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Hereditary multiple exostoses: report of a kindred

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SUMMARY In a large family with 37 members with multiple exostoses, only one person has developed sarcomatous degeneration of a lesion. Our review of published reports revealed great variation in the incidence of malignancy in multiple exostoses (10 to 25%). Most studies had sampling errors leading to the apparent overstatement of risk. In large pedigrees with essentially complete ascertainment of affected subjects, the risk of malignancy is nearer 3% or less. This lower risk for malignancy may be more appropriate in counselling affected subjects.

Hereditary multiple exostoses is an autosomal dominant trait characterised by numerous cartilage capped lesions located in areas of actively growing bone.[1–3] Although exostoses may cause complications through the compression of local tissues, the major threat to life derives from the malignant degeneration of the lesions. Earlier studies of families with multiple exostoses[4–9] reported on the wide variation in the severity of the trait and the risk of malignant transformation. We have recently had the opportunity to follow and treat an extended family of Pennsylvania German extraction. Because these families are large and stable, we were able to trace five generations and identify 37 cases of multiple exostoses out of 104 family members (table). This family study provides additional information on the incidence of sarcomatous degeneration in multiple exostoses which may be useful in the counselling and care of relatives at risk.

Family studies

With the assistance of one member of the family, questionnaires were sent to all other living members, seeking information on themselves, their parents, grandparents, children, and grandchildren. Specific data were obtained on names, dates of birth, dates and causes of death, and degree of involvement. Subjects were asked to estimate bony involvement as mild (three or fewer lesions), severe (multiple lesions usually with significant deformity in one or more extremities), or moderate. Since the family was aware of the relationship between bone malignancies and osteochondromatoses and was sensitised to the sinister implications of enlarging lesions, precise information was available for detection of bony malignancies. Every living family member responded

TABLE *Affected subjects*

Patient	*Age at death or time of questionnaire*	*Extent of disease*
I·1*	75	Extensive
II·2*	30's	
II·6*	84	Extensive
II·10*	60's	
III·1*†		
III·2*†		
III·4*†		
III·5	67	Moderate
III·8	63	Moderate
III·10	58	Moderate
III·11	54	Mild
III·12	52	Moderate
III·13		
III·15	44	Extensive
III·16*†		
IV·1	41	Extensive
IV·5	35	Moderate
IV·6	31	Moderate
IV·10		Moderate
IV·18	33	Mild
IV·19	26	Extensive
IV·20	28	Extensive
IV·22	30	Extensive
IV·23	28	Moderate
IV·24 (proband)	26	Extensive
IV·26	26	Extensive
IV·27	29	Extensive
IV·28	21	Extensive
IV·30	24	Extensive
V·2	10	Moderate
V·3	12	Moderate
V·4	5	Extensive
V·6	18	Extensive
V·27	2	Mild
V·33	10	Extensive
V·34	7	Extensive
V·35	1	Moderate

*Dead
†Incomplete data (see text)

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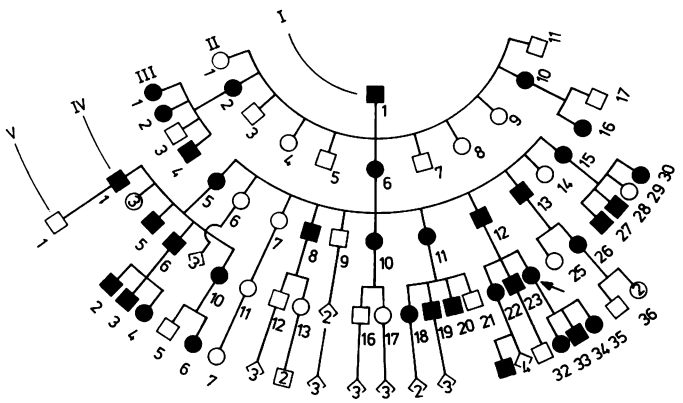

FIG 1 *Pedigree of five generations. Not included are the brothers and sisters, parents, wife, or wives' brothers and sisters for generation I, none of whom had evidence of the disease.*

to the questionnaire. Long, personally written letters were analysed and compared, permitting tracing of every member of the pedigree. Further information was obtained from family reunions and functions so that descriptions of dead relatives and ancestors could be compared. Because of intimate family ties, sufficient information about previous generations could be obtained to include accurate physical descriptions.

The founding couple of the family immigrated to Central Pennsylvania late in the 18th century. The first instance of multiple exostoses appeared in a male born in 1854 (I·1, fig 1), who was described as having multiple lesions with short arms and angular deformity at the elbows. He had nine brothers and sisters, but neither they nor their parents were clinically afflicted with multiple exostoses. There was no history of the disease in his wife's relatives. Three of his nine children were afflicted with multiple osteochondromatoses and passed the disease to the next generation. Exact birth dates and death dates could not be established for five childless members from the second generation. Four of the five had the disease, but none of them developed bony malignancies during their lifetime. A total of 104 members in five generations was investigated. Of these, 37 subjects had multiple exostoses (17 males and 20 females). Most members of the family lived to extended ages in apparent good health without known disability. Only one person had sarcomatous bone degeneration. There was no family history of other congenital malformations.

Case report

Subject IV·27, a product of a normal gestation, labour, and delivery, was noted to have extensive multiple exostoses shortly after birth. During his childhood and adolescence, osteochondromata were removed from his pelvis and humerus. In April 1971, at the age of 23, an exostosis was removed from his left scapula (fig 2) and this showed malignant changes. Histopathological examination showed a cartilaginous tumour with increased cellularity, pleomorphism, chromatin clumping, and multinucleate cells in numerous lacunae (fig 3). Accordingly, a radical scapulectomy was performed for what appeared to be a low grade chondrosarcoma. In December 1971, a local recurrence in the posterior chest was excised and subsequently skin grafted. No further recurrence has occurred in the past 8 years.

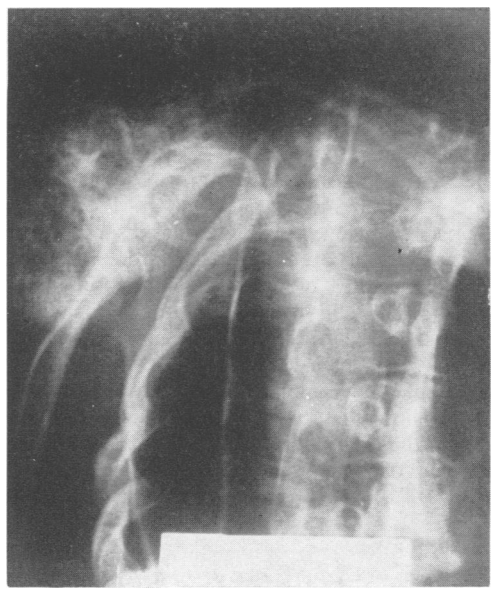

FIG 2 *X-ray of chondrosarcoma of scapula in IV·27.*

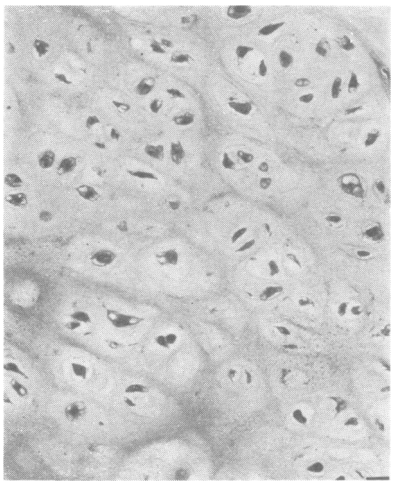

FIG 3 *Slide of chondrosarcoma showing abnormal pleomorphic cells and multicellular lacunae.*

Discussion

Physicians are frequently asked about the exact risk of bony malignancy by anxious subjects with hereditary multiple exostoses. A careful family history may be the most important factor for predicting the probable risk of malignant degeneration. The reported incidence of malignant degeneration of the exostoses varies greatly, ranging from 3 to 25%. Chondrosarcoma appeared in three of the 28 patients studied by Jaffe[10] at the Hospital for Joint Disease. However, only those family members evaluated at the hospital were included in this estimate and thus ascertainment was not complete. Based on a review of 272 cases of multiple exostoses treated at the Mayo Clinic, Dahlin[1] estimated the incidence of chondrosarcoma to be about 10%. None of the index patients in the series of Solomon[6 7 11] developed secondary sarcoma. Only one case of sarcomatous degeneration was found in the large family of Vanzant[9] which included 36 affected subjects in five generations. Similarly, in our large pedigree, only one documented chondrosarcoma was detected in about 1000 risk years of follow-up. It is possible that the incidences of Jaffe[10] and Dahlin[1] are spuriously high since they did not evaluate the entire population at risk. It appears that the risk of malignant degeneration in affected subjects is in fact low, albeit greater than the risk to the general population. The relatively low incidence of malignancy in some families and apparent high incidence in others may reflect allelic forms of multiple exostoses, chance occurrence, environmental effects, epistasis, or some combination of these factors.

Although most cases of sarcomatous degeneration occur in adults, it has been reported in subjects as young as 10 years of age.[4] Knight[5] reported bony sarcomatous changes in three brothers with the disease. Once the diagnosis is established, it is only prudent to alert the family of the potential risk of malignancy. An enlarging lesion at any age needs immediate attention. In a large family with many affected members, the risk of malignancy may be estimated from previous familial occurrences. For those subjects who represent new mutations (about 40% of the newly detected affected subjects), the risk of malignancy is probably about 3% and perhaps even less.

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