Symdrome of the month

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The Holt–Oram syndrome

J A Hurst, C M Hall, M Baraitser

The classical description of this syndrome of upper limb abnormalities and congenital heart lesions was by Holt and Oram in 1960. They were from King’s College Hospital in London and reported a four generation family with nine affected subjects. Many other families were then recognised to have the same condition, which led to a series of reports in the early 1960s. The names atriodigital dysplasia, the heart-hand syndrome, the upper limb-cardiovascular syndrome, the cardiac-limb syndrome, and the cardiomelic syndrome were suggested, but it is the Holt–Oram syndrome that has remained in common use. There have been over 200 cases published and it is found throughout the world. A genetics department in the UK near a cardiology referral centre may expect to see a new family about once every two years.

Clinical details

The features of this syndrome are abnormalities of the upper limbs and shoulder girdle, associated with a congenital heart lesion. The typical combination is considered to be a triphalangeal thumb with a secundum atrial septal defect, but there is a great range in the severity of both the heart and skeletal lesions. The face and lower limbs are normal. Growth and development are within normal ranges.

Skeletal abnormalities

The skeletal abnormalities are found in the upper limbs and shoulder girdle. The degree of involvement can range from phocomelia to minor limitation of movement of the thumbs, elbows, or shoulder (figs 1 to 4).

A triphalangeal thumb was reported in Holt and Oram’s original paper but, as can be seen in table 1, a range of thumb abnormalities can be found. The thumb may look structurally normal but the patient may be unable to oppose the thumb fully and the thenar eminence may be flat. There maybe a degree of asymmetry with a triphalangeal thumb on one hand

Figure 1  Adult male with Holt–Oram syndrome. Note sloping shoulders, abnormal muscle insertion on right arm, right thoracotomy scar, and thumb abnormalities.
The Holt–Oram syndrome

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Figure 2 Right hand of patient shown in fig 1 showing triphalangeal thumb and flat thenar eminence.

Figure 3 Left hand of patient shown in fig 1 showing absent thumb. A rudimentary hypoplastic digit was removed in infancy.

Table 1 Skeletal abnormalities in Holt–Oram syndrome.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Familial cases (refs 1, 2, 3, 4, 5, and personal cases) (n=43)</th>
<th>Smith et al* (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb abnormality</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Hypoplastic thenar eminences, non-opposable thumbs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Triphalangeal/digitalised</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Hypoplastic</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Absent</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Hypoplastic radii/short forearms</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Phocomelia</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Minor skeletal changes, normal thumbs</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Normal skeletal examination in obligate carrier</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*Unilateral lesions scored independently.

and a hypoplastic thumb on the other. Partial soft tissue syndactyly of the thumb and index finger is commonly described.

More severe upper limb abnormalities such as phocomelia are easily identified. In the most severely affected patients the humerus is rudimentary or absent and one or two digits are attached directly to the trunk. Phocomelia is found in about 10% of reported patients with Holt–Oram syndrome, though there may be a bias towards selecting patients with severe skeletal lesions. Other upper limb abnormalities found on clinical examination are inequality of arm length, limitation of movement at the elbow (especially of extension, supination, and pronation), and hypoplasia of the musculature, in particular of the deltoids. The shoulders are often described as narrow and sloping with a decreased range of movement. The clavicle may be short, or broad, or show a lateral clavicular 'hook', a feature of any congenital forearm/elbow anomaly (fig 5).
and humeroulnar
malformities
at
The
scapula
RADIOLOGICAL FEATURES
and absence, clavicular joint, Scaphoid al.7 abnormalities of
clear hypoplasia with head
In
phocomelia. The humerus is
are
large
phalanges
have
fusion.
and absence, include other additional
patients with a normal fetus
fuses with the metacarpals,
fifth
(representing a proximal
and hypoplasia. In
or triphalangeal
be shorter than normal. The thumb
bone
between the proximal and distal phalanges.
Alternatively, the thumb can be hypoplastic or
absent, it may be attached to the proximal phalanx of
the index finger, and it may be bifid (preaxial
polydactyly). Other less common skeletal abnormalities include a Sprengel deformity, chest wall
anomalies such as deficient pectoral muscles, pectus
excavatum or carinatum, and rib and vertebral anomalies (fig 6a, b). There is no association between
the severity of the skeletal and cardiac malformations. Smith et al6 reported that the left side was more
severely affected, but other authors have not found
this. Gall et al8 suggested that females had more
severe skeletal malformations than males based on 19
members of a pedigree with 22 living affected
subjects.

Cardiovascular anomalies
Those affected in the family reported by Holt and Oram1 all clinically had secundum atrial septal defects

Figure 6 Radiographs of upper limbs showing asymmetrical abnormalities. (a) On the right the first metacarpal is hypoplastic and the middle phalanges of the index and little fingers are short. (b) On the left the radius and thumb are absent. The ulna is short and bowed. The middle phalanges of the index and little fingers are short.

Figure 5 The heart is enlarged. The clavicles are short and broad with lateral clavicular 'hooks'. There is delayed ossification of the upper humeral epiphysis.

The scapula may be raised and small with abnormalities at the acromial region, a prominent coraco-clavicular joint, and a small glenoid fossa. The humerus is hypoplastic or absent in patients with phocomelia. In other patients the medial epicondyles are large and there may be deformity of the humeral head with epiphyseal irregularities (fig 5). Radioulnar and humeroulnar synostosis, radial hypoplasia or absence, and ulnar absence are all reported. The abnormalities of the carpals, metacarpals, and phalanges have been well described by Poznanski et al.7 Scaphoid anomalies are particularly common and include hypoplasia and bipartite ossification. In the normal fetus a carpal bone called the os central (representing a third row of carpal centres) usually
fuses with the scaphoid but this may not occur in
patients with Holt–Oram syndrome. There may be
other additional carpal bones. Other carpal anomalies include absence, hypoplasia, enlargement, irregularity, and fusion. The first metacarpal may have both proximal and distal epiphyses, as may the second to fifth metacarpals, as well as structural changes such as hypoplasia. In general, Poznanski et al7 reports the
metacarpals to be larger and the middle phalanges to
be shorter than normal. The thumb can be completely triphalangeal or there may be a rudimentary triangular bone between the proximal and distal phalanges.
The structural lesions depend on the severity of the cardiac lesion. Children with severe limb shortening should be referred to the appropriate local service for consideration of prostheses.

Prenatal diagnosis

Prenatal diagnosis using ultrasound in the second trimester is possible. The radius and ulna are best seen between 13 and 16 weeks' gestation. Minor skeletal abnormalities will not be detected prenatally. A detailed cardiac anomaly scan is usually performed at 18 to 20 weeks. From 16 weeks, the two great arteries, the atria, the ventricles, and the four heart valves can be seen. Severe congenital heart defects can be excluded if these are all visualised and are normal. Anomalies such as septal defects may not be detected. Mothers who have cardiac lesions will require special care during pregnancy. There is some evidence of spontaneous abortion of severely affected fetuses.

Differential diagnosis

The diagnosis is not difficult in the presence of typical clinical features and a family history. In isolated cases the differential diagnosis will include VATER, Roberts syndrome, Fanconi pancytopenia, TAR, and Aase syndromes. Thalidomide embryopathy is an important consideration in young adults whose mothers were treated with this drug in the first trimester.

Inheritance

The syndrome is inherited as an autosomal dominant trait. In the study of 39 patients of Smith et al, 15 were said to have normal parents and were considered to be new mutations. With improvements in the surgical correction of congenital heart lesion the proportion of new mutations is likely to be lower than this. When the diagnosis of the Holt–Oram syndrome has been made in a child it is important to examine both parents before counselling. Clinical examination of the hands, arms, shoulders, and thorax (including heart auscultation) should be performed. Obvious signs may be present but sometimes the significance of minor skeletal abnormalities can be difficult to interpret.

The hands should be examined to detect any thumb abnormalities either in size, shape, or inability to oppose fully. The arm lengths should be compared and forearm supination and pronation tested. The shoulders are often described as sloping and there may be restriction of movement at the shoulder joint. If there are no abnormal clinical signs then radiology is unlikely to help. However, if there are any features, then radiographs should be taken to confirm the clinical suspicion.
Most adults would have had significant heart murmurs detected in infancy and childhood. It is important to ask specifically about a history of a heart murmur. An ECG would detect rhythm disturbances which may be present in the absence of a structural lesion.

If neither parent is affected then recurrence risks for parents (not patient) are small. Known gene carriers have been described with either no cardiovascular or skeletal changes but not without both. Gonadal mosaicism remains a possible cause of recurrence. The severity of the lesion in a parent is no guide to severity in their offspring.

**Developmental basis and aetiological factors**

Most authors consider that the gene responsible for this syndrome must be active in the embryo at the time of limb bud and cardiac development. Localisation of the gene is not known and no candidate genes have been proposed. Thalidomide can cause a very similar malformation syndrome.

Cytogenetic studies have not found any consistent abnormalities. Rybak et al found a deletion in the long arm of a B group chromosome which may be the same as the deletion reported by Ockey et al on the long arm of chromosome 4. Turleau et al had two patients with a 14q deletion, but other authors of large studies found normal chromosomes in the patients.

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