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 hand3 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 Pare4 although Barsky5 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-Jensen11 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 et al14 indicate that three-quarters (77%) of cases present with unimelic involvement.

In 1960 Stevenson and Jennings15 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 Ford18 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-

Figure 1 Typical central clefts of hands and feet; wide central clefts with normal marginal (radial and ulnar) rays. In this case the child had EEC syndrome.
chological rather than functional. Only in the
less common variant monodactylyous ec-
trodactly, where radial rays are also hy-
poplastic, is function severely compromised.

Considerable anatomical variability occurs.
Cleft hand has been described with pre- and
postaxial duplication and reduction anomalies.1

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
tetarmelic 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. 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
groups' were familial. The study of Czeizel et
al13 showed a high percentage of presentation
as atypical forms, though this is based on a
“wide” interpretation as to what actually con-
stitutes 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 atyp-
ical 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. Func-
tional 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. Lim-
itation of function owing to syndactyly of
the fingers may also occur and this also can be
overcome surgically.27 In the lower limbs the
major practical difficulty encountered is one of
obtaining adequately wide fitting shoes.

Many persons with “ectrodactly” 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 re-
ports 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 find-
ings but sometimes transverse metacarpals or
proximal phalanges affect the appearance. Occa-
sionally atypical cleft hand and monodactyly
coexist (fig 2). In the EEC syndrome (the
ectodermal dysplasia, ectrodactyly, and clefting
syndrome), preaxial anomalies also may occur
together with a central cleft. While careful examination of the parents’ hands may be helpful, there is
little extra information to be gained from rou-
tine radiography of the hands and feet of par-
ents 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 in-
volve ment 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, un-
published 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”
ectrodactly, one often notes minor associated
ectodermal anomalies (of the teeth in par-
ticular).4 Language milestones should be
checked. Ectrodactly associated with con-
ductive deafness and mandibular hypoplasia
has been described in a father and son by
Patterson and Stevenson28 and more recently
with sensorineural deafness by Raas-Rothschild
et al30 although the latter report looks distinctly
similar to oligosymptomatic EEC syndrome.
The otic capsule is interestingly also of ec-
todermal origin.30 Optiz and Frias29 described
an association with cleft palate as a separate
entity, the ECP syndrome. Karsch30 recognised

| Table 1 List of conditions in which cleft limb may be a feature (McKusick No) |
|-------------|-----------------|
| EEC syndrome (129900) | Cornelia de Lange syndrome (122450) |
| Acrorenal syndrome (102520) | Focal dermal hypoplasia (305600) |
| Ectrodactyly and cleft palate syndrome (129830) | Ectrodactyly/septooval facial dysostosis (183700) |
| Ectrodactyly and macular dystrophy (185800) | Non-specific associations with several anomalies are noted by Czeizel et al and also with neural tube defects. |

Figure 2 Combined monodactyly with atypical cleft deformity showing some preservation of marginal rays in right hand.
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. 13 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. 14 In such cases no other 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, choriocorn 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 ectroductacy 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 Jennings 15 and in the familial cases of Czeizel et al 16). The significance of this is unclear. Genuardi et al 16 recently reported a family segregating a balanced translocation at breakpoint 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 family 16 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 19 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. 19 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. 16

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). 38 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 anteroposterior patterning. 39

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 colinearities). 40 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 mice 41 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 buds 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 expression of both HOX D and of HOX A represents an anomaly related to MSX1 and MSX2 dermal latero-positions strategic loci. It is interesting to note, however, that mutation of MSX2 (HOX 8) has been associated with craniosynostosis and limb defects (including triphalangeal thumb and metatarsal shortening).

Mice have been bred with dactylaplasia which closely resembles the human cleft limb. In these it has been hypothesised that the anomaly occurs as a result of effects from two loci. Whether this could be extrapolated to human cleft limb is debatable but a similar explanation was put forward by David. The association of cleft limb with absence of long bones suggests that the defect may occasionally be a result of a common defect in regional limb specification. A child exposed in utero to a retinoic acid derivative during the crucial time of limb development with absent digits and syndactyly has been reported. More recently two case reports of limb anomalies in a fetus and child with prenatal exposure to isotretinoin have been reported. One could postulate that the mechanism underlying this may be a failure of differentiation resulting from misexpression of homeobox genes. However, it may be worth noting that other teratogens such as ethanol have also been postulated to cause ectodactyly, in this particular case with no clear underlying mechanism.

Evidence is clearly accumulating to make the 7q21.2–q21.3 locus a prime candidate for isolated ectodactyly. While it has also been postulated as a locus for investigation in syndromes such as the EEC syndrome (contiguous genes), it is likely that cleft limb represents a genetically heterogeneous condition and the 7q genes represent just one potential defect affecting a common pathway for limb differentiation.

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7 Lewis T, Embleton D. Split hand and split foot deformities their types, origin and transmission. Biometrika 1908;6:26–58.


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