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Hereditary multiple Exostosis: Proposition of a new prognosis element through clinical case

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Abstract
Hereditary multiple exostosis is a rare genetic disease. Its severity is related to the risk of malignant degeneration. We report a case of a 22-yeasr-old man who consult for a mechanical gonalgia. He reported the presence of a multiple asymptomatic bone outgrowths, evolving since the age of 13, located in the limbs and the thorax. The X-rays showed typical images of exostosis. Through this clinical case, we propose a new element of prognosis based on the analysis of the patient's clinical data and a family survey.

Keywords: follow-up, hereditary multiple exostosis, prognosis

1. Introduction
Exostosis are benign bone tumours characterized by cartilage proliferation covered with normal bone cortex (osteochondromas), which may be single or multiple [1]. Multiple exostosis disease is a rare genetic disease and set up 35% of bone tumours. This pathology can affect each of the two sexes with a slight male predominance (sex ratio 1.5). The diagnosis is essentially clinical and is made by the presence of at least two palpable bone outgrowths and a similar family history [2]. The main risk is malignant degeneration, which can occur in 1 to 5% of cases, based on predefined clinical and radiological criteria. Through this clinical case, we assess an individual and a family prognosis of multiple exostosis based on the analysis of the patient's clinical data and a survey of his family members.

2. Case Report
It was a 22-years-old male, who consult for a mechanical gonalgia, occurring after an intense physical activity, without other signs. He reported the notion of outgrowth in the limbs and shoulder blade since the age of 13 years, with no recent increase in their size nor a new lesion appearance since then.
On physical examination, the patient was 169 cm tall (the smallest of his siblings). We found 16 hard, well limited and painless bone outgrowths with a smooth and regular surface, the largest one had 6 mm of great axis. They were located at the proximal and distal level of the humerus, the apex of the left shoulder blade, the lower part of the left rib cage, the lower end of the femurs and the upper end of the right tibia and also the right ankle (Figure 1**).** We also objectified a shortening of the third ray of the left hand (Figure 2). There were no other associated malformations. The examination of the knee, pelvis, spine and other joints was normal. The radiography showed a well limited bone outgrowths, without any periosteal reaction, typical of exostosis (Figure 3). The diagnosis of a multiple exostosis disease was thus mentioned.

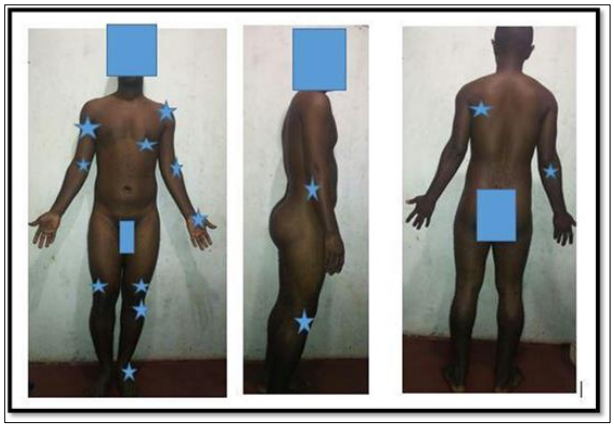

Fig 1: clinical location of exostosis in our patients (stars)

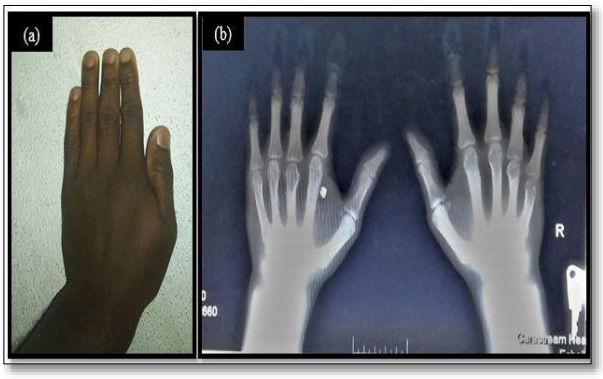

Fig 2: Shortening of the 3rd radius of the left hand (a). The radiography of the hands shows exostosis on the head of the 3rd left metacarpus (b).

Fig 3: X-rays of the patient showing multiple outgrowths with a well limited bone tonality, roughly bilateral and symmetrical at the extremity of the long bone, suggestive of exotosis : at the metaphyseal epiphysis of humerus, without periosteal reaction nor soft tissue involvement (a), sessile-based exostosis at the distal part of femur and proximal third level of tibia (b).

Our patient is the second of four siblings, and over three successive generation, six other family members had multiple exostosis, all from his maternal grandmother (figure 4). None of them had experienced a recent change in symptomatology nor an increase of outgrowths since their discovery.

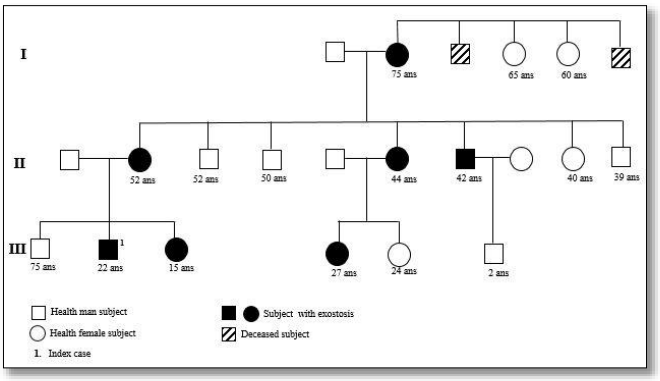

Fig 4: family tree of our patient (index case) showing the presence of Exostosis in 6 other subjects over 3 generations, with swellings mainly located on the knee, the shoulder and the ankle, with no signs of evolution since their discovery.

3. Discussion

Multiple exostosis disease (MED) or Bessel Hangen disease is a rare hereditary pathology with an estimated prevalence of 1/50,000 inhabitants per years [3]. It mainly involve indeed Amerindian ethnic groups in areas with high inbreeding rates. Few cases have been reported in Africa (4). According to our prospecting, this is the first Malagasy case reported.

This pathology is due to the mutation and loss of function of 3 loci on 3 tumor suppressor genes [5]: Exostosin 1(EXT-1), Exostosin 2 (EXT-2) and Exostosin 3 (EXT-3). These mutations are found in 60% of patients with exostosis whit a family medical history or not. These genes are bound to the biosynthesis of heparan sulfate [6]. This last one is an ubiquitous proteoglycan with various action, particularly in fetal bone growth, whose exact part in this disease is still undetermined.

This mutation is an autosomal dominant with incomplete penetrance. Men are rarely a healthy carriers, but women have a milder phenotype and can be asymptomatic sometimes. An unscathed man from an affected family does not transmit the disease, while a woman with a latent form can transmit it [7]. In our case, the maternal side seems to be the carrier of the mutated gene.

It is generally a fortuitously discovery through multiple bone outgrowth appeared during childhood. From the check out of 9 families with exostosis, Medek and *al*. settle that the age of the first exostosis discover was at 4.7 years and the age of diagnosis was 8.4 years [8]. For our patient, the late diagnosis may be explained by the fact that the pathology was mildly symptomatic so neglected by the family. This was also the case for the series by Niasse and *al*. about 2 Senegalese families where the diagnosis was delayed at the age of 21 years old on average [1]. In our case, the diagnosis delay was due to the family members exostosis cases which could not be retained unless by following family survey, with an average age of 40 years at the time of the survey. Any member of his family showed clinical signs of malignant degeneration.

Exostosis often occurs in long bones with endochondral ossification. By order of frequency, exostosis are located at the lower end of the femur (70% of the cases), the upper end of the tibia (70%), the fibula and humerus (30%). They can also sit on flat bones such as scapula and coxal bone, carpus and metacarpus bones. Out of 2 families affected by exostosis, Badara and *al* discover 2 to 7 growths per subject [9]. The same clinical aspects were discovered in our patient such on the growths number and location. Depending on their size, these benign tumours may collide with surrounding tissues, causing pain, and vascular or nerves compression [10]. Patients may have bone deformities, especially in the forearm. A small stature result the occurrence of a bone growth disorder was reported in 41% of cases [11].

Radiography is sufficient to set the radiological diagnosis of exostosis [5]. This characteristic picture are bone outgrowths in the epiphyso-metaphyseal areas, covered with cartilage, and the continuity of the spongy bone with the normal bone. Lesions are typically bilateral and symmetric and had variable sizes [12]. CT and MRI are only indicated if malignancy is suspected, for a better assessment of the bone cortex and soft tissue [13]. Genetic tests may be carried out in search for a mutation. Histology confirms the diagnosis but it is only necessary when there are signs of malignant degeneration on X-rays.

The disease mainly progresses during the growing phase. Once this is completed, there is no further growth in exostosis. Its severity remained by the risk of sarcoma degeneration (osteosarcoma or chondrosarcoma) in 1 to 5 % of cases [14]. Clinical and radiological criteria allows the suspicion of a possible evolution towards malignancy, such as advanced age, the abrupt onset of pain in exostosis, or a recent increase in their sizes, and a spinal and pelvic location.

On radiology level, a cartilage thickness more than 2 cm in adults and more than 3 cm in children, the presence of a periosteal reaction or a damage on the adjacent soft tissues; as well as, the size of exostoses >1.5cm are arguments in favor of malignant degeneration [15]. Mordenti and *al*. in 2013 proposed clinical criteria to assess the severity of this disease, taking into account the number of exostosis and the presence or the absence of deformation [16]. In this classification, our patient had a multiple exostosis disease of class I B with a few functional impact.

However, this classification only assesses functional severity but not the risk of progression to malignant degeneration. Hereditary multiple exostosis due to the exostosin 2 mutation (EXT-2) has been shown to be associated with a low or no risk of malignant degeneration compared to other mutations [17, 18]. It is probably our patient' case which, according to clinical criteria, the lack of signs of malignant degeneration over 3 generations could be due to this type of mutation.

This leads us to conclude that in the same family, the emptiness of signs of degeneration over several generations is a valid prognosis element to assess the severity of multiple family exostoses. This absence of malignant transformation was also noticed in the Medek and Badara series [8, 9]. Thus, the family survey must be systematic and the presence or absence of malignant degeneration in an individual person represents a prognosis value for the other family members.

The surveillance rythm is yearly, with X-rays to seek for signs of malignancy, taking into account that disease stop evolving at the end of growth [8, 10]. Bone scanning can be useful at the beginning of treatment to monitor a possible change on fixation, giving support to a malignant transformations.

Regarding treatment, there is no consensus. A mere analgesic are used when patient experiences severe pain [19]. Prophylactic surgery is not recommended, as the post- surgery complication risk is higher than the average risk of malignant transformation (13% versus 0.1% between 30 and 50 years) [10]. Surgery is only used for significant complications (major deformities, conflict with surrounding structures or pathological fractures). The antenatal use of exostosin inhibitor is under evaluation [20, 21].

Educating patients about monitoring is basic (seeking an increase in the size of the outgrowths, or pain)

4. Tables and Figures

Figures 1: clinical location of exostosis in our patients (stars)

Figures 2: Shortening of the 3rd radius of the left hand (a). The radiography of the hands shows exostosis on the head of the 3rd left metacarpus (b).

Figures 2: X-rays of the patient showing multiple outgrowths with a well limited bone tonality

Figures 4: family tree of our patient (index case) showing the presence of exostosis in 6 other subjects over 3 generations

5. Conclusion

Multiple exostosis disease is a rare and benign disease. This disease was often asymptomatic. However, malignant degeneration remains the fear of this disease. Family survey must be systematic and the emptiness of malignant degeneration over several generation could be used as a factor of good prognosis for the disease at an individual level.

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