Original article

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Clinical and auxological characteristics and quality of life of 50 children and adolescents with segmental overgrowth syndromes at a single center

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ABSTRACT

Introduction. Segmental overgrowth syndromes are a group of rare diseases characterized by overgrowth in one or more parts of the body, mostly related to mosaic mutations in the *AKT/PI3K/mTOR* and *RAS-MAPK* signaling pathway. Our objective was to analyze the clinical and auxological characteristics and health-related quality of life (HRQoL) in this group of patients at a tertiary care hospital.

Population and methods. Cross-sectional study of a follow-up cohort. Age, sex, sociodemographic data, anthropometric measurements of the affected and contralateral segments, complications, treatment, quality of life (PedsQL 4.0), and pain were analyzed. Central and dispersion measures were estimated. A univariate analysis between the quality of life and study variables was done.

Results. A total of 50 patients were included; 29 were males. Median age: 9.95 (r: 1.44–17.81) years. The most common diagnosis was *PIK3CA*-related overgrowth spectrum (PROS) (37/50). The median number of affected segments was 2 (r: 1–7) per patient. Vascular malformations were observed in 40, and capillary malformations, in 20 patients. Pain was the most common complication (24/50). An asymmetry of the lower extremities of < 5 cm was observed in 31 patients. In most children, height was between the 50th and 97th percentiles. A lower HRQoL was observed among girls, patients with complex vascular malformations, and those with unmet basic needs (UBNs).

Conclusions. PROS was the most common diagnosis. Pain was the most common complication. HRQoL was lower among girls, patients with combined vascular malformations, and those with UBNs.

Keywords: *overgrowth syndromes; serine/threonine-protein kinase TOR;* RASA1*; quality of life; PROS,* PIK3CA*-related overgrowth spectrum.*

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INTRODUCTION

Segmental (or localized) overgrowth syndromes are a group of uncommon diseases characterized by overgrowth in 1 or more parts of the body associated with a spectrum of growth abnormalities ranging from a single skin lesion or isolated macrodactyly with little progression, to extensive lesions involving the skin, muscle, bone, tendons, blood vessels, and nerves in 1 or more parts of the body. Somatic mosaicism was identified in the *AKT/PI3K/mTOR* and *RAS-MAPK* cell growth signaling pathways, such as the Proteus syndrome (*AKT1* gene), PROS (*PIK3CA*-related overgrowth spectrum), PHTS (PTEN hamartoma tumor syndrome), and including the Bannayan-Riley-Ruvalcaba syndrome (BRRS), the Cowden syndrome, tuberous sclerosis (*TSC1/TSC2* gene), the Smith-Kingsmore syndrome (*mTOR* gene), the Parkes-Weber syndrome, and CM-AVM1 (*RASA1* gene).[1–7]

PROS encompasses a broad group of syndromes, originally considered distinct syndromes, which are now grouped under the same term because it has been established that they are all caused by pathogenic somatic variants in the *PIK3CA* gene. PROS includes megalencephaly, capillary malformation (CM), congenital lipomatous overgrowth, vascular malformations, epidermal nevis, spinal/skeletal anomalies/scoliosis (CLOVES) syndrome, Klippel-Trenaunay (KT) syndrome, CLAPO syndrome, hemihyperplasia-multiple lipomatosis syndrome (HHML), fibroadipose hyperplasia or overgrowth (FAO), macrodactyly, infiltrative facial lipomatosis, dysplastic megalencephaly (DMEG), hemimegalencephaly (HME), and focal cortical dysplasia (FCD).[8]

These conditions may be associated with other manifestations, such as vascular malformations, epidermal lesions, renal anomalies, polydactyly, and brain malformations; also, some cases of embryonal tumors have been described, such as Wilms tumor and ovarian tumors.[9,10] While some results on new specific treatments have been encouraging, there is yet no curative treatment. Reduction or amputation of the affected segment is the therapy of choice for severe cases to maintain functionality.[11–13] The prognosis varies depending on the severity of complications, due to their deforming nature; these conditions have a high impact not only on physical health, but also on the psychological health of patients and their families.[14]

The objective of this study was to analyze the clinical and auxological characteristics and the health-related quality of life (HRQoL) of children and adolescents who have been diagnosed with segmental overgrowth syndromes related to the *AKT/PI3K/mTOR* and *RAS-MAPK* signaling pathways who were seen at a tertiary care children's hospital between June 2019 and March 2020.

POPULATION AND METHODS

This was an observational, analytical, cross-sectional study of a cohort of patients receiving follow-up at a single center. Patients were included consecutively between June 2019 and March 2020, whether they had consulted for the first time or were being followed-up by the Department of Growth and Development, the Department of Genetics, or the Interdisciplinary Team of Vascular Anomalies of Hospital de Pediatría Garrahan.

Children aged 1 to 18 years who met the diagnostic clinical criteria of syndromes related to the *AKT/PI3K/mTOR* and *RAS-MAPK* signaling pathways were included[3,5–8,15,16] (*Supplementary material*). Patients with other genetic overgrowth syndromes and those who refused to participate were excluded. Each patient was assessed by 3 observers (VW, SC, AM), who decided by consensus which patients met the inclusion criteria, and these were invited to participate in the study. The informed consent was obtained from caregivers and assent or consent from the child/adolescent as appropriate for their age.

A trained observer (VW) administered the HRQoL questionnaire, obtained the anthropometric data (weight, height, head circumference, length and circumference of the affected and contralateral segment), assessed pubertal development as per Tanner stages, administered the pain questionnaire, and recorded demographic data, level of education of the patient and their parents, perinatal data (weight, height, gestational age), age at and location of onset of the first symptom, previous diagnoses and treatments, and complications. Data on weight and height during follow-up and the number of visits to the hospital in the past year were recorded based on a review of medical records.

MEASUREMENT INSTRUMENTS

Auxological variables

Weight, height, and head circumference were measured in accordance with the

recommendations by the Sociedad Argentina de Pediatría.[17] The length and circumference of the affected and the healthy contralateral extremities were measured according to Norton et al.[18] Segment length was measured using a Harpenden anthropometer with a 1-mm precision, while segment circumference was measured using a Calibres Argentinos tape (1 mm precision). Training was conducted prior to the study, and the technical error of measurement (TEM) was estimated.

PedsQL 4.0

HRQoL was assessed using the PedsQL™ questionnaire, version 4.0, for children and adolescents aged 2 to 18 years. The questionnaire consists of a total of 23 items that assess physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items) based on questions referring to the past month using a Likert scale scoring from 0 to 4 (0 = never a problem, 4 = almost always a problem). There are 7 versions of the questionnaire: 4 are completed by caregivers (2–4 years old, 5–7 years old, 8–12 years old, 13–18 years old) and 3 are completed by children (5–7 years old, 8–12 years old, 13–18 years old). This tool has been validated in the Argentine population.[19]

Pain scale

The characteristics of pain were recorded using a questionnaire for children aged 5 to 7 years and one for those older than 7 years. These questionnaires are routinely used in the assessment of pain at the hospital's Department of Palliative Care. The questionnaires include the following variables referring to the past month: frequency, location, and description of type of pain (piercing, burning, throbbing, tiring, dull, electric shock, tingling), severity, and pain medication. Severity was measured using the Faces Pain Scale-Revised, FPS-R, which scores between 0 (no pain) and 10 (maximum pain) in both age groups.[20,21] For the group of children aged 5 to 7 years, possible values were never = 0, sometimes = 1, and almost always = 2. For the group of children older than 7 years, possible values were never = 0, almost never = 1, sometimes = 2, frequently = 3, and almost always = 4.

Statistical analysis

A descriptive analysis was performed for continuous variables using measures of central tendency and dispersion, and proportions were described for categorical variables. A univariate analysis was done for HRQoL, the dependent variable, and the independent variables, such as age, sex, unmet basic needs (UBNs), presence of pain, vascular malformation, type of vascular malformation (single versus combined), and number of affected segments.

Data for growth in terms of height were analyzed longitudinally, and the median and range of the Z-score at the last visit were estimated. The Z-score was estimated using the LMS method for the Argentine reference populations of children.[22] The Intergrowth-21st standard was used for birth data.[23] In each patient, the difference (in cm) in the circumference and length of the affected segment was obtained in comparison to the healthy contralateral segment.

Data were recorded in RedCap and analyzed using the Statistix 8.0 software.

This study was approved by the Teaching, Ethics, and Research Committee of Hospital Garrahan and was partially funded through a fellowship granted by the Sociedad Argentina de Pediatría.

RESULTS

Clinical characteristics

A total of 50 patients were included; 29 were males. Their median age at the time of the first consultation was 9.95 years (r: 1.44–17.87) and the median duration of follow-up was 3.53 years (r: 0–15.69). The sample characteristics are described in *Table 1*.

A total of 37 patients met the diagnostic clinical criteria for PROS (CLOVES: 7, KT: 6, CM: 3, FAO: 2, isolated macrodactyly: 1, unspecified syndrome in the PROS: 18); 5 met the criteria for *RASA1*-related syndromes (Parkes-Weber: 3, CM-AVM1: 2); and 3 showed clinical characteristics of alterations in the *PTEN*-gene (BRRS). It was not possible to establish a classification in 5 patients due to overlapping clinical signs, but they met the inclusion criteria. Two patients had a family history of overgrowth (CM-AVM1 and BRRS).

The first symptom reported by parents was present at birth in 46 of 50 patients and, in all cases, before 6 months of age. The first symptom was overgrowth (n = 12), vascular malformation (n = 17), overgrowth and vascular malformation (n = 19), lipoma of the trunk (n = 1), and clubfoot (n = 1). The median age at the time of overgrowth onset corresponded to the neonatal period (IQR:

Table 1. Characteristics of the population (n = 50)

Decimal age in years, median (range)	9.95 (1.44–17.87)
Sex, (M/F)	1.38
Place of origin, n (%)	
CABA	5 (10)
Province of Buenos Aires	25 (50)
Other provinces	20 (40)
UBNs, n (%)	14 (28)
UCD, n (%)	23 (46)
Age-appropriate level of education, n (%)	44 (91.7)
Developmental delay and/or ID, n (%)	11 (22)

CABA: Autonomous City of Buenos Aires; UBNs: unmet basic needs; UCD: unique certificate of disability; ID: intellectual disability; n: number.

neonate-0.33 years); in 6 patients, overgrowth was observed after 1 year old (PROS: 2, BRRS: 1, CM-AVM1: 1, and unspecified: 1); and the latest onset was in a 5-year-old child diagnosed with CM-AVM1. The most common location was overgrowth in the lower extremities. Parents indicated that the overgrowth remained stable since birth in 23 patients (46%).

The median number of affected segments per child was 2 (r: 1–7); the most common location was in the lower extremities (n = 42). Other body regions involved were the upper extremities (n = 19), head and neck (n = 18), chest (n = 8), back (n = 9), and hands (n = 13). Asymmetry in the length of lower extremities was observed in 31 patients. The median difference in the length of lower extremities was 1.3 cm (r: 0.5–5.0). Macrodactyly was observed in the hands of 9 patients and the feet of 5 patients. The second and third toes and the index and middle fingers were affected the most.

A total of 40 patients had vascular malformation (80%); of these, 50% (n = 20) corresponded to a capillary malformation and 50% (n = 20), to a combined malformation (7 had a capillary lymphatic venous malformation; 6, a capillary venous malformation; 4, a capillary arteriovenous malformation; 1, a capillary lymphatic arteriovenous malformation; 1, a lymphatic venous malformation; and 1, a capillary lymphatic malformation).

Observed skeletal complications included joint limitations (n = 6), lower limb misalignment (n = 5), and phalangeal misalignment (n = 2). Extra-skeletal complications included pain in 24 patients, lymphatic effusion (n = 2), deep vein thrombosis (n = 2), bleeding (n = 11), infections associated with vascular malformation (n = 12), and localized pruritus (n = 2). No malignant tumors were recorded in this sample. The median number of hospital visits in the past year was 5 (IQR: 2–9); the maximum number of visits was 28, in a girl diagnosed with PROS (TK).

Treatment included pain medication (n = 7), sirolimus (n = 3), pulsed laser (n = 6), lift for the short leg (n = 18), amputation of the affected segment and/or epiphysiodesis (n = 9), mass resection (n = 7), and percutaneous sclerosis or embolization (n = 3).

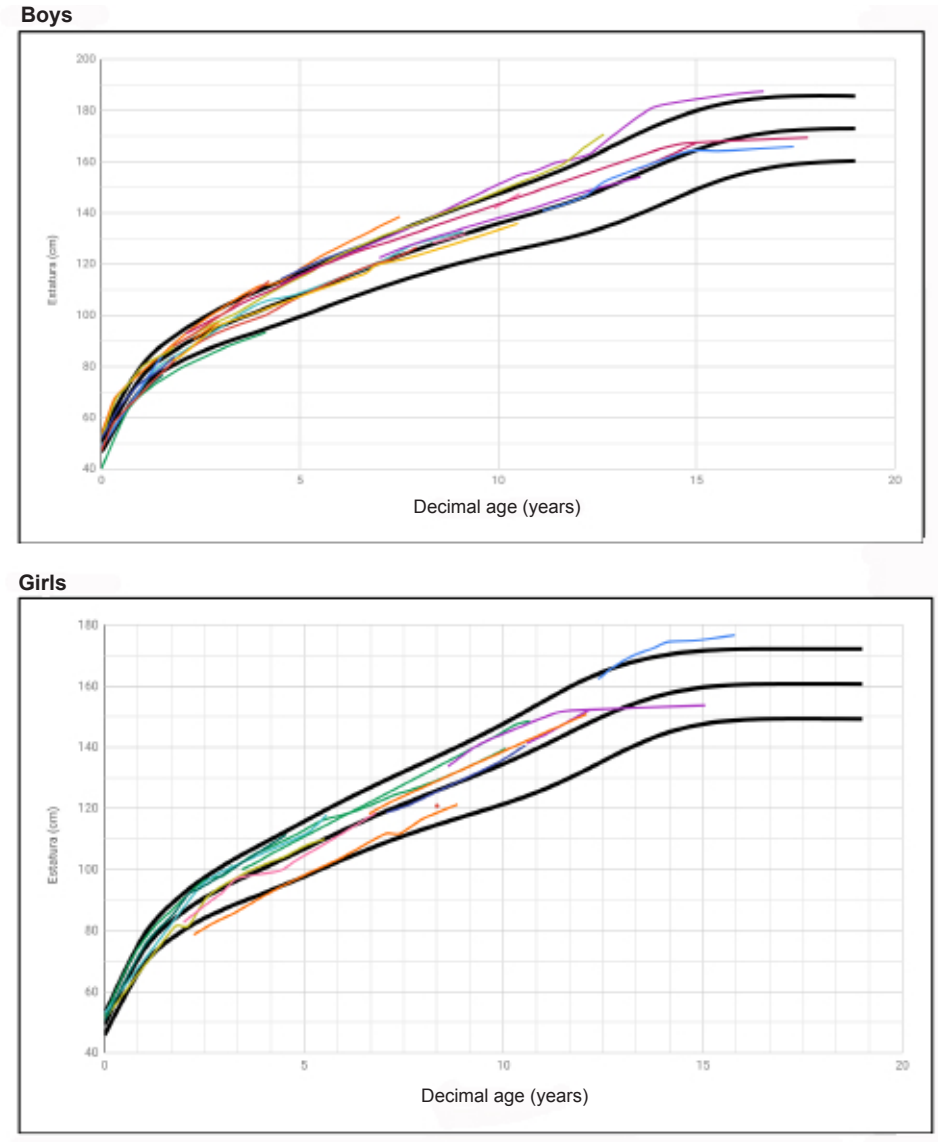
The median Z-score for birth weight in children born at term (n = 36) was 0.82 SD (IQR: 0.18–1.51) among girls and 1.14 SD (IQR: 0.11–1.42) among boys. The median Z-score for height at the time of the last consultation was 0.33 SD (IQR: -0.34–2.00) among boys and 0.17 SD (IQR: -0.41–0.74) among girls. Advanced pubertal development was noted in 5 girls and 3 boys. *Figure 1* shows height data for boys and girls plotted based on the Argentine references, where an upward percentile crossing is observed in the first years of life. In 4 boys and 1 girl, height at the time of the last consultation was above the 97th percentile.

Macrocephalus was observed in 6 patients, who were diagnosed with CM (n = 3), suspected mutation in the *RASA1* gene (n = 1), and 2 patients were unclassified (1 had a language disorder).

Quality of life

The global HRQoL score reported by the children was 70.6 (SD: 17.5) for physical functioning, 66.7 (SD: 20.9) for emotional

Figure 1. Curves of growth in height



The black lines correspond to the 3rd, 50th, and 97th percentiles of the Argentine references for height.[17]

functioning, 78.1 (SD: 21.7) for social functioning, and 63.7 (SD: 21.6) for school functioning. No significant differences were observed between the scores obtained by children and their caregivers (*Table 2*).

The HRQoL was lower in children aged 5 to 12.9 years; the psychosocial component was 5 points lower among girls, 10 points lower among children with UBNs, and, in the physical component, 4 points lower in children with combined vascular malformations (*Table 3*).

Pain

A total of 24 patients had pain; of these, 18 had associated vascular malformation, which corresponded to combined malformations in 12 of the patients. Pain was severe in 5 children. The most common characteristics of pain corresponded to piercing pain (n = 14) and tiring or heavy pain (n = 9). Drug treatment was required in 7 patients: 6 NSAIDs and 1 morphine. Of the 24 children who had pain, 10 stopped their activities of daily living; 4 stopped going to school; 3 stopped walking; 2 stopped playing; and 1 stopped sleeping.

Table 2. Health-related quality of life (PedsQL 4.0)

Children's answers				
Age/Functioning	**Physical x (IQR)**	**Emotional x (IQR)**	**Social x (IQR)**	**School x (IQR)**
5-7 years (n = 9)	68.75 (56.3–75.0)	70.0 (60.0–90.0)	100.0 (70.0–100.0)	60.0 (40.0–60.0)
8-12 years (n = 18)	71.9 (59.3–81.2)	67.5 (60.0–80.0)	70.0 (48.7–95.0)	62.5 (36.2–78.8)
13-18 years (n = 12)	73.4 (66.4–82.0)	67.5 (48.8–80.0)	87.5 (78.8–91.3)	80.0 (70.0–90.0)
Caregivers' answers				
Age/Functioning	**Physical x (IQR)**	**Emotional x (IQR)**	**Social x (IQR)**	**School x (IQR)**
2-4 years (n = 4)	73.4 (49.3–92.9)	80.0 (80.0–100.0)	95.0 (80.0–100.0)	75.0 (72.5–83.3)
5-7 years (n = 9)	78.1 (65.6–81.25)	60.0 (60.0–80.0)	80.0 (70.0–90.0)	80.0 (55.0–90.0)
8-12 years (n = 18)	71.9 (57.8–90.6)	60.0 (45.0–75.0)	80.0 (42.5–85.0)	70.0 (50.0–85.0)
13-18 years (n = 12)	81.3 (70.3–89.1)	65.0 (53.7–86.3)	90.0 (77.5–90.0)	75.0 (57.5–85.0)

x (IQR): median and interquartile range; n: number.

Table 3. Health-related quality of life in children and adolescents aged 5 to 18 years (n = 39). Univariate analysis

Variable	**Physical component X (SD)**	**Psychosocial component X (SD)**	**Overall HRQoL X (SD)**
Age (years)			
5–7 (n = 9)	65.3 (20.0)	67.4 (19.7)	66.9 (19.0)
8–12 (n = 18)	71.4 (16.2)	66.9 (19.3)	68.0 (17.8)
13–18 (n = 12)	73.4 (18.1)	75.0 (11.7)	74.6 (12.2)
Sex			
Female (n = 18)	72.6 (20.2)	66.9 (19.9)	68.4 (19.6)
Male (n = 21)	68.9 (15.1)	71.7 (14.9)	70.9 (13.7)
Pain			
Yes (n = 19)	70.9 (15.1)	70.9 (15.3)	70.9 (14.4)
No (n = 20)	70.3 (19.9)	68.1 (19.4)	68.6 (18.6)
Complex AVM			
Yes (n = 19)	70.2 (11.4)	71.1 (14.0)	70.8 (12.5)
No (n = 13)	74.5 (21.3)	73.8 (16.5)	74.0 (16.4)
UBNs			
Yes (n = 10)	69.9 (21.1)	62.2 (22.3)	64.1 (21.7)
No (n = 29)	70.8 (16.5)	72.0 (14.9)	71.7 (14.3)

X (SD): mean and standard deviation; HRQoL: health-related quality of life; AVM: arteriovenous malformations; UBNs: unmet basic needs; n: number.

DISCUSSION

Here we present the first local study about growth and HRQoL in children and adolescents with segmental overgrowth syndromes associated with the *AKT/PI3K/mTOR* and *RAS-MAPK* cell signaling pathways.

The most common diagnosis was PROS (*PIK3CA*-related overgrowth spectrum); overgrowth developed in the first 6 months of life in 33 out of 36 patients, which is consistent with what has been published by other authors.[3,8,9]

The longitudinal growth in height, although in high percentiles, was normal compared to the Argentine population. This suggests that dysregulated growth would occur at a local or segment level, and as a result of somatic, mosaic pathogenic variants in the *PIK3CA* gene, which is consistent with what has been previously published by other authors.[8]

In 60% of the patients, the asymmetry of the lower limbs was > 1 cm, but in no case > 5 cm, similar to patients diagnosed with isolated lateral overgrowth, observed in a recent publication by the same site.[24] And this was lower to what has been observed in other overgrowth conditions, such as Proteus syndrome.[13]

Body asymmetries pose a diagnostic and treatment challenge for pediatricians. Our recently published study in children with isolated overgrowth showed similar overall growth data and magnitude of asymmetry.[24] However, in this study, patients with segmental overgrowth associated with somatic mosaic pathogenic variants in the *AKT/PI3K/mTOR* and *RAS-MAPK* pathways were observed to have a more complex condition due to other accompanying signs and symptoms, and complications.

The HRQoL was lower than what has been reported in healthy Argentine children and similar to other populations of children with chronic diseases in our hospital using the same tool.[19] Although we have not found studies about the HRQoL in this group of pediatric patients at the international or local level, a meta-analysis in children and adults with vascular malformation showed a lower quality of life associated with pain and the location of the vascular malformation in the face and neck.[25,26]

In our sample, we noted a trend toward a lower HRQoL in patients with combined vascular malformations, as published by Fahrni et al.[26] in 71 patients older than 16 years. The lower HRQoL observed in the group of girls may be related to body image, although this aspect was not studied; some authors have pointed to the social stigmatization of these children.[14]

A weakness of the study is that the group of patients analyzed was very heterogeneous, including clinical conditions with varying degrees of severity and complications, as is to be expected in rare diseases associated with low or very low level mosaicism. In addition, the inclusion criteria used for diagnosis were based exclusively on clinical signs, without conducting a molecular confirmation. Although a clinical diagnosis was reached in most cases, some patients could not be classified due to overlapping clinical criteria. A strength of this study is that all anthropometric measurements were performed by a single trained observer, which reduces the technical error of measurement.

CONCLUSIONS

PROS was the most common diagnosis. Pain was a common complication and impacted activities of daily living. HRQoL tended to be lower among girls, patients with combined vascular malformations, and those with UBNs.

Collaborators

Interdisciplinary Team of Vascular Anomalies of Hospital Nacional de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan, City of Buenos Aires, Argentina. ■

Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/3017_AO_Wolf_Anexo.pdf

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