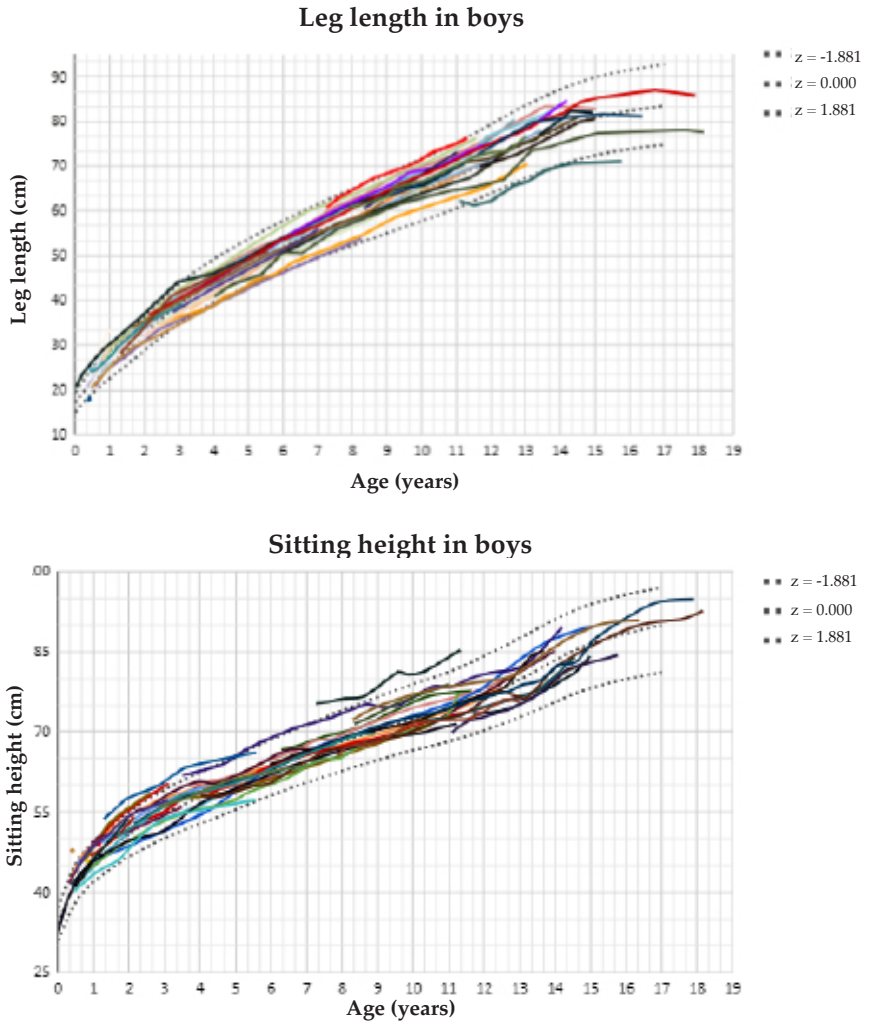
DISCUSSION

This study presents a review of auxological, clinical, and radiologic data of children with ILO assessed in our department in the last 27 years.

ILO is a lateralized body overgrowth in the absence of a recognizable pattern of malformations or genetic syndromes. This new name replaces the histopathological terms of isolated body hyperplasia/hypertrophy.[1]

When assessing growth in our cohort, we observed that height, trunk length, and leg length of the study children were normal for the

FIGURE 2. *Curves for leg length and trunk length in boys*



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Argentine population, but, in most cases, in the high centiles. Of the 8 children with height above the 97th centile, only 1 girl was tall for her parents, at 10.5 years of age, but had not yet reached her final adult height. Unlike other syndromes associated with overgrowth, longitudinal growth and body proportions in our cohort were normal, and centile crossing was observed in the first 2 years of life.

When the sample was divided into simple ILO (involvement of a single body segment) and complex ILO, the latter showed a tendency to higher birth weight, height, sitting height, and leg length than children with simple ILO. These differences were statistically significant only in relation to birth weight in term girls.

We observed a predominance of right hemibody involvement over left hemibody involvement similar to what has been reported by Hoyme et al.,[7] and a higher percentage of cases with lower limb involvement over upper limb involvement. This may be due to a referral bias in these children, since lower limb discrepancy is more frequent and easier to detect than in the upper limbs.[22]

A common question from parents during consultation is about the progression of leg length discrepancy during growth. In this regard, we observed that 75% of patients showed a progression ≤ 2 cm with a median follow-up of 9 years, between 2 and 12 years of age, similar to what has been reported by Carli et al.[11] The magnitude to consider a discrepancy as significant is still under discussion. Given that, in our cohort, several children had an initial leg length discrepancy of less than 1 cm, which progressed throughout follow-up, we suggest that all patients with discrepancy should be monitored, regardless of its initial magnitude.[1]

On the other hand, one third of our population had a discrepancy > 2 cm, but no case was > 5 cm, as in other specific bone conditions, such as congenital short femur, history of sepsis, etc. In relation to surgical management, 18.9% of patients required epiphysiodesis (epiphyseal closure) of the long limb. As in previous studies, the percentage of correction was lower when pubertal development was advanced at the time of epiphysiodesis, with very reduced remaining growth.[23]

The prevalence of Wilms tumor in our cohort was 2.6%, higher than the 1.6% observed by Dempsey-Robertson et al.,[24] lower than the 3.57% and 4.2% reported by Hoyme et al.[7] and Atik et al.,[25] respectively in cases with ILO;

TABLE 3. *Clinical and auxological characteristics by type of overgrowth*

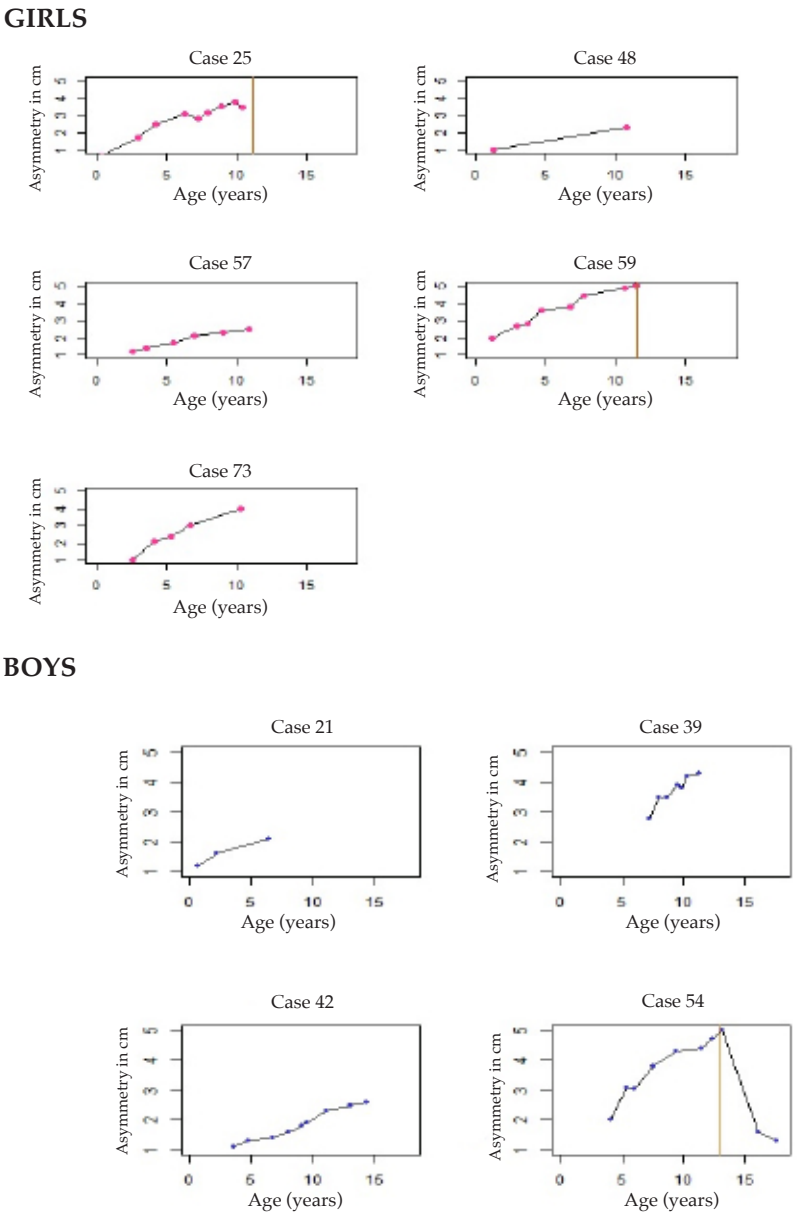
Variable	Sex	All* cases	Simple overgrowth	Complex overgrowth	*p* value for complex versus simple
Birth weight Z-score X (SD)	Girls (n = 34)	+0.26 (0.89)	-0.22 (0.66) (n = 11)	+0.51 (0.91) (n = 23)	0.033
	Boys (n = 41)	+0.31 (0.95)	-0.07 (0.71) (n = 16)	+0.45 (1.05) (n = 25)	0.25
Height Z-score X (SD)	Girls (n = 35)	+0.75 (1.03)	+0.56 (1.09) (n = 12)	+0.84 (1.01) (n = 23)	0.47
	Boys (n = 41)	+0.27 (1.03)	+0.35 (1.11) (n = 16)	+0.22 (1.00) (n = 25)	0.69
Lower limb length Z-score X (SD)	Girls (n = 30)	+0.69 (1.01)	+0.46 (1.07) (n = 9)	+0.80 (0.99) (n = 21)	0.42
	Boys (n = 40)	+0.31 (1.27)	+0.10 (1.10) (n = 16)	+0.44 (1.36) (n = 24)	0.40
Trunk length Z-score X (SD)	Girls (n = 29)	+0.57 (1.04)	+0.51 (0.94) (n = 9)	+0.60 (1.11) (n = 20)	0.82
	Boys (n = 38)	+0.36 (1.14)	+0.30 (1.15) (n = 14)	+0.40 (1.15) (n = 24)	0.80
Renal asymmetry ≥ 1 cm	Girls	n = 4	2	2	-
	Boys	n = 4	0	4	-

X: arithmetic mean; SD: standard deviation.

and higher than the 0.01% described in the general population under 15 years of age.[26] The average age at diagnosis of Wilms tumor in our sample was 0.75 years, lower than the 3.66 years described in the general population.[27] This could be due to the embryonal tumor screening protocol performed in these patients by serial abdominal and kidney ultrasounds every 3 months until 7 or 8 years of age.[7,8,28]

The limitations of this study were its retrospective design and the impossibility of having a molecular test done to exclude overgrowth associated with syndromes with minimal expression. Therefore, strict exclusion criteria and a multidisciplinary assessment in most of the included cases. A strength of this study was that all anthropometric and radiological measurements were performed by the

FIGURE 3. *Lower limb length discrepancy in girls and boys over time for cases with an upward slope pattern (Shapiro type I)*



For cases 25, 59, and 54, the vertical line shows the time when the definite distal femoral and proximal tibial epiphysiodesis was performed.

same trained observer, which reduced the error of measurement. In addition, 64.5% of patients were older than 8 years at the time of the last consultation, when the risk of developing embryonal tumors is similar to that of the general population.[7]

Multidisciplinary evaluation improves the diagnosis and the tempo of growth to plan precise treatment. Finally, screening for embryonal tumors is mandatory.[8,22]

CONCLUSIONS

Prenatal growth of children with ILO was normal, except in girls with complex overgrowth, in whom it tended to be increased. The average height of both boys and girls was in the high centiles with normal growth. Embryonal tumor screening is recommended in this group of children. ■

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