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Short Stature And Molecular Abnormalities of Shox Gene : About two Familial Cases

Ns Fedala, Aem Haddam , Belarbi,L Ahmed Ali

Summary: *Recent years have seen the emergence and identification of a large number of genes responsible for constitutional bone diseases. Among these, congenital syndrome or the Leri weill dyschondrosteosis is important which includes a wide spectrum of disease ranging from Langer mesomelic dysplasia, the most severe phenotype to the isolated Madelung deformity*

This condition is caused by a mutation or haploinsufficiency of the short stature homeobox (SHOX) gene which is located on both the X and Y chromosomes. This gene is essential for the development of the skeleton. It plays a particularly important role in the growth and maturation of bones in the arms and legs. We report observations about two patients and their family history.

Keywords: *Shox gene, Madelung deformity, short stature, bone disease*

I. Introduction

Recent years have seen the emergence and identification of a large number of genes responsible for constitutional bone diseases. Among these, congenital syndrome or the Leri weill dyschondrosteosis is important which includes a wide spectrum of disease ranging from Langer mesomelic dysplasia, the most severe phenotype to the isolated Madelung deformity wich is very characteristic and idiopathic short stature (1)

This condition is caused by a mutation or haploinsufficiency of the short stature homeobox (SHOX) gene which is located on both the X and Y chromosomes (2). The SHOX gene is part of a large family of homeobox genes, which act during early embryonic development to control the formation of many body structures. It also belongs to a family of genes called PAR (pseudoautosomal regions).Specifically, the SHOX gene is essential for the development of the skeleton. It plays a particularly important role in the growth and maturation of bones in the arms and legs (3)

We report observations about two patients and their family history.

Clinical observation:

Two young patients B.D and H.S aged 14 and 4 years respectively were brought into endocrinology consultation for exploration of short stature. their height for chronological age were below the third percentile or minus 2 sd of height standards (Table 1).

Table 1: Clinical characteristics of patients:

Patients	B.D	H.S
Age (years) (Sex)	13 (G)	04 (G)
birth weight(kg)	4,4	3.2
Size at birth (cm)	-	-
CP at birth(cm)	-	-
PM Développement	normal	Normal
target size (cm)	156.5	155
Size at first consultation (cm) - DS/M - DS/TC	124 -7 -4	89 -3 -2
Weight (kg)(BMI)	31 (>P50)	14(17.6)
Upper segment (cm)	59	45
Lower segment (cm)	65	44
Wingspan (cm)	115	85
Wingspan / size (%)	92	95
Upper segment / size (%)	47	50
Pubertal (TANNER)	S1P1A1R0	S1P1A1R0
Bone age (years)	10	02
clinical score	12	14

The clinical and paraclinical investigations could eliminate growth retardation intrauterine, inflammatory disease or visceral and endocrine causes (Table 2).

Table 2: Results of the hormone balance of patients:

Balances		B.D	H.S
FT4 pmol/l (8,02-24,5)		19.62	22.58
TSH µU/ml (0,2-4)		1.22	300.6
Test glucagon,propranolol/GH (µU/ml)	GH T0	0,35	4,77
	Nadir	0,74	81,12
	Pic	8,41	100
Test à l'insuline/GH (µUI/ml)	GH T0	7,05	-
	GH	19,54	-
Igf1		-	26,60 ng/ml

However, we have noted dwarfing mesomelic in both cases (Fig 1 and.2) and deformed Medelung as confirmed by x-ray Fig (3and4).

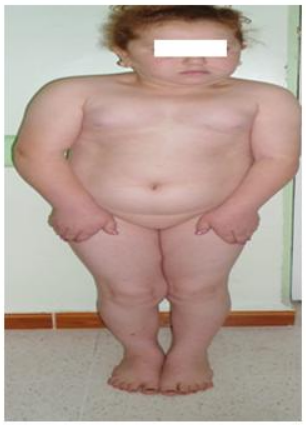

FIG1 : BD

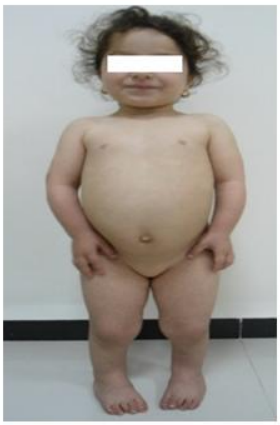

FIG2 :HS

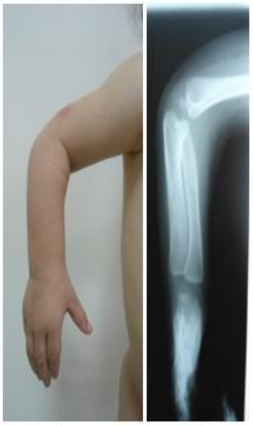

FIG3 :HS

FIG4 :BD

These two elements have helped us to guide clinical diagnosis by a clinical score (Table3) (4) to identify the disease which was 12 and 14 respectively. Both patients had a normal karyotype. Complete gene deletion (BD) and nonsense mutation (HS) in the coding region of SHOX were identified.

Table 3: Clinical score to identify patients carrying an abnormal gene SHOX (4)

sign	résult	Point
Wingspan / size	<96.5%	2
upper segment / size	<55.5%	2
BMI	<50 percentile	4
cubitus valgus	Yes	2
Forearm short	Yes	3
Forearm arched	Yes	3
Muscle hypertrophy	Yes	3
Dislocation of the ulna	yes	5
Total		24

A total of > 4 has a high sensitivity (71%) but a low positive predictive value (11%) . A total> 7 has a low sensitivity (61%) but a better positive predictive value (19%).

A family survey for the first patient showed that a maternal aunt and her two children followed for idiopathic short stature. The parents of second patient are small and their deformed Medelung was observed by radiological assay (Fig 5 and6). Genetic investigation was not performed. Parents refused to do it

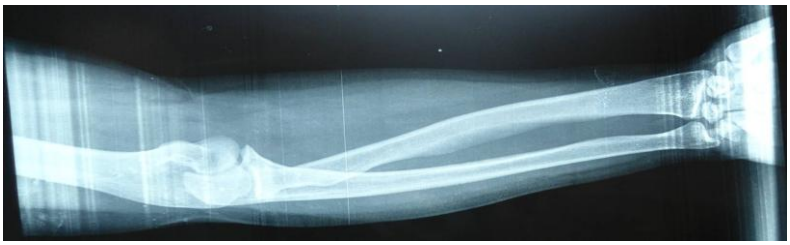

FIg5 : X-ray of the arm of the mother of the patient BD

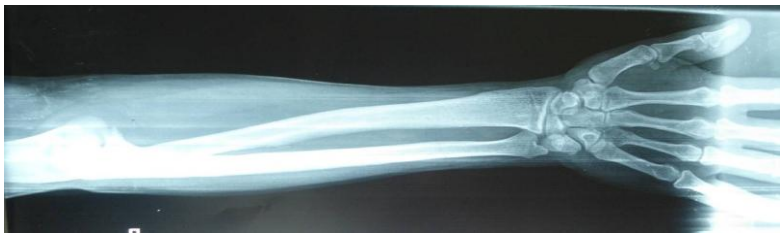

FIG6: X-ray of the arm of the father of the patient HS

Patients were placed under the treatment of biosynthetic growth hormone to improve the growth rate optimize the prognosis stature. After two years of treatment, we observed a significant growth catch-up with a height gain of 1 Standard deviation in both patients (Fig 7and 8).

II. Discussion

The dyschondrosteosis is a rare disease affecting approximately 1 cases/100, 000 . Girls seems to be more affected than boys (5). It is a condition of pseudo-autosomal dominant transmission caused by an abnormality of the SHOX gene, located in the pseudo-autosomal region 1 (PAR-1) sex chromosome (Xp22.33 and Yp11.32). Several molecular abnormalities can be observed, it may be mutation, deletion or duplication. These abnormalities may be inherited or appear de novo(6)(7).

The SHOX gene is expressed in several cell types but mainly by fibroblasts during fetal life to allow chondrocyte proliferation and skeletal development. Its haploinsufficiency disrupts chondrocyte proliferation in the combination plate (6)

The gene was first found during a search for the cause of short stature in women withTurner syndrome, in which there is loss of genetic material from the X chromosome, classically by loss of one entire X chromosome (2).

Since its discovery, the SHOX gene has been found to play a role in idiopathic short stature , Léri-Weill dyschondrosteosis, and Langer mesomelic dysplasia. The SHOX phenotype is heterogeneous. Genetic abnormalities cause a disturbance of a delicately balanced temporal and spatial expression, variations in the expression level may explain the variable severity in the manifestations of SHOX mutations . Modifier genes, epigenetic interactions, and stochastic effects are hypothesized to explain these phenomena (8).

Léri-Weill dyschondrosteosis results from genetic changes involving one copy of the SHOX gene in each cell. Most commonly, this skeletal disorder is caused by a deletion of the SHOX gene. Other genetic changes that can cause the disorder include mutations in the SHOX gene or deletions of nearby genetic material that normally helps regulate the gene's activity. These changes reduce the amount of SHOX protein that is produced. A shortage of this protein disrupts normal bone development and growth starting before birth. The resulting skeletal abnormalities are similar to those of Langer mesomelic dysplasia, although they tend to be less severe(9).

Leri weill syndrome presents with short stature and mésomélie Medelung deformation. This deformation is seen in adults, but can be diagnosed early (our patients). Clinically deformed wrist, bilateral is characterized by radius and ulnae short and arched, this is the case of two patients with dorsal dislocation of the distal ulna and limitation of movement of the wrist and elbow. Radiological signs shows shortening of the radius which is curved outwards: the radial head is dislocated or flattened. The radial articular surface is abnormally lower obliquely downward, inward and forward due to premature fusion of the medial side of the cartilage conjugation and abnormal diaphyseal curvature. Convex dorsal ulnar whose distal end is often dislocated backwards, and a triangular arrangement of the carpal bones, which are housed in the V deformation resulting from the radius and ulna (10).

Hypertrophy of the muscles can also be found without underlying muscle disease, as well as micrognathia, a high arched palate, a acromicrie a cubitus valgus, genu valgum, tibia arched, scoliosis, and a very moderate shortness of tibia and fibula (11)(12). When the diagnosis is suspected with a clinical score

highly in favor, a genetic study was performed to investigate the deletion of the region by FISH pseudoautosomique, if negative, direct sequencing of the gene is carried out (13).

It should be noted that there are other pathologies associated with SHOX growth namely, Turner syndrome, and even some cases of idiopathic short stature also observed. SHOX mutations have been detected in 2.4% of children with short stature(14).

Patients afflicted with Turner syndrome are cytogenetically characterized by a complete or partial loss of one X chromosome. About 60% have a 45,XO karyotype and the rest are either mosaics 45,XO/46,XX or have a variety of structural defects of the X chromosome (15). More than 90% of girls with Turner syndrome have short stature and SHOX represents the only related gene thus far recognized (16). Because the SHOX gene is located on the sex chromosomes, most women with Turner syndrome have only one copy of the gene in each cell instead of the usual two copies. Loss of one copy of this gene reduces the amount of SHOX protein that is produced. SHOX haploinsufficiency could lead to additional Turner skeletal abnormalities such as mesomelia and Madelung deformity (17)

The presence of one or more skeletal abnormalities, known to occur in dyschondrosteosis or Turner phenotypes, should prompt the analysis for SHOX gene deletions or mutations in children and adults with short stature. It has now been well established that a thorough clinical investigation is a crucial first step in selecting patients with a likely defect in the SHOX gene. For this purpose, detailed evaluation of the x-rays of forearms and lower limbs for subtle radiographic changes should be carried out.

Two therapeutic interventions can be considered. Since growth hormone (rhGH) therapy improves the growth pattern in Turner syndrome, despite the absence of GH deficiency (18),it may also be advantageous in patients with SHOX haploinsufficiency. Another form of intervention could be the use of gonadotrophin releasing hormone analogue (GnRHa), which can suppress gonadal steroid production and may serve to mitigate the development of skeletal features and prolong the period of growth (19). To date, there have been few reports of rhGH therapy in patients with SHOX haploinsufficiency.. No adverse effects of rhGH therapy were observed. Age appropriate advancement of bone age was seen, indicating that any height advancement from rhGH therapy may result in an improvement in final height. There was only minimal radiological progression and no clinical worsening of Madelung deformity in all patients. All patients demonstrated short-term benefit from rhGH therapy, with a mean improvement in height SDS at 12 months (20)(21)

III. Conclusion

The dyschondrosteosis is a rare cause of growth retardation who must be recognized. It must be considered in mésomélic short stature with Medelung deformation or simply an idiopathic short stature.
Its early recognition and screening of family history allows early treatment with biosynthetic growth hormone. However in the absence of support final adult height is strongly reduced

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