ABSTRACT

INTRODUCTION: Hereditary multiple cartilaginous exostoses is a syndrome characterised by the development of multiple osteochondromas. The diagnosis is typically made around the age of 12 years, and the prevalence is estimated at 1:50,000. During skeletal growth, the osteochondromas are benign, but in adult life malignant transformation into chondrosarcomas can occur.

METHODS: This study was a literature survey based on a systematic search of the PubMed database for articles with the term “hereditary multiple exostoses chondrosarcoma”. The search returned 157 articles, of which 13 had a sufficient level of evidence. These publications were examined thoroughly, focusing on the development of sarcomas, symptoms and the risk of malignant degeneration.

RESULTS: There is no consensus regarding the frequency of malignant transformation of multiple cartilaginous exostoses into sarcomas, which varies from less than 1% to 25%. The most reliable estimation seems to be 1-2%. The survey of the literature shows that no risk groups can be identified. However, exostoses in the axial skeleton are more prone to develop into chondrosarcomas than peripheral exostoses.

CONCLUSION: It is indisputable that malignant transformation occurs, and we therefore propose that a follow-up programme be launched with clinical examination by magnetic resonance imaging or bone scintigraphy every second year. The purpose of such programme would be to discover the sarcomatous development as early as possible to improve the survival prognosis of the patients. This screening programme should be centralised at tumour departments.

Multiple cartilaginous exostoses (MCE) is an autosomal dominant, inherited syndrome characterised by the development of several benign tumours in the form of osteochondromas [OC] [1-16]. Diagnosis is established by radiographic detection of more than one OC. The prevalence is estimated at 1:50,000 [3, 5, 7, 10, 11, 13] distributed equally among the sexes, but more severely expressed in men, even though MCE is probably underdiagnosed [8, 13].

MCE and OC are rarely clinically apparent at birth, but can grow in number and size until the closure of the growth plate, and the median age of diagnosis is three years (range; 0 to 12 years) [3].

Benign OC can differentiate malignantly, and this review aimed to explore the development of sarcomas in patients with MCE including symptoms, degrees of malignancy and risk assessment. In the light of these findings, the relevance of introducing a screening programme for this group of patients after termination of bony growth is discussed.

METHODS

A systematic search was conducted in the PubMed database. Many names are used interchangeably to denote the same syndrome, which complicates the search process. In this study, the initial screenings key words were “hereditary multiple exostoses” and “multiple osteochondromas”. Most articles were found using “multiple osteochondromas” owing to the fact that a limited number of patients do not have an inherited predisposition for the syndrome. When adding the MESH term “malignancy” to the search, the same initial amount of articles was identified (1,305 hits), but when confining the search from “malignancy” to “chondrosarcoma”, which constitutes the specific type of malignant degeneration found in MCE patients, the amount was reduced to 157. The abstracts of these articles were retrieved and examined thoroughly. This review excluded all casuistic papers due to their level of evidence. These constituted most of the retrieved articles, which left 13 articles eligible for inclusion. The search strategy also included crosschecking of the reference lists of the included articles.

RESULTS

Genetics and symptoms of multiple cartilaginous exostoses

OC is the most common benign bone tumour [1-16] and consists of osseous tissues covered with hyaline cartilage and continuous periost. Usually, OC grows from the metaphysis of the long bones and can be either broad-based or stalky. OCs vary in size from two to twelve centimetres in diameter, and the most common site of involvement is the distal femur, proximal tibia and fibula, both bones of the lower arm and the ankle joint (Figure 1) [3].

MCE is caused by a mutation in the family of tumour suppressor genes called exostatin (EXT), especially mutations in chromosome 8 (EXT1), 11 (EXT2) and 19...
The pathology of EXT3 mutations is unknown and accounts for a small amount of the patients [8].

The MCE patients’ clinical symptoms are localised pain, cosmetic disturbances, abnormal osseous growth and deformities of joints [1-16]. The latter can result in low stature, discrepancy of leg length, valgus deformities in the knee and ankle, asymmetric pelvine and pectoral regions and bending of the radius bone resulting in subluxation of carpus [8]. Treatment is surgical resection since this prevents or reduces the progression of deformities and functional impairment caused by an OC (Figure 3). Otherwise, treatment is not recommended in asymptomatic cases [14].

Complications of multiple cartilaginous exostoses and risk of malignant transformation

The most important complication to MCE is malignant transformation. Hameetman et al claim that in 94% of the cases, the malignant transformation will occur in the cartilage cap as a secondary chondrosarcoma; and in the rest, the transformation will occur in the stalk of the tumour as an osteosarcoma or a spindle-cell sarcoma [10].

In 2011, Pedrini et al included the largest recent series of 529 patients diagnosed with MCE. The purpose of the study was to identify risk factors related to the development of sarcomatous changes of the OC; sex, number of exostoses, genetic disposition and type of mutation were considered risk factors. The results showed no connection between these factors and the risk of malignant development [13], except for cases in which the OCs were located to the pelvis, scapula and proximal part of the femur. This association is probably related to a delayed detection of the chondrosarcomas in these areas because of fewer compression complications and obvious deformities [12].

Malignant transformation is extremely rare in the paediatric patient [1-16], but seems to occur around the age of 30 years with an increasing risk with age (Figure 4) [1, 2, 3, 12].

There is no consensus with regard to risk assessment of malignant transformation among patients with MCE; Table 1 shows that the estimated risk from different studies varies from less than 1% to 36%.

Consensus is not achieved through the literature; however, Schmale & Raskind used a theoretical sum to support their risk assessment. They estimate that in a population where the prevalence of chondrosarcomas is 1:250,000-1:100,000, 5% would also suffer from MCE. The prevalence of MCE is 1:50,000, giving a 1,000-2,500 (0.95/200,000: 0.05/4 ≈ 2,500) higher risk of developing...
chondrosarcomas than in a non-affected individual, and a lifetime risk of malignant transformation of approximately 1-2% [3].

**Diagnosis of chondrosarcomas**
The chondrosarcoma is often recognised by an increase in size of the tumour after the termination of bone growth in the adult patient. The patient can experience pain, neuropraxia due to compression of nerves and pressure-related symptoms at other nearby organs [1-16]. Malignancy should also be suspected when an increasing thickness of the cartilaginous cap is seen; under normal circumstances the cartilage thickness is only a few millimetres unless the patient’s growth plates are still open [14]. Peterson claimed that a thickness of more than one centimetre should raise suspicion [2], whereas Pierz et al and Hameetman et al set the limit to more than two centimetres [7, 8, 10].

Malignant transformation causes a surface irregularity and unorganised chalk deposits with light areas in the middle of the tumour as well as in the cartilage cap. Sometimes calcifications are seen in the surrounding organs [2, 9]. However, definitive diagnosis requires a biopsy.

**Treatment and screening programmes**
Patients with MCE seem to develop low-grade chondrosarcomas as well as differentiated tumours [1-16]. These tumours grow slowly, and rarely metastasise haematologically to other organs. Chondrosarcomas cannot be treated with radiation or chemotherapy; surgical removal is the only radical treatment option [1-16].

The survival prognosis is good for patients with secondary chondrosarcomas treated surgically and without metastasis. Solomon found that 87 out of 106 patients who did not receive any or only insufficient treatment died during a 10-year period [16].

Despite the considerable disagreement in the risk assessment for malignant transformation among patients with MCE, the risk is incontrovertibly present and the good treatment prognosis begs an evaluation or discussion of the relevance of a screening programme in this group of patients. Comparison of the MCE patient group to similar data from breast and cervix cancer patients illustrates the relevance of a screening programme. The lifetime incidence of breast cancer for women in Denmark is 11.1% and the five-year survival prognosis is 81% [17]. Cervix cancer has a lifetime incidence of 0.9% and the five-year survival prognosis is 64% [18]. These data are an important part of the argument for regular breast and cervix cancer screening of women of certain age groups in Denmark.

It seems that the risk of sarcomatous change among patients with MCE is of the same magnitude as for the aforementioned types of cancer, which would indicate that a screening programme is needed for patients with MCE after the termination of bone growth around the age of 16. Such a follow-up programme should include all adult patients with MCE according to Pedrini et al [13], since no certain factors are connected to the risk of malignant transformation [1, 2, 3, 12] with a closer follow-up of exostoses located in the axial skeleton [1-16]. However, Roach et al recommend a full columnar magnetic resonance imaging (MRI) every second year in children with MCE in order to identify intraspinal exostoses and potential intramedullary affection, but this recommendation aims solely at preventing neurological disorders.
The frequency of malignant development among the patients is uncertain. Based on this literature screening, the incidence of chondrosarcoma development is at least 1-2%.

Systematic screening of the patients every second year is recommended. Systematic screening of the patients every second year is recommended.

There is a need for further investigation into the disease and its consequences; this could easily be achieved by establishing a national register for MCE with follow-up of patients with MCE every second year along the lines of the proposed regime.

CONCLUSION
Conclusively, no consensus exists in regard to estimation of the frequency of MCE and the risk assessment for malignant transformation. However, the risk of malignant transformation is present and to an extent that indicates that a follow-up programme is needed. Furthermore, there is a need for further investigation into the disease and its consequences; this could easily be achieved by establishing a national register for MCE with follow-up of patients with MCE every second year along the lines of the proposed regime.

CORRESPONDENCE: Emilie Sonne-Holm, Ortopædkirurgisk Afdeling, Hvidovre Hospital, Kettegård Allé 30, 2650 Hvidovre, Denmark. E-mail: e.sonneholm@gmail.com.
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LITERATURE