# Hereditary Multiple Exostoses – A Tale of 50 years

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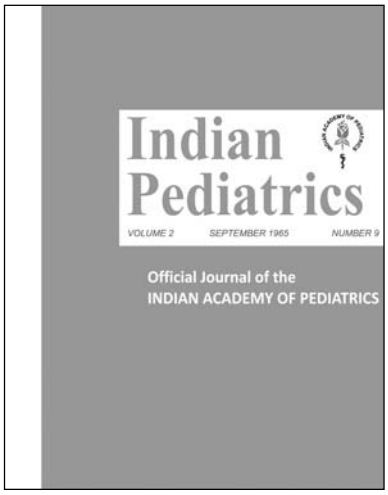
We continue our expedition into the past while reviewing an article from the September 1965 issue of Indian Pediatrics. This comprised of 41 pages with four research papers (ECG changes in progressive muscular dystrophy, a mathematical method to estimate gene frequencies, antenatal illnesses in villages of Punjab and a case series), two case records (pulmonary agenesis, polyarteritis nodosa), book reviews, current literature and news. We selected the case series of Hereditary multiple exostoses (HME), primarily to showcase the meticulousness with which the authors attempted to trace back the pedigree [1]. After briefly discussing the scientific knowledge that existed then, we will touch upon the recent advances that have evolved in understanding this disorder at the molecular and genetic levels.




## THE PAST

*The study* published in this issue by Sharma, *et al*. [1] from King George Medical College Lucknow, reported two affected Indian children. The first patient was an 11-year-old boy who developed multiple, hard, painless, gradually increasing swellings over a year. At presentation, lower ends of both femurs, tibiae and radii, upper ends of humerii and 6th /7th ribs were involved. There was no significant family history (traced till the second generation). The second patient was an unrelated 12-year-old boy with similar swellings since the age of six years. Medical attention was sought only when an injury lead to a swelling on his left arm becoming tender and fungating. On elicitation of details, a strong family history was unearthed (probably accounting for the apparent indifference exhibited prior to injury). Pedigree analysis (***Fig.* 1**) revealed 17 asymptomatic (except cosmetic) males belonging to 7 preceding generations with a striking absence of disease in females. This was not discussed by the authors but it may simply reflect missing data due to less severe forms associated with females or the gender bias in healthcare seeking behavior. In both of the cases, calcium, phosphorus and serum alkaline phosphatase levels in serum were normal. The only salient diagnostic findings were radiological (described later). Biopsies demonstrated proliferative chondroid tissue. The fungating mass in the second case was infectious, not malignant. The discussion of this article dwelt on various nomenclature, demographic characteristics, hereditary pattern (64% familial, remaining unknown or due to a new mutation), and clinical and radiological features (bony projections of various size and contour with the apex pointing towards the shaft and away from the nearest epiphysis, heterogeneously radio-opaque with interspersed areas of translucency).

*Historical background and past knowledge:* A patient with multiple exostoses was presented in a lecture by Hunteras as early as 1786, while another with familial involvement was reported in 1814 [2,3]. Various terms based on the typical clinical and histopathological features (*i.e.* multiple osteochondromas, cartilaginous exostosis, deforming chondrodysplasia, diaphyseal aclasis) were in use. The prefix 'hereditary'was added once the familial nature was recognized. HME remained an enigma till the 1950s when some groundbreaking research emerged. Solomon, *et al.* [4] delineated the clinical, radiological, pathological and genetic characteristics of HME in 1963. In this paper, it was stated that exostoses were cartilage-capped bony outgrowths from the juxta-ephipyseal regions of rapidly growing ends of bones originating in cartilage. Long bones and less commonly flat bones were described to be involved with sparing of face and skull. It was described that lesions appear by the end of the first decade, increase during puberty, and become dormant with cessation of growth. The number, size and location of exostoses were reported to vary between and within families.

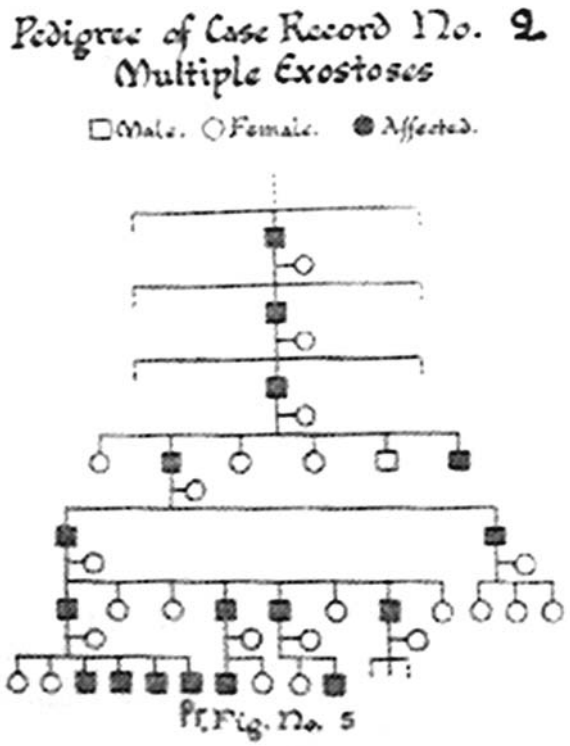



**FIG. 1** *Pedigree chart of case 2 as published in the original case record in September 1965. (Note absence of involvement of female family members).*

## THE PRESENT

The term 'Multiple osteochondromatosis (MO)' adopted by World Health Organization is preferentially used as it accurately denotes that the lesions are cartilaginous processes that ossify, rather than bony outgrowths (as 'exostoses' implies) [5]. Inheritance is autosomal dominant with 100% penetrance in males and 96% in females [6,7]. Sporadic de-novo mutations account for the 10% of cases in which family history is negative. Diagnosis is established by the presence of ≥2 typical radiological lesions with or without positive family history [5].

There are two variants of MO with genotypic-phenotypic correlation. Type I due to mutations in tumor suppressor genes *EXT1* (exostosin-1) on chromosome 8q23-24.1 is more severe, commonly involves flat bones, and is associated with shortened stature and malignant transformation [8]. Type II is due to mutations in the *EXT2* (exostosin-2) genes on chromosome 11p11-13 [9]. Both these genes encode glycosyl transferase necessary for biosynthesis of heparan sulfate in many cells, including chondrocytes. In the latter, proteoglycans are secreted into the extra-cellular matrix during endochondral ossification within the growth plate. Mutations result in truncated gene products interfering with normal chondrocyte proliferation and differentiation, abnormal bone growth and development of exostoses [10]. These are detected by Polymerase Chain Reaction (PCR) and/or Multiplex ligation-dependent probe amplification (MLPA) for definitive and prenatal/pre-implant diagnosis.

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