Morphologie (2016) xxx, xxx—xxx

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CASE REPORT

Fibrodysplasia ossificans progressiva. A case report and focus on the BMP signaling pathway

La dysplasie fibreuse ossifiante. Cas clinique et rôle de la voie de signalisation des BMP

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KEYWORDS
Fibrodysplasia ossificans progressiva;
BMP;
Ossification;
Pathophysiology

Summary Fibrodysplasia ossificans progressiva is a very rare heritable disease characterized by a progressive heterotopic endochondal ossification, occurring in the first decade of life, and leading thereafter to a severe ankylosis of the spine, limbs and jaw, with a progressive and severe functional disability. To date the cause of the disease remains unknown and no medical treatment has been proved efficient. It has recently been shown that a recurrent mutation in activation domain of the activin-receptor IA (ACVR1), a BMP receptor, could lead to an abnormal signalling pathway of BMP-4 and contribute to the occurrence of the devastating lesions characteristic of the disease.

MOTS CLÉS
Dysplasie ossifiante progressive ;
BMP ;
Ossification ;
Physiopathologie

Résumé La fibrodysplasie ossifiante progressive est une affection héréditaire très rare, caractérisée par un processus d'ossification hétérotopique. Elle débute vers l'âge de 10 ans, évolue ensuite par poussées progressives d'ossification périarticulaires, paraspinales et thoraciques, juxtamandibulaire, conduisant à une ankylose dramatique des patients atteints. La cause de la maladie est inconnue et aucun traitement efficace n'est connu. La démonstration récente de mutations du récepteur IA (ACVR1) de l'activine suggère que des anomalies de la voie de signalisation impliquant la BMP-4 pourraient jouer un rôle déterminant dans la genèse des lésions caractéristiques de la maladie.

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http://dx.doi.org/10.1016/j.morpho.2016.01.004
1286-0115/

Please cite this article in press as: Bouvard B, et al. Fibrodysplasia ossificans progressiva. A case report and focus on the BMP signaling pathway. Morphologie (2016), http://dx.doi.org/10.1016/j.morpho.2016.01.004

Introduction

Fibrodysplasia ossificans progressiva (FOP) (OMIM #135100) is a very rare heritable disease; the estimated worldwide prevalence of 1 in two million individuals, without any ethnic or gender predisposition [1]. The transmission is autosomal dominant from mother or father [1]. This disorder of connective tissue may have been first described by Guy Patin in 1692 and in 1736 by John Freke [1,2].

The disease is characterized by a progressive heterotopic endochondal ossification, occurring in the first decade of life, and leading thereafter to a severe ankylosis of the spine, limbs and jaw, with an erratic progression of the disability. Clinical features also include congenital malformations of the big toes and fingers, ossifying lumps, radiological evidence of ectopic ossifications visible in different axial or peripheral sites... [3]. Different situations may influence the course of the disease: trauma to the muscles, intramuscular injections, surgical excisions of ectopic bone, unnecessary biopsies, and dental care. To date, no medical treatment has been proved efficient and the cause of the disease remains unknown. Nonetheless, it has recently been shown that bone morphogenetic protein-4 (BMP4) may be involved in the pathophysiology of FOP [4]. The hope is to be able in the future to either modify the abnormal signalling pathway observed in the disease or suppress the immunological or environmental factors leading to the occurrence of the devastating heterotopic ossifications characteristic of FOP [1].

Case report

We report the case of a male, born in 1986, diagnosed with FOP at the age of 5. His parents and his brother are in good health and do not have any sign or malformation in relation with FOP.

The first symptoms at the diagnosis were pain and stiffness of the right hip neck, with malformation of big toes and fingers (Fig. 1). The evolution was marked, spontaneously or most often after minor traumas, by severe painful flare ups on the trunk, the neck, the dorsal region or near some joints (left shoulder, knees, wrists), sometimes secondary to falls or traumas; the sequence was always identical with a soft tissue swelling followed in the following days or weeks by a limitation of mobility and the occurrence of ossifying paraspinal lumps or ectopic ossification in other sites. In 2006, the patient suffered spontaneously from a diffuse and painful swelling of the left calf. Because of the ossification of the left popliteal fossa, an episode of sural thrombophlebitis was suspected; ultrasonography did not confirm the diagnosis but showed an extrinsic compression of the venous system by the bony process (Fig. 2). Progressively, all joints have been severely affected by the heterotopic ossification. In 2007 after a fall and a direct trauma on the skull a MRI was performed; no brain lesion was detected. At the posterior part of the occiput the heterotopic formation, also visible on the brain scanner is in relation with the ossification of both *longus capitis* observed on the standard X-ray (Fig. 3). This bony formation may have largely contributed to the ankylosis of the neck in this patient. At the same period, radiographs of the thorax showed multiple heterotopic ossifications on the intercostal muscles, malformations or ankylosis of the costovertebral joints, explaining a severe decrease of the chest expansion around 2 to 3 cm. The exostoses observed on the X-ray of the left shoulder, alleviated any motion of this joint (Fig. 4). A similar ankylosis was observed on both hips in relation with an extensive ossification. An aspect of osteochondromatosis can be seen at the left hip (Fig. 5).

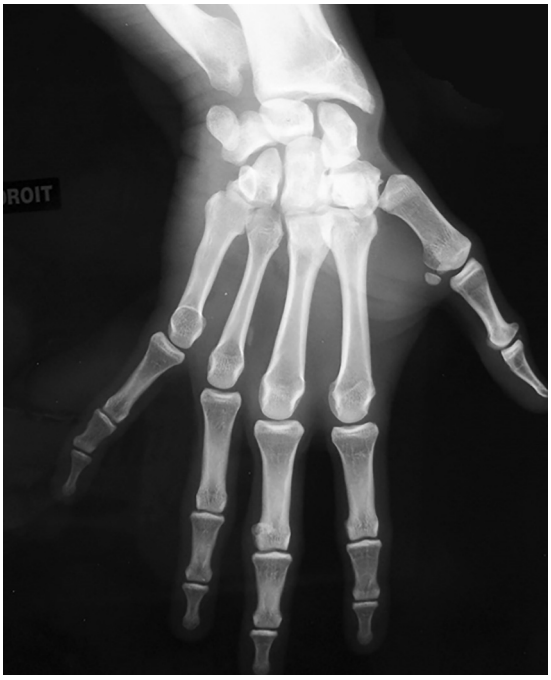

Figure 1 X-ray of the right hand of the patient; note the short size of the 1st metacarpal.
Radiographie de la main droite du patient, notez la brièveté du 1er métacarpien.

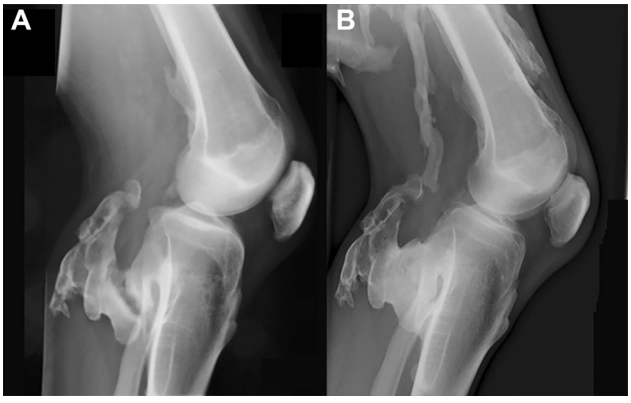

Figure 2 A. X-ray of the right popliteal fossa at the age of 17 showing a heterotopic ossification. B. Same view of this anatomical site with a dramatic extension of the ossification process at the age of 29.
A. Radiographie de la région poplitée du patient à l'âge de 17 ans montrant une ossification hétérotopique. B. Cliché similaire pratiqué à l'âge de 29 ans montrant une extension du processus d'ossification.

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