Syndrome of the month

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Hereditary multiple exostoses

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Hereditary multiple exostoses (HME) is a skeletal disorder which primarily affects enchondral bone during growth. It is characterised by multiple exostoses, usually arising in the juxtaepiphyseal region of the long bones.

Exostoses that affect "almost every bone in the body" were first mentioned by John Hunter in his Lectures on the principles of surgery in 1786. The first family affected by HME was described by Boyer in 1814. Virchow named the disorder multiple exostoses in 1876, and Keith suggested the name diaphysal aclasis; this term is still popular in the UK. Several other names have been used in the past and are still used today, including 'osteogenic dysplasia', 'chondral osteogenic dysplasia', 'chondral osteoma', 'dyschondroplasia', 'deforming chondrodysplasia', 'multiple hereditary osteochondromata', 'multiple cartilaginous exostoses', or simply 'exostosis' or 'exostotic dysplasia'.

Papers that were especially important in further delineating the disorder were those of Jaffe, Solomon, and Shapiro et al. HME may be found not only in man, but also in horse, cattle, dog, cat, lion, and lizard. A large exostosis was even found on the scapula of a dinosaur.

Incidence

The frequency of HME is still uncertain. Krooth et al found 21 affected persons among the relatively closed population of the Chamorros of the island of Guam, giving a prevalence of approximately 1 in 1000. Solomon estimated that three new patients were diagnosed each year at the Royal National Orthopaedic Hospital in London, which handles approximately 7000 new patients annually. Sugiuara et al found three to four new cases among the 7000 annual new patients at the Department of Orthopaedic Surgery in Nagoya. The population prevalence in the UK has been estimated to be 9 per 1 000 000. The present author has knowledge of 31 affected living subjects in the population of 2 300 000 inhabitants who are served by the Clinical Genetics Centre in Utrecht. This may indicate a minimal population prevalence of 13 to 14 per 1 000 000. HME is predominantly reported in Caucasians, and to a lesser extent in Orientals, but may be found in other ethnic groups as well.

Clinical features

The diagnosis of HME may be established at birth, but this occurs usually because a specific search is made for it. In most patients the first symptoms arise in childhood: between 65% and 89% of patients are identified before their sixth year. The first lesion is most often found in the tibia or scapula, probably because they are the most conspicuous sites in the child. Radiography invariably shows exostoses at other sites as well. The locations of exostoses in HME are tabulated according to their frequency in table 1. Fig 1 shows a severely affected person. Exostoses are rarely found in tarsal and carpal bones and there has only been one patient reported with an exostosis in the skull base; facial bones always remain free. The number of lesions varies considerably and there may be as many as 80 visible on x rays. The mean number of locations has been found to be 15 to 18. There is no intrafamilial correlation in site or number of exostoses. The family reported by Solomon with exostoses mainly in the hands and a few in the long bones, and the family with exostoses in the heel only may well present distinct entities.

HME lesions usually continue to grow until closure of the growth plates at the end of puberty. No new lesions develop thereafter, although regrowth of an exostosis after surgical removal is possible. Spontaneous disappearance of exostoses in childhood or puberty has often been reported. Some of
Table 1  Locations of exostoses in HME according to frequency (n=274).7 9 13 16

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femur, distal end</td>
<td>90</td>
</tr>
<tr>
<td>Tibia, proximal end</td>
<td>84</td>
</tr>
<tr>
<td>Fibula, proximal end</td>
<td>76</td>
</tr>
<tr>
<td>Humerus, proximal end</td>
<td>72</td>
</tr>
<tr>
<td>Femur, proximal end</td>
<td>66</td>
</tr>
<tr>
<td>Tibia, distal end</td>
<td>64</td>
</tr>
<tr>
<td>Ulna, distal end</td>
<td>61</td>
</tr>
<tr>
<td>Radius, distal end</td>
<td>60</td>
</tr>
<tr>
<td>Fibula, distal end</td>
<td>57</td>
</tr>
<tr>
<td>Foot</td>
<td>35</td>
</tr>
<tr>
<td>Scapula</td>
<td>34</td>
</tr>
<tr>
<td>Hand</td>
<td>33</td>
</tr>
<tr>
<td>Rib</td>
<td>31</td>
</tr>
<tr>
<td>Pelvis</td>
<td>28</td>
</tr>
<tr>
<td>Clavicles</td>
<td>22</td>
</tr>
<tr>
<td>Radius, proximal end</td>
<td>18</td>
</tr>
<tr>
<td>Ulna, proximal end</td>
<td>15</td>
</tr>
<tr>
<td>Tarsal bones</td>
<td>9</td>
</tr>
<tr>
<td>Carpal bones</td>
<td>7</td>
</tr>
<tr>
<td>Vertebræ</td>
<td>7</td>
</tr>
<tr>
<td>Humerus, distal end</td>
<td>5</td>
</tr>
<tr>
<td>Sternum</td>
<td>1</td>
</tr>
</tbody>
</table>

These patients may not suffer from HME, but from metachondromatosis,20 which is similar to HME but differs in distribution and radiographic appearance, and in which spontaneous regression is the normal course. Another explanation may be ceasing of growth of the exostosis while the affected bone enlarges normally, thus obscuring the once prominent exostotic projection.6 A proven disappearance of an exostosis has not been found in any of the patients known to the present author.

The characteristic radiographic appearance of exostoses may vary from broad based (sessile) (fig 2) to pedunculated. The cortex of exostoses is continuous with that of the underlying bone. They originate in the metaphysis in long bones and migrate to the diaphysis as growth continues in the epiphysis.6 The cartilagenous cap is usually radiolucent, but after puberty irregular zones of calcification may appear. Extensive calcification with irregularities of the cap should suggest the possibility of malignant change.21 The configuration of exostoses may be completely different, not only within different bones of a particular patient, but even within one affected bone. Exostoses prevent normal bone tubulation resulting in metaphyseal widening and growth retardation. Generally, the height of affected persons is somewhat shorter than usual (0.5 to 1.0 SD).6 9 This becomes more evident with age, especially during puberty. The sitting height averages 1.0 SD above height, indicating a mildly disproportionate short stature.9 Comparable findings are reported for arm span and symphyseal height.9 The lack of height is seldom so severe that patients fall below the 3rd centile. Sometimes individual bones are more severely
In some reports about 10% of all affected persons developed an osteosarcoma. These figures, however, were obtained at tertiary treatment centres and are, thus, severely biased towards patients with complications. More reliable estimates point to an occurrence of malignancies in HME of 0.5 to 2%. Ochsner collected data on 59 patients with an osteosarcoma in HME. The mean age of onset of malignant degeneration is 31 years; it seldom occurs before the 10th or after the 50th year. The upper end of the femur and the pelvis are the main locations, but they may also be found in the shoulder girdle and the ribs. The first clinical signs are usually a sudden increase in size, pain, and sometimes neurological symptoms. The development is usually slow, and metastasis (lungs) is late. Therapy of choice is complete surgical removal. Because local recurrences are frequent, the resection has to be complete. Radiation therapy has no effect. It seems useful to obtain radiographs of the pelvic and shoulder girdle in every young affected adult for later comparison.

Affected. The most striking deformity may be the shortened and bowed forearm (fig 3). This has been reported in 7%, 13 40%, 5 9 50%, and even 60% of all patients. These differences in incidence may be caused by differences in definitions and groups of patients studied. Exostoses should be removed in patients when they cause disability or for cosmetic reasons, but the mere presence of an exostosis is not a reason for prophylactic excision. A complete review of therapeutic measures in HME has recently been reported by Wood et al.

Complications

The main complications in HME are hindering of normal articular function, pressure on neighbouring tissues (spinal cord, large blood vessels, peripheral nerves), and malignant degeneration. Impaired movement occurs most often in the elbow (especially pronation) but can be found in nearly every joint.

Vertebral exostoses may cause medullary compression at the cervical or thoracic level. At least 26 such patients have been described, aged generally between 10 and 40 years. Surgical treatment was of benefit in 21 of them. Compression of peripheral nerves occurs in 1 to 2% and may cause pain or paraesthesiae. Sometimes a large blood vessel may be involved: at least six persons with HME and a rupture of the popliteal artery have been described. Occasional other complications are pelvic involvement, causing problems during pregnancy, and infections of bursae formed between the exostoses and overlying muscles. However, it should be remembered that in the majority of patients exostoses are asymptomatic and interfere little with general health.

The most severe possible complication is malignant degeneration. In some reports about 10% of all affected persons developed an osteosarcoma. These figures, however, were obtained at tertiary treatment centres and are, thus, severely biased towards patients with complications. More reliable estimates point to an occurrence of malignancies in HME of 0.5 to 2%. Ochsner collected data on 59 patients with an osteosarcoma in HME. The mean age of onset of malignant degeneration is 31 years; it seldom occurs before the 10th or after the 50th year. The upper end of the femur and the pelvis are the main locations, but they may also be found in the shoulder girdle and the ribs. The first clinical signs are usually a sudden increase in size, pain, and sometimes neurological symptoms. The development is usually slow, and metastasis (lungs) is late. Therapy of choice is complete surgical removal. Because local recurrences are frequent, the resection has to be complete. Radiation therapy has no effect. It seems useful to obtain radiographs of the pelvic and shoulder girdle in every young affected adult for later comparison.

Figure 3 Severely affected forearm.

Figure 4 Unilateral shortened second toe; radiography showed exostoses on metacarpal and proximal phalangeal bone.
Differential diagnosis
The main differential diagnosis is with trichorhino-
phalangeal syndrome type II (Langer–Giedion
syndrome).
27 However, the facial, ectodermal, and
mental symptoms make differentiation easy. Meta-
chondromatosis may be mistaken for HME.
20 The
main features are exostoses, primarily in the hands
and feet, and enchondromata in the ends of long
bones and iliac crests. Most regress spontaneously.
Dysplasia epiphysealis hemimelica is a non-hereditary
developmental disorder of childhood, characterised
by cartilaginous overgrowth of the epiphyses of the
carpal or tarsal bones, mostly in a single extremity.
28
Microscopically the lesions are indistinguishable from
HME, but otherwise the differences are obvious.
There are numerous other entities in which exostoses
may be found.
29–45

Pathology and pathogenesis
Exostoses are covered by thickened peristeum that
closely adheres to the cartilaginous cap. In children
the cap is prominent and surmounts a thin cortex.
Some areas of cartilage may have the appearance of an
epiphyseal growth plate. Beneath this, spongy bone
forms the bulk of the lesion. With aging, the
cartilaginous cap ossifies and becomes thinned to a
narrow lining or even disappears locally.
5 7 13 The
marrow cavity of exostoses is continuous with the
cavity of the underlying bone. Microscopically, in
young patients, the cartilage tissue consists of
chondroid basal substance with chondrocytes lined
up in columns.
5 Later on, the organisation of the
chondrocytes is less strict. The spong bone often
consists of an irregularly organised trabecular
network.

Exostoses are found especially at the site of
tendinous insertions of major muscles. In animal
experiments it has been shown that functional inactiv-
atization of muscles by transsection may prevent
formation of exostoses.
46 This may indicate that
muscle tension can be a secondary factor in the
pathogenesis of HME. The primary factor remains
uncertain, although numerous theories exist.
21
Mutation(s) in a gene that controls proliferation and
differentiation of chondroblasts, which may lead to
malignant degeneration under the influence of a
second 'hit', seems the most plausible explanation at
present.

Genetics
HME follows an autosomal dominant mode of
inheritance. About 60 to 70% of the patients have a
positive family history.
5 8 15 16 The mutation rate has
been calculated to be \(9 \cdot 1 \times 10^{-6}\).
47 Sugiura et al.
13 estimated the penetrance to be 0·667. This reduced
penetrance was calculated on the presence of four
families with more than one affected child born of
apparently unaffected parents. However, in none of
these families were both parents fully investigated,
including radiography, which leaves this reduction in
penetration unproven. Other authors were unable to
find non-penetrance if parents were fully investigated
(personal observations).

There are several reports that mention a pre-
ponderance of affected males.
5 16 48 Others have reported an equal sex distribution.
8 15 21 One of the main explanations for this distorted sex ratio
is probably the diminished expression in a minority of
females.
5 12 21 The equal expression found by
Solomon
7 and Sugiura et al.
13 may be at least partly
carried by their source of patients, that is, tertiary
orthopaedic clinics. Jaffe
5 reported on the increase in
affected offspring in the course of successive male
transmissions. This may point to some influencing
mechanism, for instance, imprinting.
49 Anticipation
was not detected.
8 11 To investigate this further, all
published families were gathered in which the diag-
nosis was reliable, and for which full information on
both affected and unaffected family members was
given. These data were pooled together with our own
data and analysed further (table 2). Affected fathers
had more affected than unaffected offspring (99:67)
while in affected mothers this ratio was about equal
(79:61). This difference, however, was caused by only
a few families in which a remarkable male pre-
ponderance was found
21 (personal observations). It
seems probable that in most families the sex distribution
is equal, but that in a minority of families some
additional influence is operating. This needs further
clarification.

Chromosome studies, both in horses and man,
10 51 52 and DNA polymorphism analysis in horses,
53 have been inconclusive until now. Buhler and Malik
54 have suggested that the mutation of HME may be sited in
the region 8q23–8q24.1, closely linked to the locus for
trichorhinophalangeal syndrome (TRP) type I. They
stated that TRP types I and II are possibly not
separate entities, but that in TRP type II the deletion
is larger and also involves the locus for HME. This
theory was recently supported by the description of a
patient with TRP type I and 8q deletion.
45 It is of
interest to note that in TRP type II the deletion of 8q
was found to be of maternal origin.
56 Restriction
fragment length polymorphism analysis in man is at

<p>| Table 2: Affected and unaffected offspring of 80 nuclear families with HME. |
|-----------------------------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Affected fathers</th>
<th>Affected mothers</th>
</tr>
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<tbody>
<tr>
<td>Affected sons</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>Unaffected sons</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Affected daughters</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>Unaffected daughters</td>
<td>40</td>
<td>43</td>
</tr>
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</table>