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Hereditary Multiple Exostoses HME of the Spine; is Really a Benign Bone Tumour Syndrome? Editorial

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Introduction

Hereditary multiple exostoses (HME) is the most common type of bone dysplasia, which was first described by Boyer in 1814 [1-3]. It is characterized by the growth of cartilage-capped benign bone tumours (osteochondromas and exostoses) around areas of active bone growth, particularly the long bones metaphysis. Exostoses can involve all bones, but invariably spare the skull and the face. It is a rare pathology that occurs in around 1 in 50,000 individuals [3,4]. HME is a bone disorder with an autosomal dominant pattern and incomplete penetrance [5] associated with the mutation of: WXT 1, of the long arm of chromosome 8; EXT 2 and EXT 3 of the short arm of chromosome 19 [2]. Spinal involvement is rare, represent roughly 3% of cases and any portion of the vertebral body may be affected, anterior and posterior. A review of the literature since 1843 revealed 53 cases of vertebral osteochondromas. Although it is a benign bone disease, malignant degeneration is possible; it represents 20% of the patients affected by HME [6]. A careful analysis of the symptoms and their characteristics as the progression and the age of onset, can lead to the suspect of malignant transformation and its evolution in chondrosarcoma.

Diagnosis

Less than 10% of primary bone tumours occur in the spine. Although, osteochondromas are the most common benign skeletal tumour, reportedly 3% occur in the spine. The occurrence of spinal exostosis is likely under reported in relation to the true incidence because most are asymptomatic. HME is diagnosed by clinical criteria: 1) at least two osteochondromas of the juxta-epiphyseal region of long bones seen radiologically; 2) a positive familiar history and/or mutation in one of the EXT genes. This disease is characterized by the progressive increase in the number of exostoses from generation to generation, and the progressive increase in size of the lesions. The patients with a positive familiar history could have exostoses demonstrable with radiographic exams present by 1 year of age. Therefore, in family members at risk to develop this disease we recommend a complete skeletal survey at that age in order to determine if a new child is or is not affected or even before that age they can make diagnosis by palpating exostoses in an affected child (most commonly along the medial or superior border of the scapulae, along the ribs, or along the tibiae). Exostoses may continue to grow throughout childhood, tend to show a spurt of activity during adolescence and become silent during puberty. Indeed, any increase in size of exostoses in adult life should be studied by additional evaluation regarding possible malignant transformation.

Genetic Analysis

HME has an autosomal dominant pattern that means that an adult with this disorder have a 50% of chance to have a child with this poorly functional gene. About one-third of affected patients will be born to unaffected parents. The gene changes are fully penetrant (that means that anyone with the gene change has at least mild manifestations of the disease) but markedly variable in expression with a greater severity in males than in females. HME is caused by the mutation of three loci: Ext1, of chromosome 8q24, Ext2 on 11p11, 11p12 and Ext3 of the short arm of chromosome 19. The gene EXT products exostosin, endoplasmic reticulum localized glycoproteins which form a complex expressed at the cell surface that is active during endochondral bone formation. The malignant transformation is associated with chromosomal instability and EXT gene's loss of heterozygosity. This because the encoding gene is probably a tumor suppressors. HME results in an autosomal dominant pattern when one of the genes is affected. Disruption of the other gene then allows malignant transformation [7-9]. Multiple osteochondromas also occur in metachondromatosis and Langer-Giedion syndrome or trichorhinophalangeal syndrome type II. The exostosis from metachondromatosis and dysplasia epiphysealis hemimelica do not come from the EXT genes.

Malignant Transformation

The overall risk of malignant degeneration is variable in the literature. Probably it may occur in up to 1-5% of patients with HME and the lifetime risk is probably only about 2%. Malignancy never arises in childhood and usually is diagnosed between 20 and 50 years of age (mean age 31 yrs). These are mostly chondrosarcomas and most often arise in the pelvis. Malignant transformation of spinal localization is extremely rare, but possible. The risk for chondrosarcomas to metastasize is possible but slow, this is why the excision can be curative. The growth of the tumour after puberty, the presence of pain, or a thickness over 1 cm of the cartilaginous cap is indicative of suspicious of secondary chondrosarcomas. Patients should report any change in size of the already known and palpable exostoses that arises after reaching maturity. Skeletal survey to document sites of exostoses should be completed in late adolescence. With any suspicion of change in size (or onset of new pain) a radiographic exam has to be performed. Scintigraphic bone scan can be used for screening (high false positive rate but low or nonexistent false negative rate). If bone scan or plain radiographs are positive, a magnetic resonance imaging of the area of concern has to be performed. If MRI is positive or suspicious then excisional biopsy is indicated. In cases of malignant transformation a surgical treatment is indicated with a complete removal of the lesion,

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with resection margins free of disease [9]. In the cases in which the excision of the lesion is total, the prognosis is generally good.

Spinal Involvement

N the spine, lesions associated with HME also occurred most commonly in the cervical segment (32-57%). However, thoracic lesions were more common than lumbar lesions (20-36% and 2-4%, respectively). The most common site for exostoses associated with HME was C2 (11-19%). Even if the spinal involvement is uncommon and exostoses are rarely symptomatic, the clinical consequences can be relevant. The pain can be caused by 1 - the lesion 2 - the joint limitation that results from the growth of the lesion near the articular masses or in the spinal canal. The spinal cord compression can lead to debilitating neurological deficits for the patient, even if slow onset. The symptoms most commonly reported were 1 - root disturbances 2 - spastic paraparesis 3 - sphincter disturbances 4 - spastic gait. In the case of malignant transformation it is important an en bloc resection of the lesion. This goal cannot always be satisfied in spinal surgery, in relation to the anatomical complexity of the surgical site and to the proximity of the structures of the CNS.

Treatment

Intraspinal exostoses causing spinal cord compression have to be excised, as the neurological function improves after surgical treatment. The recurrence rate is low, whereas asymptomatic extraspinal lesions may be treated by observation. Intralesional excision of the exostoses is associated with a high risk of recurrence rate and should be avoided; In case of malignant transformation of exsostosis the goal an en bloc excision with clear margins should be performed. The surgical removal can then be completed with anterior or posterior stabilization if the removal causes loss of stability of the spine. Radiation therapy seems to have an important role when the complete surgical removal in not possible, as orthopedic studies report. Follow up controls have to be carried out periodically in case of incomplete surgical removal, to monitor the lesion and to highlight the onset of new lesion. Radiological control as scintigraphy and PET can be useful to identify additional lesions throughout the skeleton as ipercaptant areas, but the gold standard for the diagnosis and for the follow-up control remains the MRI and CT scan.

Conclusions

Although spinal involvement of HME is rare, spinal exostoses most commonly occurs in the cervical spine. Neurological symptoms associated with spinal exostoses are more common than reported previously. Lesions associated with HME tend to affect younger patients and have a higher incidence of neurological symptoms than solitary lesions. MRI and CT are the main preoperative radiographic exams obtain optimal information about the lesion and aid treatment options. Intralesional excision of the exostoses is associated with an high recurrence rate and should be avoided. The malignant transformation of osteochondromas in patient affected with HME is rare but possible. This possibility can be suspected when there is a rapid growth of the lesion and a progressive worsening of symptoms, usually in adulthood. These lesions require surgical removal in order to halt the progression of the disease. Radiation therapy seems to have an important role when the complete surgical removal in not possible, an event nor uncommon in case of cervical lesions.

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