Unexpected high frequency of skeletal dysplasia in idiopathic short stature and small for gestational age patients

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Abstract

Objective: To assess the prevalence of skeletal dysplasias (SDs) in patients with idiopathic short stature (ISS) or small for gestational age (SGA) status.

Setting: Rare Endocrine/Growth Diseases Center in Paris, France.

Design: A prospective study on consecutive patients with ISS and SGA enrolled from 2004 to 2009.

Method: We used a standardized workup to classify patients into well-established diagnostic categories. Of 713 patients with ISS ($n=417$) or SGA status ($n=296$), 50.9% underwent a skeletal survey. We chose patients labeled normal or with a prepubertal slowdown of growth as a comparison group.

Results: Diagnoses were ISS (16.9%), SGA (13.5%), normal growth (24.5%), transient growth rate slowing (17.3%), endocrine dysfunction (12%), genetic syndrome (8.9%), chronic disease (5.1%), and known SD (1.8%). SD was found in 20.9% of SGA and 21.8% ISS patients and in only 13.2% in our comparison group. SD prevalence was significantly higher in the ISS group than in the comparison group, especially (50%) for patients having at least one parent whose height was < -2 SDS. Dyschondrosteosis and hypochondroplasia were the most frequently identified SD, and genetic anomaly was found in 61.5 and 30% respectively. Subtle SD was found equally in the three groups and require long-term growth follow-up to evaluate the impact on final height.

Conclusion: SD may explain more than 20% of cases of growth retardation ascribed to ISS or SGA, and this proportion is higher when parental height is < -2 SDS. A skeletal survey should be obtained in patients with delayed growth in a context of ISS or SGA.

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Introduction

Idiopathic short stature (ISS) is diagnosed when the conventional workup identifies none of the established causes of short stature such as growth hormone deficiency, malnutrition, chronic disease, or genetic abnormalities (1, 2). However, some patients classified as having ISS may exhibit conditions that are not detected by the

conventional workup. ISS accounts for 0.9–60% of all cases of short stature, depending on the country (percentage of malnutrition) or the population of the study (whole population or subgroup of small children) (3, 4, 5, 6, 7, 8, 9, 10, 11). To date, only three studies have routinely investigated patients with ISS for skeletal dysplasia (SD),

which was found in 2.3 (9), 5.6 (3), and 11.4% (11) of cases respectively. Comparatively, there is no identified cause for many children born small for gestational age (SGA) and the catch-up is not predictable. The identification of SD in these two categories of patients (ISS and SGA) can lead to a better understanding of the growth evolution and growth hormone treatment can sometimes be indicated and efficient.

Knowledge about SD has improved considerably over the last decade (12, 13, 14, 15). Many patterns of SD have been described (14), and the underlying genetic mechanisms have been more often identified (16). More specifically, two genes, namely, the short stature homeobox gene (*SHOX*) and the gene encoding fibroblast growth factor receptor 3 (*FGFR3*), have been shown to be responsible for a wide phenotypic variability ranging from dyschondrosteosis and hypochondroplasia, respectively, to 'isolated' short stature. Consequently, the prevalence of SD is probably underestimated among individuals with short stature classified as having ISS or ascribed to SGA status. In dyschondrosteosis, for instance, the bayonet-like forearm deformity (Madelung's deformity) is not consistently observed, final height can be within the normal range (about -1 SDS), and considerable phenotype variability occurs within families (17, 18, 19, 20, 21, 22, 23, 24, 25). *SHOX* haploinsufficiency has an estimated prevalence of 1/2000 and has been reported in patients with ISS and no clinical manifestations of SD (18, 21, 23, 24, 26, 27, 28, 29, 30). Short stature in family members of children with ISS is a key feature for the diagnosis of familial SD (17, 18, 23, 24).

We therefore hypothesized that SD may be more common than generally believed among children with ISS or SGA status and that the rate is particularly high in the event of parental short stature. To assess this hypothesis, we prospectively studied a cohort of children referred to a pediatric teaching hospital for abnormal growth.

Subjects and methods

We prospectively enrolled consecutive patients referred to our reference center for growth disorders at the Necker Enfants Malades pediatric hospital in Paris, France, over the 6-year period from January 1, 2004, to December 31, 2009. We excluded adopted patients, patients for whom no knowledge was available on the biological parents and birth, and patients who did not complete the diagnostic workup.

Etiological evaluation

All patients underwent a standardized workup (Fig. 1). The results were used to classify the patients into eight well-established diagnostic groups (Table 1) (1).

All patients in the ISS and SGA groups underwent a skeletal survey to look for SD (14, 15, 31). We excluded patients with an associated organ malformation (heart defect, spina bifida, mental retardation, etc.). The radiation dose exposure was 1.8 mSv. The thoracolumbar spine was evaluated for lumbar spinal stenosis and size and form of vertebrae; the left wrist and forearm for Madelung's deformity, metacarpal/phalange sizes, and carpal

Figure 1

Standardized workup for classifying patients into eight etiological groups. ESR, erythrocyte sedimentation rate; Ab, autoantibodies; TSH, thyroid-stimulating hormone; FT₄, free thyroxine; IGF1, insulin-like growth factor 1; GH, growth hormone.

Table 1 Definition of the eight etiological groups.

1.	Normal patients: normal growth velocity and height between -2 SDS and $+2$ SDS (based on French reference data by Sempé, Sempé and Pedron, Livre d'Auxologie Méthode et Séquence, Laboratoire Théraplix, 1979)
2.	Physiological prepubertal growth stasis: height initially between -2 SDS and $+2$ SDS followed by transient slowing of growth during the prepubertal period then catch-up to the initial growth curve during puberty
3.	SGA: born small for gestational age (length and/or weight)
4.	Endocrine disorder: growth hormone deficiency (two deficient stimulation tests with GH peak <20 mUI/l), hypothyroidism, Cushing's syndrome, hypogonadism
5.	Genetic syndrome: identified genetic syndrome or severe polymalformative syndrome
6.	Chronic disease: known chronic disease explaining the slow growth rate (renal failure, celiac disease, chronic inflammatory disease)
7.	Known skeletal dysplasia: patients diagnosed with skeletal dysplasia before the first appointment with a pediatric endocrinologist and referred to our center for further endocrine investigations or growth hormone therapy
8.	Idiopathic short stature: growth under -2 SDS with no identifiable etiology

ossification; and the pelvis for iliac wings, shortness of the femoral necks, and metaphyseal and epiphyseal anomalies (21, 32, 33, 34). All radiographs were read by a panel of specialists including geneticists from the French reference center for skeletal dysplasia, radiologists, and pediatric endocrinologists.

When dyschondrosteosis or hypochondroplasia was suspected, genetic testing was proposed. Genetic analysis could not be done on the patients without radiographic evaluation as they either were lost to follow-up or refused any further investigations. Molecular screening for *SHOX* gene was carried out as previously described, using MLPA before 2007 and *SHOX* direct sequencing combined with MLPA after 2007 (30). For *FGFR3*, direct sequencing of exons was only carried out (35). Subtle SD was defined as the presence of skeletal features not specific of a well-characterized SD, for instance, presence of an epiphyseal or metaphyseal defect, small epiphysis, isolated lumbar spinal stenosis, or shortness of the femoral necks.

Skeletal surveys from patients classified as having normal growth or a transient prepubertal growth velocity decline were used as a comparison group. However, the patients in these groups who underwent skeletal surveys were not taken at random; instead, they were selected based on height between -2 and -1.5 SDS, or height more than 1.5 SDS from target height, or context of familial short stature, or SD diagnosed in a relative, or clinical features of SD. The radiographs were examined by the same panel of specialists as those from the ISS and SGA groups. We chose this subgroup as a comparison group as it would be ethically unacceptable to expose normal children to the radiation dose required for a skeletal survey.

For all patients, parents signed an agreement for the usual care.

Statistical analysis

Groups were compared using the χ^2 test or Fisher's exact test, depending on sample size. Mean comparisons were done by Student's *t*-test. *P* values lower than 0.05 were considered significant.

Results

Patients

During the study period, 2546 patients were evaluated for suspected growth disorders. After exclusion of 34 adopted patients and 16 patients with missing data, 2496 patients were left for the study.

At referral, mean age was 9.5 years (0.02–21.3 years) and mean height was -1.79 SDS (Table 2). Height below -2 SDS was significantly more prevalent among girls than among boys (51 vs 42.9%, $P=0.00006$). Mean target height was -0.3 SDS in boys and -0.5 SDS in girls, and target height was below the national mean for 66.1% of patients overall (60.8% of boys and 72.2% of girls). Mid-parental height was below -2 SDS in 3.71% of patients overall (2.5% of boys and 5.3% of girls).

Of the 2496 patients, 611 (24.5%) had normal growth, 432 (17.3%) transient slowing of the growth rate, 298 (12%) an endocrine disorder, 223 (8.9%) a genetic disorder, 126 (5.1%) a chronic disease, and 45 (1.8%) already an identified SD before the first appointment with a pediatric endocrinologist (Table 3).

We identified 337 patients (13.5%) with a history of being born SGA (48.9% boys), with a mean height of -2.24 SDS, 74.5% with no signs of puberty (average age 5.43 years) (Table 2). During the first 4 years of life, 78 (23.1%) had a spontaneous catch-up of growth from <-2 SDS to >-2 SDS. Eleven patients had Silver–Russell

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Table 2 Characteristics of the cohort.

		Height ≤ -2 SDS	Father's height ≤ -2 SDS	Mother's height ≤ -2 SDS	Both parents' height ≤ -2 SDS
Overall cohort					
<i>n</i>	2496	1160	145	188	23
Mean height (SDS)	-1.79 (-9.2 to +3)	-2.59 (-9.2 to -2)	-2.38 (-5 to +1)	-2.05 (-4.5 to +2)	-2.22 (-4 to 0)
Boys	1402 (56.2%)	602	70	101	11
Girls	1094	558	75	87	12
Prepubertal patients	64.5%	–	–	–	–
ISS					
<i>n</i>	424	All	60	46	10
Mean height (SDS)	-2.39 (-9.2 to -2)		-2.54 (-4 to -2)	-2.36 (-4 to -2)	-2.63 (-4 to -2)
Boys	220		28	22	2
Girls	204		32	24	8
SGA					
<i>n</i>	337	233	25	38	5
Mean height (SDS)	-2.24 (-6 to +1)	-2.6 (-6 to -2)	-2.65 (-4.3 to -0.5)	-2.41 (-3.7 to -1)	-2.63 (-3.5 to -1)
Boys	165	108	10	17	3
Girls	172	125	15	21	2

ISS, idiopathic short stature; SGA, small for gestational age.

syndrome (genetically confirmed, all growing under -2 SDS); 18.1% ($n=61$) had at least one parent with a final height under -2 SDS (P-SGA subgroup). The percentage of patients without catch-up growth was not significantly different between the P-SGA and non-P-SGA subgroups (78.7 and 72.5% respectively).

The 424 remaining patients were classified as having ISS, 51.8% boys, with a mean height of -2.39 SDS (Table 2). At first consultation, 67.9% had no signs of puberty (average age 7.6 years). Among the patients seen for the first time at final height ($n=55$), 32 had grown above -2 SDS but had a final height < -2 SDS; 23.3% ($n=99$) had at least one parent with a final height < -2 SDS (P-ISS subgroup).

SD prevalence

For the evaluation of SD, we excluded seven ISS patients and 41 SGA patients who each had an isolated birth defect. Overall, the skeletal survey was performed in 56.1% (234/417) of ISS patients and in 43.6% (129/296) of patients born SGA (Table 5). There was no difference between patients with ISS who did or did not have a skeletal survey. However, the mean height of SGA patients who had X-rays was significantly lower (Table 4). In our comparison group made of patients considered normal (N) or with prepubertal slowdown of growth (PS), 19.6% (204/1043) had X-rays (22.4% in N and 15.5% in PS). Reason for not performing the skeletal survey was family refusal (167/296 (56.4%) for SGA and 183/417 (43.9%) for ISS). In case of familial short stature (at least one

parent with height < -2 SDS), the rate of obtained X-rays was 63.6% of the ISS (P-ISS) (no significant difference of X-ray ratio for P-ISS and ISS, $P=0.08$) and 59% of the SGA (P-SGA) patients (X-rays were accepted by the families significantly more frequently by P-SGA than SGA, $P=0.007$).

Table 3 Skeletal dysplasias (SD) identified.

Known SD ($n=45$)	
Hypochondroplasias	15
Dyschondrosteosis	5
Multiple epiphyseal dysplasias	7
Achondroplasias	2
Pseudohypoparathyroidism	2
Chondrodysplasias	2
Spondylo-metaphyseal dysplasias	2
Pycnodysostosis	2
Fibrosis dysplasias	2
Metaphyseal dysplasia	1
Osteopetrosis	1
Brachymetacarpia	1
Pseudoachondroplasia	1
Exostosis	1
Vertebral malformations	1
Diagnosed SD ($n=105$)	
Dyschondrosteosis	57
Hypochondroplasias	17
Multiple epiphyseal dysplasias	12
Epiphyseal and metaphyseal dysplasias	5
Brachymetacarpias	5
Metaphyseal dysplasias	3
Weill-Marchesani syndromes	2
Brachyolmia	1
Acromicric dysplasia	1
Floating-Harbor syndrome	1
Albright syndrome	1

Clinical Study	I Flechtner and others	Impact of skeletal dysplasia on growth	170:5	681
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Table 4 Comparison of the clinical characteristics of ISS and SGA patients with or without skeletal survey.

	X-ray	Refused X-ray	P
ISS			
n	234	183	
Mean height (SDS)	−2.41	−2.33	NS ($P=0.1$)
Boys	51.7%	53.6%	NS
Mean age	9.35	9.26	NS
Mean maternal height (cm)	158.3	158.9	NS
Mean paternal height (cm)	170.7	170.8	NS
SGA			
n	129	167	
Mean height (SDS)	−2.39*	−2.03*	* $P=0.00023$
Boys	47.3%	52.1%	NS
Mean age	7.9	7.26	NS
Mean maternal height (cm)	158.4	159.4	NS
Mean paternal height (cm)	171	171.9	NS

ISS, idiopathic short stature; SGA, small for gestational age; NS, non significant.

Overall, SD was diagnosed in 105/567 (18.5%) patients (ISS+SGA+comparison group): dyschondrosteosis (54.3%), hypochondroplasias (16.2%), and multiple epiphyseal dysplasia (11.4%) were the most frequent (Table 3).

Of 129 SGA patients in whom a skeletal survey was obtained, 27 (20.9%) had SD (Table 5). Interestingly, only one patient had a catch-up growth and 6/10 patients with dyschondrosteosis had at least one parent < -2 SDS. We found no significant difference in the SD frequency between P-SGA and non-P-SGA patients.

Of 234 ISS patients in whom a skeletal survey was obtained, 51 (21.8%) had SD (Table 5). The SD rate was significantly higher in the P-ISS subgroup (21/42, 50%) than in the non-P-ISS subgroup ($P=0.009$). Dyschondrosteosis was significantly more common in the ISS group than in the SGA group ($P=0.035$).

Frequency of SD was significantly higher in the ISS+SGA group vs the comparison group (78/363 vs 27/204, $P=0.015$) and in the ISS group vs the comparison group (51/234 vs 27/204, $P=0.019$), but neither for SGA vs the comparison group nor for ISS vs SGA group.

When dyschondrosteosis or hypochondroplasia was diagnosed, genetic analysis was proposed. In the dyschondrosteosis group ($n=57$), deletion located in the PAR1 region or *SHOX* point mutation was found in 61.5% (24/39) when genetic analysis was done (Table 6). In the hypochondroplasia group ($n=17$), an *FGFR3* mutation was found in four of 12 patients analyzed.

Subtle SD

We identified subtle bone dysplasia (SSD) like epiphyseal or metaphyseal defect, small epiphysis, isolated lumbar spinal stenosis, or shortness of the femoral necks, not specific of a well-described SD but which could not be considered as normal however. The frequency was close to the frequency of SD (11.8–17.8%, Table 5), without any significant difference between the groups.

Skeletal anomalies were sometimes found in one or both parents < -2 SDS but not in the child at the time of the skeletal survey in 16 cases.

Table 5 Prevalence of skeletal dysplasia in the idiopathic short stature group, small for gestational age group, and comparison group.

	n	X-ray % (n)	SD	SD/X-ray (%)	SSD % (n)
SGA					
SGA	235	39.6 (93)	16	17.2	18.2 (17)
P-SGA	61	59 (36)	11	30.5	22.2 (8)
Total SGA	296	43.6 (129)	27	20.9	17.8 (23)
ISS					
ISS	318	53.8 (171)	30	17.5	18.7 (32)
P-ISS	99	63.6 (63)	21	33.3	9.5 (6)
Total ISS	417	56.1 (234)	51	21.8	16.2 (38)
Comparison group					
N	611	22.4 (137)	24	17.5	8 (11)
PS	432	15.5 (67)	3	4.5	19.4 (13)
Total	1043	19.6 (204)	27	13.2	11.8 (24)

SGA, small for gestational age; ISS, idiopathic short stature; P-ISS and P-SGA, patients with ISS or SGA respectively, with at least one parent whose height is ≤ -2 SDS; N, patients from the normal group; PS, patients from the transient prepubertal slowdown of growth velocity group; SD, skeletal dysplasia; SD/X-ray, percentage of identified SD in X-rayed patients; SSD, subtle skeletal dysplasia.

Clinical Study	I Flechtner and others	Impact of skeletal dysplasia on growth	170:5	682
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Table 6 Genetic analysis in the identified dyschondrosteosis and hypochondroplasia.

Type of SD	Total n	ISS	SGA n	Controls	Identified mutation	Not identified mutation	Parental refusal of investigations	Under investigation
Dyschondrosteosis	57	34	10	13	<i>SHOX</i> 24	<i>SHOX</i> 15	15	3
Hypochondroplasia	17	6	6	5	<i>FGFR3</i> 4	<i>FGFR3</i> 8	3	2

SD, skeletal dysplasia; ISS, idiopathic short stature; SGA, small for gestational age; *SHOX*, short stature homeobox gene; *FGFR3*, fibroblast growth factor receptor 3 gene.

Bone age

The gap between chronological age and the first available bone age (before growth hormone or sex steroid treatment) showed no significant differences across diagnostic categories, except for the PS group, in which a gap >2 years was more common, as expected. This gap was not significantly different between patients with and without SD.

Discussion

We found a high frequency (21%) of SD in ISS and SGA patients, SD which had not been diagnosed by the pediatrician, who sent the child to our endocrinology unit because of insufficient growth. Clinical features of SD can be subtle and not always acknowledged by the physician and are not always sought for. Recognizing radiological signs of SD may also be difficult and requires a systematic analysis by experienced clinicians. Systematic clinical search of Madelung deformity, small arm span, large and short hands and feet must be done for every child with growth anomaly. X-rays must be carried out when no other etiology can be found before classifying the child as ISS especially and also for SGA. Special attention is required when one parent at least has a final height <−2 SDS, as the frequency of SD goes up to 50% for ISS in this context.

We found SD in 13.2% of patients who had neither ISS nor SGA. However, these reference patients were selected for skeletal survey based on height ≤ -1.5 SDS, or height more than 1.5 SDS below target height, or familial short stature, or SD diagnosed in a relative, or clinical features of SD. Had our comparison group been composed of healthy children without one of those characteristics, the prevalence of SD would have been lower without doubt and the difference with the ISS and SGA groups even greater. However, it would be ethically unacceptable to expose normal children to the radiation dose required for a skeletal survey.

A significant proportion of our patients had only SSD (epiphyseal or metaphyseal defect, small epiphysis,

isolated lumbar spinal stenosis, or short femoral necks) that did not meet criteria for well-characterized SD. We are monitoring these patients to determine whether their skeletal abnormalities are clinically relevant or merely variants of normal.

Genetics can be helpful in SD but the mutation/deletion is not always found (approximately in 70% of dyschondrosteosis (29, 30, 36, 37, 38) and 60% of hypochondroplasia (35)). However, the systematic search of *SHOX*/PAR1 anomaly in ISS can lead to the identification of mutations (18, 22, 23, 26, 39): up to 21% of ISS without any clinical feature, and normal proportions in Huber's study (24). In our study, we chose to carry out genetic analysis widely when clinical and/or radiologic feature of dyschondrosteosis or hypochondroplasia was found. However, we were not able to test every child not having a skeletal survey, mainly because the parents refused any further investigation and also because it would be too expensive to search for a *SHOX* or *FGFR3* mutation at random, without any clinical or radiological argument. The frequency of 61.5% of *SHOX* identified anomaly is in concordance with the literature but the 30% of identified mutations of *FGFR3*, lower than reported usually, is certainly explained by this large screening.

Our study has several limitations. First, clinical features such as arm span and upper-to-lower extremity ratio were not measured and may help the clinician to suspect SD. The observation of a Madelung deformity or any other clinical feature of SD was only reported when obvious, but when mild or suspected, the description was not precise enough to be used in this study. Second, the ratio of carried-out X-rays of ~50% can also be considered as a bias. However, the clinical characteristics of the patients and families who refused to complete the explorations are not different from the X-rayed group, except for the patient's median size in the SGA group. X-ray examination was required after the biological results turned out to be normal and many families were lost to follow-up (despite several phone calls and mail) or 'tired' of undergoing medical examination. In the SGA group,

the skeletal evaluation was logically more frequently refused when the patient was taller, explaining the significant difference in the mean height between the patients having and not having X-rays. The interpretation of the SD radiological features can sometimes be subjective and needs trained clinicians, which was the case in this study as we are part of the French Reference Center for Skeletal Dysplasia.

Identifying SD in patients with short stature has several benefits. First, some SD require orthopedic surveillance; others can have a negative influence on the pubertal growth spurt and reduce projected final height. There are also therapeutic implications in some situations (40). For instance, in France, growth hormone treatment is approved for patients with dyschondrosteosis but not for patients with ISS. On the opposite, growth hormone can be contraindicated in some SD.

In keeping with earlier data, dyschondrosteosis was more common in the ISS group than in the SGA group. We found that the prevalence of SD in our study was the highest when at least one parent had short stature. Consequently, the height of the parents should be obtained routinely when evaluating a child with short stature. Examining the patients and the parents, for instance for disproportion with a short arm span or upper-to-lower extremity ratio, may show abnormalities suggesting SD. In some SD, the radiographic abnormalities take time to develop. A follow-up skeletal survey may therefore be indicated if growth velocity is slow. Finally, we found no association between a large gap between bone age and chronological age, on the one hand, and SD on the other. Again, these patients will be monitored closely to determine the impact of this gap on final height (41).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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