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Heredity and dysmorphic syndromes in congenital limb deficiencies

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Abstract

Isolated limb deficiencies are usually sporadic occurrences. However, if they are associated with other abnormalities or a family history, the risk to future pregnancies may be as high as 50%. A thorough history, examination and investigation of the baby as well as the parents is essential before assessing this recurrence risk. The syndromes associated with limb deficiencies are presented.

Introduction

Limb deficiency has an incidence of approximately 1:2,000 births and in some families there may be a significant recurrence risk (Calzorali *et al.*, 1990). After a parent has recovered from the initial shock of finding their baby has a problem, two important questions arise. The first is about the implications of the anomaly for the child. The second question involves the risks of the problem happening again.

To answer this, it is necessary to determine whether the baby's anomalies fit into a "pattern" which constitute a syndrome. A pregnancy history, including drug or alcohol exposure, should be taken, as should a full family history concentrating on limb abnormalities. The baby should then be examined for dysmorphic features arising from abnormal embryogenesis. Recognition of a pattern of malformations may enable conclusions to be drawn about the mechanism and timing of the anomalies. Certain investigations such as blood count, bone marrow aspirate and chromosome analysis may be needed in addition to X-rays. Finally the parents should be examined and if necessary X-rayed for signs of minor anomalies which may represent reduced expression of a dominant gene.

The classification of limb deficiencies has previously been made on anatomical grounds (O'Rahilly, 1969). To illustrate this article we have made a causal and genetic classification (Tables 1 and 2) but this is not meant to replace the former, as the majority of defects are sporadic with ill-explained mechanisms.

Anomalies such as duplication, polydactyly, brachydactyly, syndactyly and the pterygium syndromes are not discussed, neither are skeletal dysplasias. We have concentrated on conditions presenting as limb reduction or deficiency.

Single gene disorders

Disorders caused by a defect in a single gene follow the patterns of inheritance described by Mendel. There may be heterogeneity within a particular diagnostic category. For example the typical split hand anomaly can be inherited in any one of the three Mendelian ways: autosomal dominant, autosomal recessive or X-linked recessive, or it may be sporadic or part of a syndrome. The family pedigree and clinical presentation may allow confident counselling.

Autosomal dominant disorders

Autosomal dominant disorders affect both males and females and can often be traced through many generations of a family. Affected people are heterozygous for the abnormal allele and transmit the gene for the disorder on average to half their offspring, whether male or female. Estimation of risk is apparently simple but in practice, factors such as variable

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Table 1: Syndromes presenting with limb deficiency.

Aetiology	Syndrome	Limb deficiency
Single gene disorders:		
Autosomal dominant:	EEC	split hand/foot (ectrodactyly)
	Adams Oliver	transverse defect
	Holt Oram	longitudinal all degrees
	LADD	absence thumb/radius
	Duane	absence to hypoplasia radius/thumb
	Split hand/foot	split hand/foot
Autosomal recessive:	Roberts	longitudinal affecting whole limb
	Grebe	hypoplastic radii, ulnae, tibiae
	Fanconi	hypoplasia to absence thumb/radius
	TAR	absence of radius — thumb present
	AASG	hypoplasia of radius
	Miller	hypoplasia to absence ulna/5th ray
	Weyers	oligodactyly, hypoplasia ulnar ray
	Split hand/foot	split hand/foot
X-linked recessive:	Split hand/foot	split hand/foot
Chromosomal:	trisomy 18	longitudinal all degrees
	trisomy 13	radial absence
	13q−	hypoplastic thumb
	4q−	hypoplasia/absence thumb
Drugs:	alcohol	longitudinal all degrees
	thalidomide	longitudinal all degrees
	aminopterin	hypoplasia (forearm), hypodactyly
Infection:	varicella	hypoplasia and hypodactyly
Aberrant development:	MZ twinning	transverse defect
	amniotic bands	transverse defect
Sporadic syndromes: (unknown cause)	aglossia-adactyly	adactyly
	Poland/Moebius	hypoplasia forearm, oligodactyly
	spleno-gonadal	transverse defect
	VATER	absent radius
	Cornelia de Lange	micromelia, hypoplasia ulna
	FFU (also A.R.)	hypoplasia femur, fibula, ulna
Associated with maternal diabetes:	Caudal dysplasia	hypoplasia lower limb
	femoral hypoplasia + unusual facies	hypoplasia/absence femur, fibula and humerus

expression and penetrance may cause difficulties in counselling. The severity of many dominant conditions vary considerably among affected members within a family. The likely severity is difficult to predict and a mildly affected parent may have a severely affected child.

Adams Oliver syndrome: A parent with minor terminal reductions of toes and fingers may have a child with severe limb defects such as bilateral transverse leg deficiencies (Fryns, 1987). The associated scalp defects are midline skin defects located on the vertex with occasional defects of the skull and meninges.

Holt-Oram syndrome: There is a wide variability of expression of both the cardiac and upper limb anomalies (Fig. 1). There are all gradations of defects in the upper limb ranging from clinodactyly and carpal fusion to more severe longitudinal deficiencies, the most typical being a thumb anomaly. The cardiac lesion, may be an atrial septal defect (common), ventricular septal defect, patent ductus arteriosus or mitral-valve prolapse. There is no correlation between the severity of

Fig. 1. Holt Oram syndrome: note bilateral radial absence.

the limb defect and the cardiac defect. Before a new mutation is presumed to have occurred and a low recurrence risk is given to apparently normal parents of an affected child, detailed physical examination with X-rays of wrist, hand and arms and cardiac assessment with echocardiography are necessary.

EEC syndrome: Each of the three main features of ectrodactyly, ectodermal dysplasia and clefting syndrome shows a variable degree of expressivity. The ectodermal part of this syndrome involves the hair (dry and sparse with absent eyebrows and eyelashes), teeth (small or absent) and nails (brittle and ridged). Limb abnormality consists of defects in midportion of hand and feet, varying from syndactly to a split hand/foot anomaly. Mental development is usually normal and facial clefting, is common but not an essential part of the syndrome.

LADD (lacrimo-auriculo dento-digital) syndrome: Phenotypic variation is seen. (Thompson *et al.*, 1985). The characteristic features of this condition are absence of lacrimal puncta/canaliculi leading to epiphora and chronic eye infections, cup-shaped or malformed ears with sensoneural or conductive deafness, abnormalities of the teeth and radial ray defects of variable severity.

Table 2. Classification of syndromes by anatomical criteria.

Limb deficiency		*Syndromes*
a) Transverse defect: previously known as:		MZ twinning
	amelia	Adams Oliver
	hemimelia	amniotic bands
	acheiria	aglossia adactyly
	adactylia	EEC
	ectrodactyly	varicella
	apodia	alcohol
b) Proximal longitudinal: absent radius, thumb present hand attached at shoulder foot attached to hip		thalidomide Roberts Grebe aminopterin TAR varicella
c) Longitudinal	i) radial ray:	VATER Holt Oram Nager Fanconi Levy Hollister trisomy 18 Duane AASG
	ii) ulnar ray:	Cornelia de Lange Miller FFU Weyers
d) Split hand/foot:		Cornelia de Lange EEC split hand/foot XLR, AD and AR

Duane syndrome: Radial ray defects associated with Duane anomaly follow an autosomal dominant pattern in some families (MacDermot and Winter, 1987). The radial defects range from thenar eminence hypoplasia to radial absence. The Duane anomaly is an unusual congenital form of strabismus characterised by limitation of abduction in association with retraction of the globe and narrowing of the palpebral fissures on adduction.

Split hand/foot: Autosomal dominant inheritance is the commonest mode of transmission in familial isolated split hand/split foot anomaly. The anomaly may be of the lobster claw variety (absence of central rays) or monodactyly type (deficiency of radial rays with no cleft). Gradations between these types occur and cases of each type are seen in some families with the appearance of skipped generations.

Autosomal recessive disorders

Autosomal recessive disorders occur in a person whose healthy parents carry the same recessive gene. The risk of recurrence for future offspring of such parents is 1 in 4 (25%). Consanguinity increases the risk of a recessive disorder because both parents are more likely to carry the defective gene which has been inherited from a common ancestor.

The following are examples of some of the conditions following this pattern of inheritance.

Roberts syndrome: The main clinical features are severe symmetrical shortening of the limbs with end longitudinal deficiency (Fig. 2), a characteristic face with hypertelorism, severe cleft lip, prominent premaxilla, mid-face capillary haemangioma, cloudy corneas or cataracts and dysplastic ears. Many affected infants die in the newborn period, survivors are mentally retarded. Clinical and genetic data suggest it is probably the same condition as has been described as SC phocomelia. Chromosome analysis in both conditions shows premature centromeric separation (Romke *et al.*, 1987).

Grebe syndrome: This condition is characterised by severe shortening of the upper

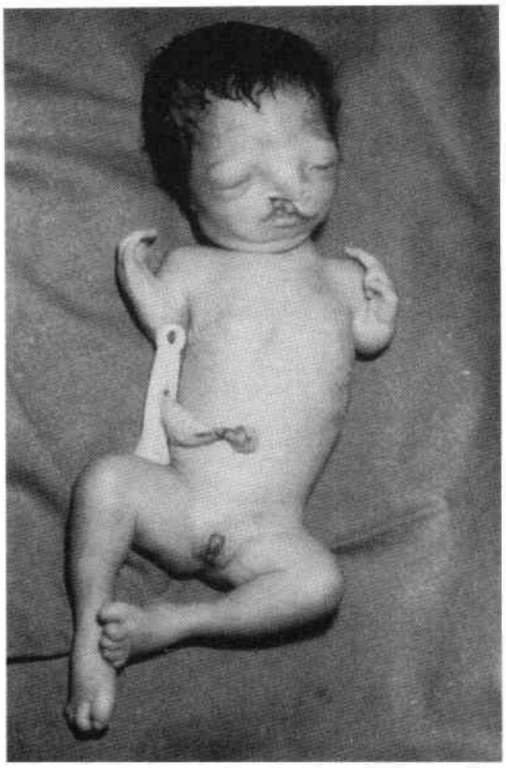

Fig. 2. Roberts syndrome: note characteristic facial pattern with cleft palate and symmetrical deficiency worse in upper limbs.

and lower limbs so that the eventual height can be as small as 3 feet. The hand and fingers are particularly tiny, the digits resembling stubby toes. The head, trunk, and intelligence of survivors are normal.

Fanconi anaemia: This disorder presents as a pancytopenia (mean age of onset — 8 years), associated with a variety of congenital malformations. The malformations affect one or more systems, including the skin, skeletal, ocular, auditory, renal, genital and central nervous systems. Radial defects comprising hypoplasia or absence of the thumb, first metacarpal and radius are the most common skeletal malformations (Glanz and Fraser, 1982). This variation of number and severity of the congenital malformations precludes the establishment of hard and fast diagnostic criteria on clinical grounds only. In recent years, cytogenetic studies have demonstrated that affected persons have an increased frequency of chromosomal breaks, even in the pre-anaemic stage. The chromosomal breaks can also be demonstrated in the cultured amniotic fluid cells allowing prenatal diagnosis of infants at risk (Auerbach *et al.*, 1985).

TAR (thrombocytopenia and absent radius): The clinical features include haematological abnormalities (mainly of platelets), skeletal abnormalities (primarily of both arms and legs), cardiac abnormalities (particularly tetralogy of fallot and atrial septal defect), and cow's milk allergy. The most striking skeletal abnormality is bilateral radial absence with preservation of the thumbs. The hypomegalokaryocytic thrombocytopenia is of early onset. Anaemia, eosinophilia and leukaemoid granulations may be seen. If the infant survives, the haematological features become less severe.

AASE — triphalangeal thumb with congenital anaemia: A congenital erythroid hypoplastic anaemia is associated with triphalangeal thumbs which lie in the same plane as the other digits. Sloping narrow shoulders, hypoplasia of the radius and radio-ulnar synostosis have been noted in some cases. The anaemia usually responds to steroids and improves with age. There is controversy about the existence of this condition as a separate entity from Blackfan Diamond congenital erythroid hypoplastic anaemia (Alter, 1978).

Weyers oligodactyly: The main features of this syndrome which was first described by Weyer are deficiency of the ulnar and fibular rays, antecubital pterygia, reduced sternal segments and malformations of the kidney and spleen with cleft lip and palate. Two affected siblings were reported by Elejalde *et al.*, (1985) suggesting autosomal recessive inheritance.

Miller (postaxial acrofacial dysostosis) syndrome: The characteristic features are postaxial limb deficiency, cup-shaped ears and malar hypoplasia. The limb defects are distinctive, consisting of an absence or incomplete development of the fifth digital ray of all four limbs (Donnai *et al.*, 1987). Most cases have shortened forearm with ulnar hypoplasia. The facial features are similar to Nager syndrome in which the limb deficiencies are preaxial.

Split hand/split foot anomaly: Recessive inheritance is less common than the dominant type but has been observed in inbred communities (Freire Maia, 1971). It should be diagnosed with caution because of variable expression of the autosomal dominant type.

X-linked recessive disorders

In X-linked recessive disorders the mutant gene is on the X chromosome, hemizygous males (with the mutant gene on their single X chromosome) are affected, heterozygous females (=Carriers) are usually healthy but may occasionally show some features of the condition. A female carrier will transmit the disorder on average to half her sons, and half her daughters will be carriers. All the daughters of an affected male are obligate carriers and none of the sons are affected.

Split hand/split foot anomaly: Ahmed *et al.*, (1987) reported a large (7 generations) inbred kindred from Pakistan in which an isolated type of split hand/split foot anomaly is transmitted as an X-linked recessive disorder. Affected males show full expression of the trait, carrier females show only features such as syndactyly. There is no male to male transmission.

Chromosomal abnormalities

The correct amount of chromosomal material is essential for the normal formation and function of a baby, any imbalance usually results in multiple congenital malformations and mental retardation. Common groups of chromosomal abnormalities include trisomies (extra chromosome present), deletion and duplication (part of chromosome is missing or duplicated) and mosaics (abnormal chromosomal pattern present in only some cells).

There are a few well recognised syndromes associated with autosomal trisomies — Down's syndrome (Trisomy 21), Edward's syndrome (Trisomy 18) and Patau's syndrome (Trisomy 13). Congenital limb deficiencies have been described in Edward's and Patau's syndrome. At least 10% of cases of Edward's have radial and or thumb absence, the characteristic hand deformity being tight flexion of the fingers with the 2nd and 5th digits overlapping the 3rd and 4th. In Patau's syndrome the characteristic hand deformity is post-axial polydactyly, absence of the radial rays although the radius is sometimes present. The majority of trisomies arise from non-disjunction at meiosis, and the recurrence risk for these is low.

Sometimes only part of a chromosome is missing or duplicated. There are many such conditions and only a few are common enough to have a recognisable "named" pattern of malformations. Chromosomal analysis should therefore be considered in any baby with multiple congenital abnormalities, particularly if associated with a low birth weight. Limb deficiencies with hypoplasia to absence of the thumb have been described in cases with partial deletion of the long arm (q) of chromosomes number 13 and 4. Duplication of part of chromosome 3 gives an appearance similar to de Lange syndrome.

As with the translocation trisomies, chromosomal structural abnormalities may arise as *de novo* events or from a balanced rearrangement in one of the parents. Parental karyotypes are indicated for any child with a chromosomal abnormality other than the regular trisomies. Extended family studies will be required if a parent has a balanced structural abnormality. The recurrence risk varies with the type of chromosomal rearrangement and sex of the carrier. Prenatal diagnosis with amniocentesis or chorionic villous biopsy should be offered to all women whose pregnancies are at increased risk.

Drugs

Skeletal limb deficiencies have been produced in the rat and mouse experimentally using a number of drugs in common use today (Freire Maia, 1969). There are only a few agents which have been firmly implicated in man. The best known is thalidomide (Millen, 1962), which may cause a wide range of longitudinal defects up to complete absence of all four limbs. Administration between the 38th and 47th day of pregnancy is most dangerous. Thalidomide still has an important role in leprosy therapy and we may not have seen the last affected infant with thalidomide embryopathy.

The folate antagonists aminopterin (Thiersch, 1952) and methotrexate (Milunsky *et al.*, 1968) have been associated with limb deficiency. Aminopterin was used as an abortifacient drug and anomalies noted

included growth deficiency, cranial dysplasia with broad nasal bridge and short limbs especially in the forearm, with hypodactyly.

The foetal alcohol syndrome occurs when the foetus is subjected to large quantities of alcohol in pregnancy. Infants are usually small hypotonic and jittery. They are microcephalic with short palpebral fissures and a smooth under developed philtrum. There may be cardiac lesions. Limb deficiency is rare but can be severe with reduction or even total absence (Pauli and Feldman, 1986).

Infection

The only infection definitely associated with limb defects is varicella. Infection in early pregnancy can lead to a number of anomalies including: cicatricial skin, chorioretinitis, growth and mental deficiency and seizures. The limb may be hypoplastic with rudimentary digits, perhaps because of viral or inflammatory damage to the nerves of the developing limb. Only a small percentage of mothers with proven infection have an affected baby (Paryani and Arvin, 1986).

Other known mechanisms

Monozygous twinning: This may cause a number of effects by various means (Schinzel *et al.*, 1979). Death of one twin may lead to thromboplastin or embolic release into the circulation of the co-twin causing a transverse defect by vascular disruption.

Amniotic bands: These have long been implicated in the production of limb deficiencies and are often called Streeter's bands (Streeter, 1930). The exact mechanism of their origin is still unclear. Limb defects include constriction rings, secondary syndactylies and amputations.

Poland and Moebius anomalies: Poland anomaly consists of unilateral absence of the pectoralis muscle and ipsilateral symbrachydactyly. Transverse defects especially distally may co-exist. In the Moebius anomaly there is unilateral or bilateral palsy of the sixth and seventh cranial nerves. The third, fifth, ninth and twelfth may also be affected. Limb deficiencies are similar to those that occur in Poland anomaly. There can be considerable overlap between the two conditions.

A common mechanism for the two has recently been proposed (Bouwes Bavinck and Weaver, 1986). This involves disruption of the blood flow at a critical stage of embryogenesis (day 37–42). If this occurs in the subclavian artery it will result in Poland anomaly and if it occurs in the basilar or vertebral arteries Moebius anomaly results. If interruption occurs at both sites the conditions could co-exist, as they often do clinically.

Other syndromes

VATER: The non-random association of vertebral defects, anal atresia, tracheo-oesophageal fistula, radial aplasia, and renal anomalies, has been reported (Temtamy and Miller, 1974). This has been extended to *VACTERL* more recently to incorporate cardiac and other limb abnormalities. These include hypoplasia of the humerus andy varying degrees of aplasia in the lower limb (Fig. 3) (Fernbach and Glass, 1988). This disorder is sporadic and of unknown cause.

Cornelia de Lange: This is a very well characterised condition. Infants are small, and mentally retarded with microbrachycephaly. They have bushy eyebrows and synophrys and a small nose with anteverted nostrils. Micromelia affects the legs predominantly, however there can be severe longitudinal deficiency and oligodactyly in the upper limbs and the ulnar ray is often involved. The condition is sporadic but because it occurs relatively frequently and has all the hallmarks of a chromosome deletion syndrome, it may well be caused by gene imprinting (Hall, 1990). Duplication of the chromosome 3q25–29 band gives a very similar phenotype (Wilson *et al.*, 1978).

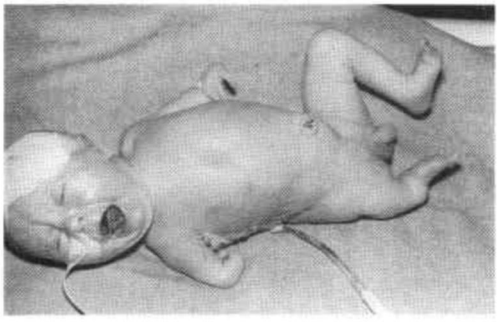

Fig. 3. VATER: note assymmetrical limb deficiency

Counselling

The majority of limb defects, especially those affecting one limb only, are sporadic and parents can be given a low recurrence risk. However there are pitfalls to this as the occurrence of isolated limb deficiencies may be due to autosomal recessive genes (Hecht, 1981). The presence of associated abnormalities may allow a diagnosis of a recognised syndrome. There are varying reports as to the frequency of these, Calzorali *et al.* (1990) estimate 12% with half representing known syndromes. Generally parents can be given a high (50–25%), medium (10–5%), or low recurrence risk. The Mendelian conditions would give a high risk. The medium risk would be appropriate when it was thought that complex genetic mechanisms or multifactorial inheritance was involved. Low risk is usually appropriate to isolated transverse deficiency, ulnar absence and quadruple amelias. A low risk can also be given if a known mechanism such as varicella or a drug was involved. Care must be taken however with the foetal alcohol syndrome as there are often several affected siblings with markedly different phenotypes. Another difficult area is that of a consanguineous marriage in a situation where a low risk would normally be given (Freire Maia, 1969). Caution is necessary in such circumstances.

Parents seen at or soon after the birth, by a clinical geneticist, should be seen again a few months later for formal genetic counselling. Virtually all parents experience some guilt feelings and will have their own (often far-fetched) explanations for why the abnormality has occurred. It is important to allow parents the opportunity to vent these concerns. At the formal counselling session parents may be looking to the future and wish to discuss the recurrence risks and possible prenatal diagnosis. Genetic counselling aims to give information to allow parents an informed choice and does not presume to advise people on a "correct" course of action. Ultrasound has markedly improved the possibilities of prenatal diagnosis and when appropriate, a detailed scan should be offered.

Conclusion

The authors have outlined the syndromes associated with limb deficiency. Although these represent only a small proportion of the total number of individuals with limb deficiency it is important that these are identified in order to give accurate genetic counselling to relatives.

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