Cleft hand/foot: clinical and developmental aspects

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Abstract
Isolated limb reduction defects occur in approximately 1 in 2000 live births within which central ray anomalies are an important subgroup. Most affected persons have mild or moderate functional impairment. Considerable psychological morbidity may also occur. While there have been major strides forwards in our understanding of vertebral limb development, the mechanisms responsible for central ray deformities remain poorly understood. Several case reports of central clefting anomalies associated with chromosomal rearrangements or interstitial deletions of 7q21.2-q21.3 suggest that this chromosomal region is important for limb development.

While the term ectrodactyly literally means “missing digits”, it is now used as a descriptive term for a central ray anomaly that presents clinically as a central cleft of the hands or feet.\(^1\) Historically, terms such as “lobster claw”\(^2\) and split hand\(^3\) have been used to describe this defect which results from absence, or reduction, of one or more of the three central digits (fig 1). The earliest known description of cleft hand was that by Pare\(^4\) although Barsky\(^5\) suggested that this report represented two fingered hemimelia rather than true cleft hand. Central ray defects, according to Swanson’s modified classification, represent terminal longitudinal limb anomalies.\(^6\) Cleft limb has a number of associations and as a result it can be a useful major feature for syndrome diagnosis.

Large families with isolated cleft limbs have been described which usually show autosomal dominant inheritance and marked variability in expression and penetrance,\(^7\) although several autosomal recessive pedigrees have also been reported.\(^8-10\) Birch-Jensen\(^11\) estimated the incidence of cleft hand deformity at 1 in 90 000 births. More recent epidemiological studies suggest the incidence of central ray anomalies to be closer to 1 in 10 000 (approximately 0.7 per 10 000 live births).\(^12-13\) The data of Czeizel \textit{et al}\(^4\) indicate that three-quarters (77\%) of cases present with unimelic involvement.

In 1960 Stevenson and Jennings\(^15\) suggested an abnormal segregation pattern in families with isolated ectrodactyly (pedigree analysis showed an excess of affected sons of affected fathers). David,\(^16\) when describing three pedigrees with isolated cleft limbs, suggested the possibility of germinal mosaicism. X linked inheritance has also been described in a seven generation Pakistani kindred.\(^17\)

Ford\(^18\) hypothesised that “ectrodactyly” represented an anomaly that could be explained by a structural chromosomal defect although at that time it was acknowledged that techniques for chromosome analysis were poor. Since then a number of case reports have indicated that the 7q21.2-q21.3 region is a candidate site for cleft limbs.\(^19-20\) These have resulted in considerable molecular interest in this region.

Clinical features
Clinical problems associated with isolated cleft hand and foot are usually cosmetic and psy-
chological rather than functional. Only in the less common variant monodactylyous ectrodactyly, where radial rays are also hypoplastic, is function severely compromised. Considerable anatomical variability occurs. Cleft hand has been described with pre- and postaxial duplication and reduction anomalies.7 Absence of the central digits is the major feature with varying association with both bony and soft tissue syndactyly. Many cases will merely have one limb affected and others can have tetramelic involvement. Birch-Jensen11 found that 58% of cases of cleft hands were bilateral with an equal sex distribution. These clinical findings were confirmed by Barsky.7 The majority of cases of cleft hand are sporadic. In Birch-Jensen's study,11 50% had a family history of limb defects while only 20% of Barsky's group were familiar. The study of Czeizel et al14 showed a high percentage of presentation as atypical forms, though this is based on a "wide" interpretation as to what actually constitutes atypical split hand/foot. The definition of this varies between published reports but actually serves relatively little clinical purpose. It is also subject to wide differences in clinical interpretation. A consensus might be that atypical cleft limb occurs when there is not total absence of the long finger or when there are, in addition, reduction anomalies affecting the marginal rays. This tends to be (though not always) sporadic and unilateral, affecting mainly the upper limbs.

Clinically, few functional problems occur in the upper limbs provided opposition is possible. However when a preaxial anomaly coexists or when monodactyly (a single digit) occurs, marked limitation of function can result. Functional limitation can result when central clefts are particularly wide or deep and operative management to close these can often result in significant improvement in function. Limitation of function owing to syndactyly of the fingers may also occur and this also can be overcome surgically.22 In the lower limbs the major practical difficulty encountered is one of obtaining adequately wide fitting shoes.

Many persons with "ectrodactyly" experience psychological problems. These often emerge in mid-childhood as a reluctance to use hands, even a need to hide them. Non-verbal communication may be affected by this and common important gestures, such as hand shaking, are often avoided. These problems have frequently not been overcome even in adult life (Buss, unpublished data). Providing adequate reassurance to parents of affected children may allow them to help their children develop a positive body image. Anecdotal reports of cases with tetramelic involvement who are professional artists, speed typists, and even marathon runners may also be of considerable reassurance.

Radiology usually reflects the clinical findings but sometimes transverse metacarpals or proximal phalanges affect the appearance. Occasionally atypical cleft hand and monodactyly coexist (fig 2). In the EEC syndrome (the ectodermal dysplasia, ectrodactyly, and clefting syndrome), preaxial anomalies also may coexist with a central cleft. While careful examination of the parents' hands may be helpful, there is little extra information to be gained from routine radiography of the hands and feet of parents who are clinically normal.

Differential diagnosis: clinical approach
Recognition of a central ray deformity may be a useful clue for the diagnosis of a number of underlying disorders (EEC syndrome, Cornelia de Lange syndrome, acrorenal syndrome, etc) (table 1). When presented with a neonate with a central ray defect diagnostic difficulties may arise. In such cases magnification of nails and dental x rays may help in identifying involvement of ectodermal structures (difficult in the neonate/infant with oligosymptomatic EEC syndrome). It is also worthwhile reviewing these children during the first year to confirm normal development of ectodermal structures and, if uncertain of this, electron microscopic examination of the hair shaft may be helpful in diagnosing ectodermal dysplasia (Buss, unpublished data). In the newborn it is important to document hair distribution and birth weight. A renal ultrasound scan may help make the diagnosis of the EEC or acrorenal syndrome. In older children and adults with "isolated" ectrodactyly, one often notes minor associated ectodermal anomalies (of the teeth in particular).4 Language milestones should be checked. Ectrodactyly associated with conductive deafness and mandibular hypoplasia has been described in a father and son by Patterson and Stevenson26 and more recently with sensorineural deafness by Raas-Rothschild et al although the latter report looks distinctly similar to oligosymptomatic EEC syndrome. The otic capsule is interestingly also of ectodermal origin.30 Opitz and Frias13 described an association with cleft palate as a separate entity, the ECP syndrome. Karsch5 recognised

Table 1 List of conditions in which cleft limb may be a feature (McKusick No)

<table>
<thead>
<tr>
<th>Condition</th>
<th>McKusick No</th>
</tr>
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<tbody>
<tr>
<td>EEC syndrome</td>
<td>129900</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
<td>122430</td>
</tr>
<tr>
<td>Acrorenal syndrome</td>
<td>102520</td>
</tr>
<tr>
<td>Focal dermal hypoplasia</td>
<td>305600</td>
</tr>
<tr>
<td>Ectrodactyly and cleft palate syndrome</td>
<td>129830</td>
</tr>
<tr>
<td>Ectrodactyly and mandibulofacial dysostosis</td>
<td>183700</td>
</tr>
<tr>
<td>Ectrodactyly and macular dystrophy</td>
<td>185800</td>
</tr>
</tbody>
</table>

Non-specific associations with several anomalies are noted by Czeizel et al24 and also with neural tube defects.
an association with impaired vision owing to cataract and macular dystrophy.

For parents of isolated cases empirical recurrence risks are low but there is a potential risk to offspring of affected persons of 50%. With possible heterogeneity and altered penetrance risks may be lower.30 Certainly isolated cleft limbs can produce some very difficult diagnostic as well as counselling situations. Constriction amputation of digits may be difficult to distinguish from unimelic atypical cleft limb. Clues as to a constrictive aetiology might include the observation of amniotic strands at birth or lymphoedema distal to a possible constriction ring. Soft tissue syndactyly also occurs in constriction anomalies but is usually distal.31 In such cases no bony anomalies are usually radiologically present and occasionally the astute neonatal resident will have asked for the placenta to be examined showing an amniotic tear. Unilateral limb reduction deficits may also have a vascular origin and the clinician should be aware of relevant points in the history, for example, chorionic villus sampling, presence of twins (reversed arterial perfusion), and any occurrences that may have compromised fetal circulation. It can be difficult to separate some of these potential causes and in the atypical isolated unimelic case explanation of a number of potential aetiologies may occasionally be necessary.

Cleft hand and foot malformation and 7q abnormalities

Eight recent case reports of ectrodactyly and 7q21.2–q21.3 anomalies are summarised in table 2. It is of interest that six of seven isolated cases reported are male (note the preponderance of males observed by Stephenson and Jennings35 and in the familial cases of Czeiezel et al.36). The significance of this is unclear. Genuardi et al.37 recently reported a family segregating a balanced translocation with a breakpoint at 7q22.1, in which two out of nine translocation carriers had limb deficiencies (similar abnormalities were present in a further five persons in whom chromosome analysis was not possible). Overall there is a wide range of clinical involvement from apparently isolated cleft limbs to ectromelia associated with fatal anomalies. None of the isolated cases had unilateral cleft limbs, although three members of a family38 showed unimelic involvement. The majority of the reported cases have typical cleft limbs.

Few other reports exist that link central ray anomalies with chromosome 7. Klep-de Pater et al.39 described a female infant with cleft palate and digital reduction deformities of the second and fifth digits of the right hand (not typical central cleft) and no evidence of ectodermal dysplasia.39 This case had a karyotype 46,XX, del(7)(q11→q22). A number of additional case reports of deletions involving the 7q22 band have not been associated with ectrodactyly.40

Aetiology and developmental aspects

The general association of cleft limb with anomalies of ectodermal structures is not particularly surprising as there are similarities in limb development to that of several ectodermal structures. Wolpert’s experiments which confirmed earlier observations of a crucial reliance of embryonic limb ectoderm on the underlying mesoderm are not merely of historical importance.37 He postulated the presence of a signalling mechanism (probably a diffusible morphogen) which could be interpreted as a positional signal for regional development within the progress zone of the developing limb bud mesoderm. Historically it has seemed likely that the endogenous signalling morphogen in the limb bud of mammals may be related to retinoic acid (possibly 3′4′didehydroretinoic acid).39 However an exciting recent report indicates that a newly identified gene encoding the signalling molecule, Sonic hedgehog, may be involved in establishing polarising activity in the developing limb bud and hence antero-posterior patterning.48

Developmental digit anomalies such as those seen in central ray anomalies, however, are not easily explained by a diffusible morphogen model. Homeobox genes are consistently expressed in the developing limb bud and digits in a way that reflects their location within a homeobox cluster (temporospatial colinearity).43 These genes are activated sequentially by varying concentrations of retinoic acid within the limb bud. The expression of genes of the homeobox 4 (HOX D) type is necessary for normal limb development in mice41 and chick.42 Transcript expression can be predictably
altered in experimental animal models by implantation of retinoic acid soaked beads in strategic positions within the developing limb bud with resultant anomalies including mirror hands and polydactyly. Central ray digit reduction anomalies have not yet been observed in these experiments. It may be that the anomaly represents a localised disturbance of HOX expression at the ectodermal/mesodermal junction. Recent work has shown distinct expression of MSX1 (HOX 7) and MSX2 (HOX 8) at this site in limbs and teeth. Additionally combined tiguous genes, for limb patterning genes anomalies production in these differentiation in anomaly and represents a later been made the progress truncus. It occurs as a result of MSX1 (HOX 8) in the early limb bud. The msh of the bud and teeth.46 it has also been putatively that the mechanism underlying this result in a balanced split translocation with a breakpoint on q22.1. Am J Med Genet 1993;47:823-31. Nett NJ, Platt AE. Congenital central hand defect. J Hand Surg 1981;6:48-60. Patterson TJS, Stevenson AC. Craniofacial dysostosis and malformation of the feet. J Med Genet 1964;1:112-14. Raas-Rothschild A, Noram A, Bern-Ami T, et al. Newly recognized ectrodactyly/deafness syndrome. J Craniofac Genet 1989;9:121-7. Mikaelian DO, Der Kalousten V. The Institute of limb development and malformation. Br Med Bull 1976;32:65-70.
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