Limb reduction defects

Of all congenital anomalies, limb reduction defects maintain a high profile with the public. In the early 1960s, high rates of limb reductions were associated with expectant mothers taking the drug thalidomide. As a result of this, congenital anomaly surveillance systems were established to try and prevent further such episodes. In the late 1980s limb reductions were found to be associated with chorionic villus sampling in early pregnancy, leading to changes in obstetric practice. A further scare occurred in the early 1990s when newspapers reported clusters of cases of limb reduction defects around coastal areas of the UK, although this finding was not supported by subsequent epidemiological studies.

The finding of a limb reduction defect in an otherwise healthy baby can be very disappointing for expectant parents. The complexities of coping with this kind of disability seem daunting at first and are often associated with feelings of guilt and anger:

Is this due to something I did?, medicines I have taken? Is some environmental hazard to blame?

Embryology

Upper and lower limbs form from lateral plate mesoderm. The 4\textsuperscript{th} and 5\textsuperscript{th} weeks after conception are the most sensitive period for teratogen induced limb defects as this is a key stage in development of the limb buds and rudimentary hands, as shown below.

<table>
<thead>
<tr>
<th>conception</th>
<th>upper limb buds begin to form</th>
<th>lower limb buds begin to form</th>
<th>rudimentary hand present</th>
<th>skeleton is cartilaginous digital rays present</th>
<th>limbs formed but not ossified</th>
</tr>
</thead>
<tbody>
<tr>
<td>day 0</td>
<td>day 26</td>
<td>day 28</td>
<td>day 32-34</td>
<td>day 40</td>
<td>day 56</td>
</tr>
</tbody>
</table>

Patterns of limb reduction defects

The upper limb is twice as commonly affected by reduction defects than the lower limb.\textsuperscript{1}

Abnormalities of the limbs vary in the part of the limb(s) affected and may involve complete absence of a limb (amelia) or partial absence (meromelia).

?? Defects involving absence of the distal parts of the limb are known as terminal transverse defects.

?? Sometimes, the long bones may be absent, with rudimentary hands and feet attached to the trunk by small, irregularly shaped bones (phocomelia). These are known as proximal intercalary defects.

?? In other cases, absence or severe hypoplasia of the long bones may affect one side of the arm, but not the other. These are known as longitudinal defects and are classified as:

?? Post-axial - involving the little finger / 5\textsuperscript{th} metacarpal / ulna or little toe / 5\textsuperscript{th} metatarsal / fibula

\textsuperscript{1} EUROCAT report 7. 15 year of surveillance of congenital anomalies in Europe 1980-1994
Pre-axial - involving the thumb / 1st metacarpal / radius or big toe / 1st metatarsal / tibia.
Congenital absence or deficiency of the radius usually results from a genetic abnormality and is associated with malformations in other body structures, together with defects in other digits and a short curved ulna.

Cleft hand consists of an abnormal cleft between the 2nd and 4th metacarpal bones with the 3rd metacarpal bones and finger absent. Other fingers either side of the resulting cleft are often fused. This results in 2 parts to the hand that are somewhat opposed to each other and act like a lobster claw, giving rise to the term “lobster claw” hand. A similar situation may also arise in the foot.

Multiple limb defects may occur together, giving a mixed picture of any of these patterns.

Figure 16: Examples of limb reduction defects
(from David)

Ultrasound appearances
An anomaly scan at 18 to 20 weeks includes an assessment of long bones and the hands and feet. A closer look at all the bones is indicated if the femur is short for gestational age.
Limb reduction defects are often easy to diagnose and should prompt a systematic survey of fetal anatomy because of the association with certain syndromes. Most upper limb defects are isolated events but those involving lower limbs are often part of more complex anomalies or syndromes.

Possible causes of limb reduction defects
Various influences on limb growth can cause a reduction defect.

An intrinsic abnormality of limb development
An external influence acting on a normally developing fetus
A physical restraint on limb development after normal formation

Intrinsic Limb Development Abnormality
Example
Limb reduction defects (especially those involving the radius or thumb) have been associated with chromosomal anomalies. It has been calculated that, when limb reduction defects are present, the chance of having trisomy 18 is 1 in 17. ²

External Influences

Example
Twice in recent history the effects of modern medicine and technology have caused devastating results on the next generation.

Thalidomide
Thalidomide was used in the early 1960s as a drug for morning sickness in the United Kingdom. Despite early reporting of abnormalities, as many as 800 babies were affected with limb defects. The drug was withdrawn at the time but is now being used as pain relief particularly for leprosy. Compliance problems with contraception for those taking thalidomide has meant that this cause of iatrogenic limb defects is still with us.

Early chorionic villus sampling
In 1991 a report from Oxford first suggested the link between chorionic villus sampling (CVS) and severe limb deficiencies. Further studies confirmed this association with defects where the distal part of one or more limbs or digits is missing across its entire width (transverse terminal deficiency). The earlier in pregnancy that CVS took place the more extensive the defect. It is thought that it causes disruption of the normal blood supply to cartilage. The risk decreases as pregnancy advances, so CVS is now not performed before 10 weeks gestation.

Physical Restraint on Limb Development

Examples

Amniotic Bands
These can appear on ultrasound as a band of membranes lying within the uterine cavity. (Figure 1) Why they should form is not clear. One theory is that bands are formed as a reaction to rupture of the amniotic sac in early pregnancy. The pregnancy carries on but this band of tissue becomes attached to the developing fetus and affects subsequent growth in that area. Various anomalies can be caused by amniotic bands ranging from minor constrictions of digits to cleft lip and palate. The recurrence risk in subsequent pregnancies is negligible.

Figure 17: Antenatal ultrasound – amniotic bands
From David

Welsh data

So far, 104 cases of limb reduction defect have been reported to CARIS for the years 1998-2000. 4 of these are cases of sirenomelia and are often not counted as true limb reductions. The remaining 100 cases give an overall gross rate of 10.3 cases/10,000 births (95%CIs 8.3-12.3). Of these 100 cases 62 resulted in live or

stillbirth, giving a birth prevalence of 6.4/10,000 total births (95% CIs 4.8-8.0). This rate is of the same order as that reported by other countries, although it is statistically higher than that reported by ONS for England and Wales as a whole. The possibility of higher rates of limb reduction defects in Wales than England cannot be excluded. However, this finding may well be due to improved reporting of congenital anomalies in Wales since CARIS came into operation.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Number of LB / SB cases</th>
<th>Number of births</th>
<th>LB / SB Rate per 10,000 births</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>1998</td>
<td>43</td>
<td>58,555</td>
<td>7.3</td>
<td>5.1 - 9.5</td>
</tr>
<tr>
<td>South America (ECLAMC)</td>
<td>1998</td>
<td>94</td>
<td>142,477</td>
<td>6.6</td>
<td>5.3 - 7.9</td>
</tr>
<tr>
<td>Finland</td>
<td>1998</td>
<td>37</td>
<td>57,346</td>
<td>6.5</td>
<td>4.4 - 8.5</td>
</tr>
<tr>
<td>Wales (CARIS)</td>
<td>1998-00</td>
<td>62</td>
<td>97,325</td>
<td>6.4</td>
<td>4.8 - 8.0</td>
</tr>
<tr>
<td>USA (Atlanta)</td>
<td>1998</td>
<td>23</td>
<td>45,257</td>
<td>5.1</td>
<td>3.0 - 7.2</td>
</tr>
<tr>
<td>Australia</td>
<td>1997</td>
<td>120</td>
<td>250,751</td>
<td>4.8</td>
<td>3.9 - 5.6</td>
</tr>
<tr>
<td>Czech Rep</td>
<td>1998</td>
<td>39</td>
<td>90,829</td>
<td>4.3</td>
<td>2.9 - 5.6</td>
</tr>
<tr>
<td>Japan</td>
<td>1998</td>
<td>37</td>
<td>96,303</td>
<td>3.8</td>
<td>2.6 - 5.1</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1998</td>
<td>20</td>
<td>55,848</td>
<td>3.6</td>
<td>2.0 - 5.2</td>
</tr>
<tr>
<td>England &amp; Wales (ONS)</td>
<td>1998</td>
<td>210</td>
<td>638,950</td>
<td>3.3</td>
<td>2.8 - 3.7</td>
</tr>
<tr>
<td>Canada</td>
<td>1997</td>
<td>84</td>
<td>262,741</td>
<td>3.2</td>
<td>2.5 - 3.9</td>
</tr>
</tbody>
</table>

(data apart from CARIS is taken from the International Clearing House of Births Defects annual report, 1998)

The type of limb defects in each case is shown in Figure 2. Terminal transverse defects were the most common. Although 3 cases had intercalary defects, the presence of additional reduction defects led these to be included in the “multiple defects” category.

**Figure 18:** Pattern of defect reported for 100 cases of limb reduction defects reported to CARIS with pregnancy ending 1998-2000
Of the 100 Welsh cases,

12 were associated with constriction bands. In 3 cases the effects of the bands were limited to the limbs, whilst in the remaining 9, other parts of the body were also affected.

41 had an underlying syndrome that may account for development of the limb defects. These are summarised in Figure 3. The 13 cases of chromosomal abnormality included:

- 4 trisomy 18,
- 4 triploidy / polyploidy,
- 2 Edwards syndrome
- 1 trisomy 21 (Down syndrome)
- 2 others

This supports the previous finding of an association between chromosomal defects and limb reductions.

**Figure 19: Known underlying causes of limb reduction defect reported to CARIS, 1998-2000**

?? 26 cases had no apparent underlying cause for the limb defects but were associated with other congenital anomalies affecting a variety of body systems, with no particular group of anomalies predominating.

30 cases were classified as isolated limb reductions, with no obvious cause or associated anomalies. These cases correlate to those investigated in the early 1990s, when epidemiological studies were undertaken into a possible link to coastal areas. No link could be proven. A map showing the distribution of these cases around Wales is shown in Figure 4. The map shows that most cases occur in urban areas, where the majority of the population live. This includes the centres of population living along the coast in North Wales and around, Swansea, Cardiff and Newport.
Of the 100 CARIS cases, 67 had upper limb defects only and 16 had lower limb. Combined upper and lower limb defects affected in 14 cases and in the remaining 3, the site was not specified.

39 / 67 (48%) cases of upper limb defects were associated with other anomalies or syndromes. This proportion rose to 81% (13/16) for lower limb defects and 86% (12/14) where both upper and lower limbs were affected.

Prescribed medication was reported in 16/100 cases although the stage of pregnancy at which taken was not clear. Apart from 1 case on sodium valproate were known teratogens and they covered a wide spectrum of therapeutics.

2/100 cases were known to have had chorionic villus sampling: 1 at 12 weeks and 1 at 19 weeks.

Of the 100 cases, over half (55) were liveborn, with 7 stillborn and 11 spontaneous losses before the 24th week of pregnancy. In the remaining 27 cases, pregnancy was terminated. The majority of terminations (21/27) involved cases with other major abnormalities or underlying syndromes.

Among the liveborn cases, 7 died in infancy. All of these had other major anomalies or underlying syndromes.

**Conclusions**
Recent history reminds us of the importance of constant vigilance in terms of recording and monitoring congenital anomalies. The pattern of limb reduction defects
in Wales is as expected. No obvious causative factors are identifiable but, as with all congenital anomalies, this needs to be kept under close review.