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ORIGINAL ARTICLE

Lateralized overgrowth as a guiding sign of abdominal neoplasms for pediatric orthopedic surgeons

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The term hemihyperplasia, defined as the pathological growth process that involves an abnormal proliferation of cells, has been replaced with the term hemihypertrophy, defined as the increase in size of existing cells.[1]

Recently, newly proposed terms have been used rather than these histopathological and non-clinical concepts, as asymmetric regional body overgrowth and lateralized overgrowth (LO), are used synonymously to indicate a significant increase in the length and/or girth of most or all of one side

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ABSTRACT

Objectives: This study aims to increase the awareness of the association between lateralized overgrowth (LO) and abdominal tumor among the pediatric orthopedic community and to evaluate its incidence in our center.

Patients and methods: Between January 1997 and December 2021, a total of 166 patients with Wilms tumors and hepatoblastomas were retrospectively analyzed. Data including age, sex, initial clinical signs (hematuria, abdominal mass with or without general discomfort), type of asymmetric regional body overgrowth (isolated or in relation with any syndrome), and tumor stage at diagnosis were recorded. In addition, age at which asymmetric regional body overgrowth was described and age at the time of tumor diagnosis were noted.

Results: Of a total of 166 patients, 133 were diagnosed with Wilms tumors (nephroblastomas) and 33 were diagnosed with hepatoblastomas. In 94% of the cases, the initial clinical signs were an abdominal mass and/or hematuria. Overall, five (3%) patients presented with LO. Four patients with Wilms tumor presented it at the initial clinical examinations. In three of these cases (2.3%), we found it isolated and, in the remaining patient (0.75%), it was associated with Beckwith-Wiedemann spectrum. Only one patient affected from hepatoblastoma (3%) presented with an isolated LO at the time of tumor diagnosis.

Conclusion: Our study results show an incidence of LO in relation to intra-abdominal tumors of 3%. The latest updates recommend genetic testing to identify subgroups with a higher risk for tumor development that are more likely to benefit from tumor protocol surveillance.

Keywords: Intra-abdominal tumor, isolated lateralized overgrowth, hepatoblastoma, pediatric orthopedics, Wilms tumor.

of the body compared to its contralateral side. It can be also accompanied by the asymmetric growth of internal organs.[2]

Isolated LO (ILO) is a congenital overgrowth disorder that results in the absence of a recognized pattern of dysplasia, malformations, or morphological variants. The incidence of ILO in the literature between the 1950s and 1960s ranged from 1:13,000 to 1:86,000 live births, respectively.[3-5] In 2019, Vaiman et al.[6] estimated its incidence in adolescents as approximately 1:3,000.

Lateralized overgrowth may also occur in association with a variety of highly heterogeneous malformation syndromes, such as Beckwith-Wiedemann spectrum (BWSp), Klippel Trenaunay, and Proteus. Both ILO and LO associated with syndromes, particularly in patients with BWSp, lead to an increased risk of intra-abdominal neoplasms, mainly Wilms tumors, hepatoblastomas, and adrenal cell carcinoma.[5,7-10] Until date, recommendations for tumor screening and its connection to surveillance have been made; however, there is no consensus protocol with significant scientific evidence for frequency and duration of screening according to specific patient populations.

In the present study, we hypothesized that being aware of the clear relationship between LO and intra-abdominal tumors in the pediatric age for orthopedic surgeons was associated with an earlier diagnosis of such intra-abdominal tumors. We, therefore, aimed to analyze the diagnosed cases of Wilms tumors (nephroblastomas) or hepatoblastomas in our institution associated with LO, isolated or related to any syndrome, comparing it to the published incidence, to increase awareness about its association among pediatric orthopedic community. We also aimed to discuss this association in the literature and the most appropriate screening protocols described to date.

PATIENTS AND METHODS

This observational, retrospective study was conducted at Children's Hospital Sant Joan de Deu, University of Barcelona, Department of Paediatric Orthopaedic and Trauma Surgery between January 1997 and December 2021. We collected data from medical records from the time of tumor diagnosis until the last registered consultation. Inclusion criteria were patients younger than 18 years old who were affected by Wilms tumors or hepatoblastomas. In this group, we analyzed those in which a LO was described in the medical data. Exclusion criteria were failure to attend to follow-up appointments and missing information in clinical charts and, the presence of musculoskeletal disease with the exception of dysplasia caused by LO. Finally, a total of 166 patients were included in the study.

Data including age, sex, initial clinical signs (hematuria, abdominal mass with or without general discomfort), type of asymmetric regional body overgrowth (isolated or in relation with any syndrome), and tumor stage at diagnosis were recorded. In addition, age at which asymmetric regional body overgrowth was described and age at the time of tumor diagnosis were noted.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable.

RESULTS

Of a total of 166 patients, 133 were diagnosed with Wilms tumors (nephroblastomas) and 33 were diagnosed with hepatoblastomas. In 94% of the cases, the initial clinical signs were an abdominal mass and/or hematuria. Of the 133 Wilms tumor patients aged ≤5 years, four (3%) presented with LO at the initial clinical examinations, located in the right lower limb (n=2), left lower limb (n=1), and right upper limb (n=1). In these four cases of Wilms associated with LO, we found ILO (Figures 1 and 2), and the affected side coincided with the laterality of the Wilms tumor.

Only a five-year-old patient with lower limb involvement required telemetry to quantify the real lower limb dysmetria and, thus, decide whether any surgical intervention was necessary. In his clinical follow-up, similar to the rest of the three patients with lower extremity involvement, the dysmetria did not progress and did not require any specific therapeutic approach. The patient with upper extremity involvement did not require any diagnostic or therapeutic approach by the orthopedic surgeons, beyond regular clinical follow-up.

In all patients with hepatoblastoma, there was an appearance of an abdominal mass and/or general discomfort. Of all the patients who presented with hepatoblastoma, only one (3%) presented with an ILO at the age of five years in the right lower limb at the time of tumor diagnosis (Table I).

Of 166 patients with Wilms tumors and hepatoblastoma, five (3%) presented with LO (4 Wilms tumors and 1 hepatoblastoma), of whom four had

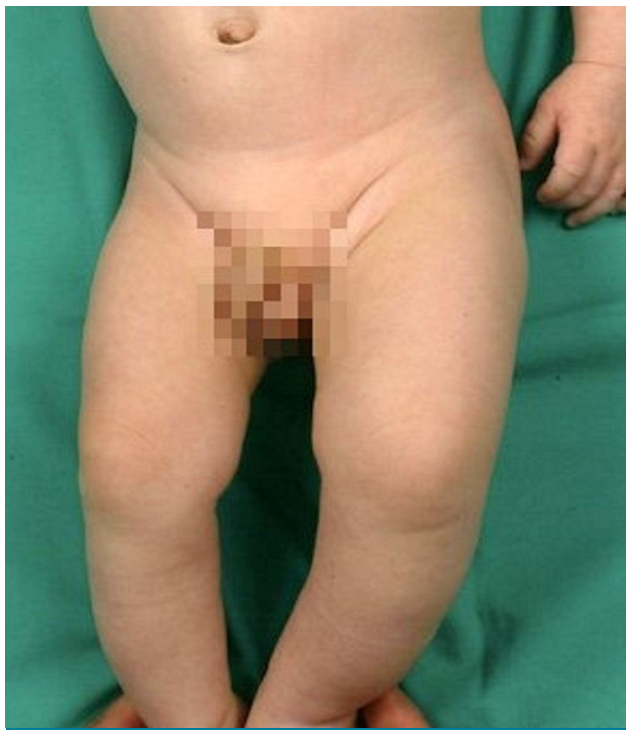

FIGURE 1. Left lower limb isolated lateralized overgrowth.

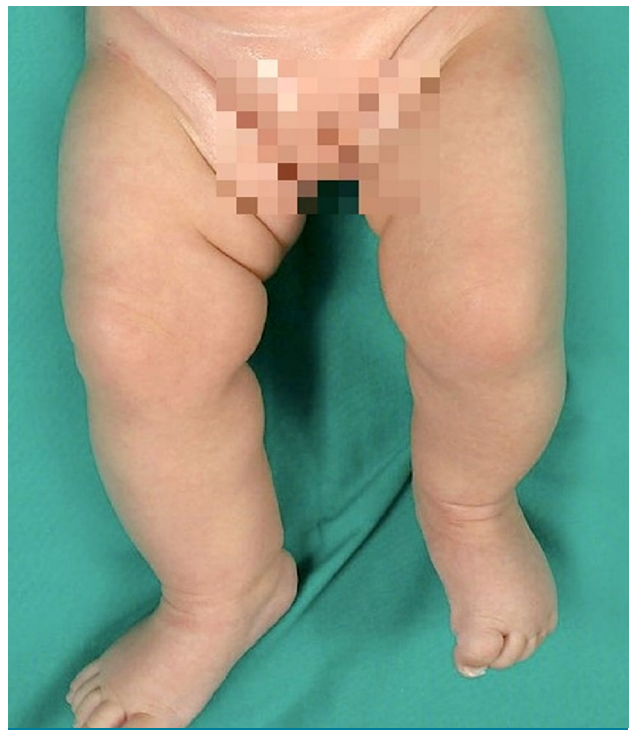

FIGURE 2. Right lower limb isolated lateralized overgrowth.

a Stage I tumor and one had a Stage III tumor. The mean follow-up was 12.6±4 (range, 8 to 17) years with a favorable evolution, and none required bone surgery due to unequal limb length, which was well tolerated.

DISCUSSION

An increased risk of intra-abdominal embryonal tumors in LO cases has been reported, such as Wilms tumors, hepatoblastomas, neuroblastomas, and adrenocortical tumors, with an incidence ranging between 1 and 6% in various case series[4,7,8,11] and are usually diagnosed before 10 years of age.[12]

In the current study, we found an incidence of LO related to intra-abdominal tumors (Wilms tumor and hepatoblastoma) of 3%, consistent with the literature. According to the literature, the presence of LO correlates with tumors diagnosed at an earlier stage and better prognosis. Our results support this

TABLE I
Cases of intra-abdominal tumors associated with asymmetric regional body overgrowth

Cases	Sex	Asymmetric regional body overgrowth	Location of the asymmetric regional body overgrowth	Age at which asymmetric overgrowth is recorded (years)	Age at tumor diagnosis (years)	Intra-abdominal tumor and its stage
1	M	Isolated	Left lower limb	1	5	Left Wilms tumor. Stage I
2	F	Isolated	Right lower limb	0 month	10 months	Right Wilms tumor. Stage I
3	F	Isolated	Right upper limb	4	4	Right Wilms tumor. Stage III
4	F	Isolated	Right lower limb (extremity segment-calf muscle)	0	2	Right Wilms tumor. Stage I
5	M	Isolated	Right lower limb	5	5	Hepatoblastoma. Stage I

statement, as four out of five patients were affected in tumor Stage I. Consequently, it is important to increase awareness in the orthopedic surgical community about this fact, as identifying an LO can be helpful in the early diagnosis and better prognosis of intra-abdominal tumors.[13]

Overgrowth phenotypes show that, in 38% of cases, an upper or lower limb is entirely involved and, in 17%, only a limb segment is affected.[8] A lower limb is the most common location (73%).[7] Consistent with the literature, all patients with LO in our study presented with lower or upper limb involvement, mostly lower limb.

Lateralized overgrowth may be associated with several syndromes. Frequency of intra-abdominal tumors tends to be higher (9%) in BWSp, combined with LO, whereas its association with Klipple-Treanauny, Goltz, or Proteus syndromes, among others, does not have a reported increased incidence. Patients with ILO and BWSp have an increased risk for the development of childhood tumors compared to the general population.[14] Due to clinical overlap and similar tumor associations in BWSp and ILO patients, epigenetic studies have been published describing common specific 11p15 defects, particularly paternal uniparental disomy and hypermethylation of H19 which predisposes to abdominal tumors and conditions a body asymmetry. Nevertheless, some authors have shown that more than half of ILO cases are unaffected by these epigenetic abnormalities, in contrast to BWSp cases, of which 80% are affected, and as the genetic or epigenetic alteration is present, an increased incidence of abdominal neoplasms is reported.[14,15]

The data regarding the ideal goal of screening recommendations would concern stratifying the degree of neoplasm risk in individuals with LO and identifying tumors at an early stage, when treatment is most effective and less aggressive. Therefore, the International Society of Paediatric Oncology - Renal and Host Genome Group made some recommendations for LO patients.[16] They should be referred to a clinical geneticist, and

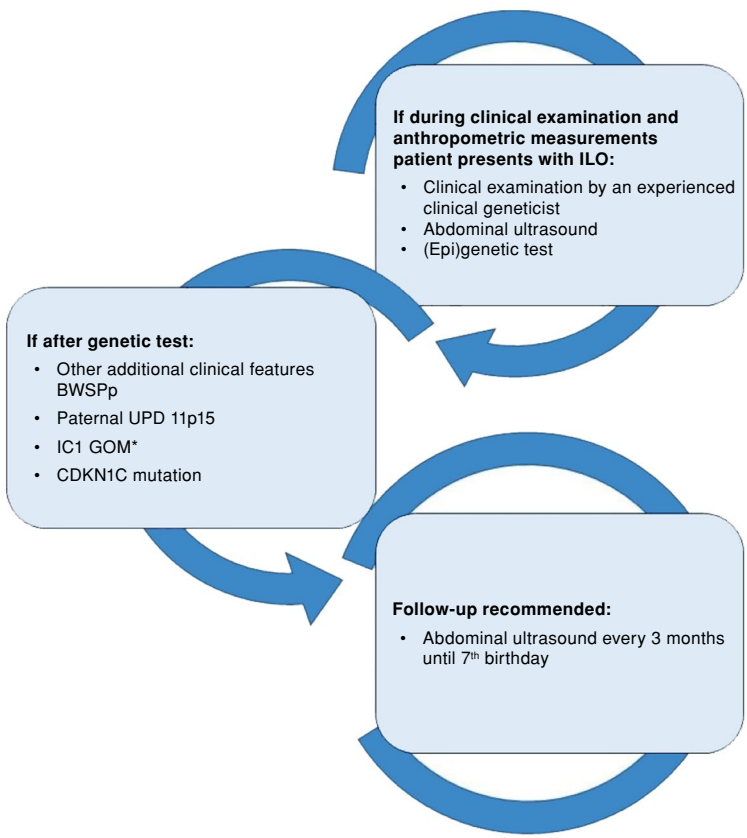

FIGURE 3. A recommendation protocol for asymmetric regional body overgrowth since diagnose. UPD (Uniparental Disomy), IC1 GOM (Imprinting Center 1 Gain of Methylation).

an examination and molecular testing including 11p15.5 analysis in deoxyribonucleic acid (DNA) should be performed.[17-19] Baseline abdominal ultrasonography is advised to assess the presence of organomegaly. For significant ILO, the advice is to establish the underlying (epi)genetic cause and initiate surveillance while awaiting the test results. If any other clinical feature of BWSp is present or an (epi)genetic change is found, an abdominal ultrasound every three months until the age of seven is warranted (Figure 3). Most authors do not recommend routine ultrasound surveillance in patients with Imprinting Center 2 loss of methylation, as the tumor risk is less than 5% for this specific group.

The main limitation to our study is that, due to the lack of coding of the clinical signs of LO in previous years, we could not reliably obtain a group of patients with this clinical sign to evaluate the risk of tumor appearance. The retrospective data collection based on the diagnosis of the main intra-abdominal tumors provided us another option to analyze the incidence of LO and tumors from medical databases obtained from a national and European reference children's hospital, such as our institution, and allowed us to collect information on pathologies that are uncommon in our daily practice.

In conclusion, it is critical to identify patients with this condition to diagnose genetic alterations associated with intra-abdominal tumors at our consultations of pediatric orthopedics. Therefore, (epi)genetic testing is recommended in all patients affected by LO or ILO to rule out a possible genetic alteration and identify subgroups with a higher risk for tumor development, who are more likely to benefit from tumor protocol surveillance. However, further multi-center, large-scale, prospective studies including LO and ILO patients are required and improved molecular genetic techniques may define specific surveillance recommendations in patients with this specific isolated overgrowth syndrome.

Ethics Committee Approval: The study protocol was approved by the Sant Joan de Déu Barcelona Hospital Ethics Committee (date: 29.04.2021, no: PIC-21-21). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: In order to comply with all applicable laws and regulations concerning the privacy and/or security of personal information and according to the ethical committee, all data was pseudonymized due to the impossibility of collecting the informed consent of all patients who are not under present follow-up. Additional informed consent was obtained from all individual participants for whom identifying information, such as images, is included in this article.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, data collection and/or processing: L.M.P.L., I.P.A.; Design, literature review: L.M.P.-L., I.P.A., H.S., R.G.G.; Control/supervision, writing the article, critical review: I.P.A., H.S., R.G.G., L.M.S., C.G.F., F.T.R., L.M.P.L.; References and fundings, materials: L.M.P.L., I.P.A., H.S.

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