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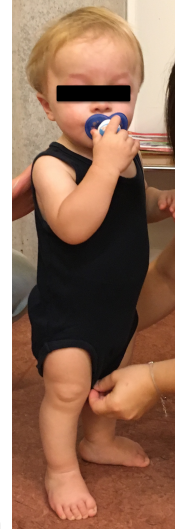
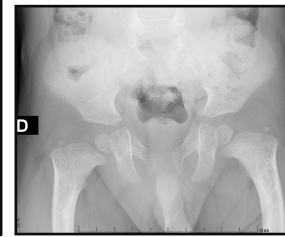
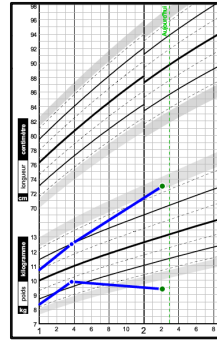
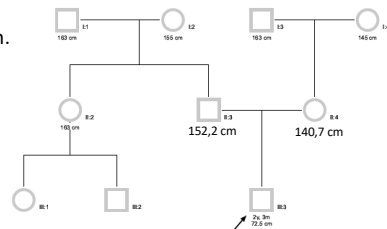
Background. The differential diagnosis in a case of short stature in children is wide and difficult. Potential diagnosis include either endocrine dysfunction or primary skeletal dysplasia. The last two decades have seen serious advances in our understanding of the genetic underlying growth process with the identification of numerous monogenic causes of growth disorders. New algorithms have been proposed focusing on the medical evaluation of children with short stature including genetic workup : single gene-based tests, tests of panel genes and exome sequencing.

Methods. A young boy initially aged of 6 months was investigated for a severe growth retardation (height – 5,4SD) , dysmorphic features and a coxa vara at the limit of the normal range.

-Both parents presented an isolated short stature.

-The father is described with fragile teeth.

-Prenatal US : shortening of long bones.



Results.

General biology : normal
Hormonal biology : normal
Array CGH : 46,XY

SHOX : negative
FGFR3 : negative
RASopathy panel : negative
GNAS : in process

Short Stature panel : **pathogenic variant in COL1A2 (class 5) , c.1171G>A p(Gly391Ser), inherited from the father.**

Definition of Osteogenesis Imperfecta (OI).

« A heterogeneous group of diseases characterized by susceptibility to bone fractures with variable severity and presumed or proven defects in collagen type I biosynthesis » . (Van Dijk et al., 2010)

Classification of OI.

In 1979, the original Sillence classification of OI in four types (OI type I to IV), was based on clinical findings with a radiological subclassification. This description assumed that OI is an heterogeneous syndrome. In 2004 and 2007, an expanded classification included a total of 8 types. (Van Dijk et al., 2010)

The clinical features can be resumed according to the types of OI (the main 4 types). It appears that no description correlate with our clinical observation. An alternative phenotype of OI will probably emerge in the next years to better describe such patients.

TYPE	Severity	Fractures	Bone deformity	Stature	DI	Sclerae	Hearing loss
Classic OI	Mild	Few to 100	Uncommon	Normal	Rare	Blue	About 50%
Lethal OI	Perinatal lethal	Multiplies	Severe	Severely short	+	Dark blue	/
Progressively deforming OI	Severe	Thin ribs, platyspondyly, many fractures, popcorn epiphyses	Moderate to severe	Very short	+	Blue	Frequent
Common variable OI	Moderate to mild	Multiple	Mild to moderate	Variably short stature	+/-	Normal (to grey)	Some
Alternative phenotype		No	No	Severe short stature	+	Normal	No

OI and isolated short stature

Cases of OI with severe short stature and without any fractures are rarely described in the literature.

In a case reported by Tulun et al., an exome sequencing performed to explore a short stature in a child identified a COL1A2 class 4 variant in the mother. The reported mother size was 126 cm without medical story of bone fragility.

In cases of familial idiopathic osteoporosis, some genetic studies reveal pedigrees with COL1A1/A2 mutations with description of fractures in adulthood and some degree of short stature in the adult patients but mainly linked to the bone fragility. Among the children described in these cohorts, all of them have a normal height or a relative short stature (-1 or -2 SD). (Al Kaissi et al., 2017)

Dentinogenesis imperfecta (DI)

Classically, it is reported that patients with DI are more likely to have fractures at birth and have a globally higher fractures frequencies. Patients with DI presented with a more severe short stature and more severe skeletal deformities. (Andersson K et al., PlosOne 2017)

➤ Here we expand the spectrum of the phenotype with patient presenting DI as the only clinical symptom associated with a significant short stature.

Regulation of childhood growth is a combination of molecular mechanisms. Genetic defect can affect every step leading to growth plate.

Dysregulation of COL1A1/A2 lead to an alteration of the organic matrix skeletal tissue. COL1A1/A2 encode for the collagen type I which constitutes 85% of the skeletal tissue and forms a framework for mineral deposition, rendering bone the tensile properties needed to withstand torsion and bending powers.

Collagenopathies due to mutation in COL2, COL9, COL10, and COL11 are known to be associated with several dysplasia phenotypes. Alterations of the synthesis of non collagen matrix proteins led to dysfunction of the growth plate chondrocytes. (Andrade et al., 2017 ; Jee et al., 2017 ; Lindhal K. et al., 2015)

COL1A1/A2 is the principal component of the bone matrix. It is supposed that an alteration in the bone structure causes an alteration in molecular interactions for the growth plate chondrocytes. Alike, more genes implicated in the extracellular matrix formation will probably be discovered as related to idiopathic short stature.

Growth failure : Different steps of molecular mechanisms

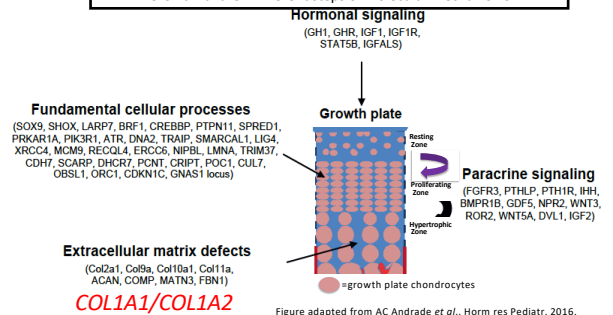


Figure adapted from AC Andrade et al., Horm Res Pediatr, 2016.

Conclusion.

At our knowledge, few patients have been described with a COL1A2 mutation and a severe short stature without fractures. In our clinical report, the father present an OI with short stature and DI without fractures and bone deformities. The child is extremely short, with normal bone phenotype until now. In the era of exome sequencing, similar cases will probably be collected. Series of patients could be described to better characterized the correlation with genotype and phenotype and delineated an alternative phenotype of OI.

A long term evaluation of these patients could be interesting with a particular attention for the bone phenotype, the growth velocity and the dentinogenesis.

A multidisciplinary follow up specific for OI is even recommended for these patients.

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