Recognition of thalidomide defects

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Thalidomide: a brief history
Thalidomide (alpha-phthalimido-glutarimide) was developed by the German firm Chemie Grunenthal as an anticonvulsant drug. Early trials showed it to be unsuitable for this purpose but indicated that it had sedative properties. Furthermore, it had one remarkable property: overdoses simply caused prolonged sleep, not death. The drug was first marketed in Germany in 1957 under the name Contergan, and in the UK in April 1958 as Distaval. Later, compound preparations which combined thalidomide with other drugs were marketed for a wide variety of indications: Asmaval for asthma, Tensival for hypertension, Valgraine for migraine, and so forth. The promotion of these products laid great stress on the safety of thalidomide, based on the remarkable property described above.

German paediatricians and geneticists began to see children with gross limb malformations of a most unusual pattern. When two cases were shown at a paediatric meeting in Kassel by Kosenow and Pfeiffer in October 1959, few people present had ever seen similar limb defects. Wiedemann in 1961 described 13 affected infants who had been referred to him over a period of 10 months, and noted that this amounted to an epidemic. He drew attention to a number of associated malformations in these children, including congenital heart disease, microphthalmos and coloboma, intestinal atresia, renal malformations, abnormal pinnae, and facial naevus.

In November 1961, Lenz suggested that these deformities resulted from the mothers having taken thalidomide. By a remarkable coincidence, the same suggestion was made at about the same time by McBride in Australia. Confirmation of this suggestion came rapidly from all parts of the British Isles, Kenya, Japan, Sweden, Belgium, Switzerland, Lebanon, Israel, Peru, Canada, Brazil, the Netherlands, and the USA. The drug had been released only for clinical trials in the USA because of concerns following reports from Europe of irreversible peripheral neuritis as a side effect of thalidomide. Consequently there were very few cases. By contrast, it had been on sale over the counter in Germany, and there were consequently more affected children there than anywhere else. In the UK the drug was available on prescription only, but it was used very widely for, among other problems, common symptoms of early pregnancy.

Thirty years later, subjects are still coming forward (albeit, in small numbers) with claims that they have birth defects which have (or may have) been caused by thalidomide taken by their mothers during early pregnancy, and that they should therefore be accepted as beneficiaries of whatever forms of financial assistance may be available. In the UK, this is the Thalidomide Trust.

Thalidomide caused a wide variety of birth defects, not one of which was unique to that drug. Nevertheless, the nature and pattern of the defects are, in most cases, characteristic enough to be recognisable to an experienced eye. Indeed, many of the present beneficiaries of the Trust have been accepted on the basis of clinical judgements, without direct evidence of thalidomide exposure. As the number of doctors with wide experience of this problem is small (possibly only three in the UK) and will become smaller with the passage of time, and as new claims continue to arise, it seems timely to record, in as much detail as possible, the observations which underlie these clinical judgements.

As well as describing the defects and patterns associated with thalidomide, it will be appropriate to discuss 'differential diagnosis', that is, recognisable defects and syndromes which, to a greater or lesser degree, resemble thalidomide defects. Some of these are unlikely to confuse an experienced eye: others can present considerable difficulty.

In considering a new claim, attention will obviously be paid to the claimant's date of birth. In the UK, thalidomide was first marketed in April 1958, initially in very small quantities, so it is not to be expected that it would damage anybody born before January 1959 (unless supplies had been obtained from West Germany). Sales in the UK stopped in November 1961. Had consumption stopped at the same time, no 'thalidomide babies' should have been born after August 1962. However, many people still had tablets containing thalidomide in their homes, and either did not hear promptly of its dangers, or did not realise that their tablets contained thalidomide. In fact, children with defects accepted as attributable to thalidomide (though not necessarily with documentary evidence of prescription) continued to be born up to about May 1963, and, very exceptionally, beyond this date.

In trying to establish a yardstick or benchmark for bona fide thalidomide defects, it is necessary to start with cases in which there is
very good evidence of thalidomide intake in early pregnancy. Unfortunately, the investigator has never seen the pregnant mother swallow a tablet. Absolute certainty is therefore unattainable, and we must settle for a scale of probability. The evidence may include the following.

(1) A dated prescription for thalidomide, the date falling within or before (but not too long before) the period of embryonic sensitivity to the drug (34 to 50 days after the beginning of the last menstrual period).

(2) A doctor's statement, preferably a sworn affidavit, that he supplied such a prescription at such a time, but kept no record of it.

(3) A mother's statement (preferably sworn) that she took thalidomide at the relevant time, with an indication of its source (which is not necessarily a prescription).

(4) A mother's ability to identify the tablet she took, when shown a selection of tablets. Fortunately, all tablets containing thalidomide were readily identifiable and could be recognised or described by reasonably observant people.

At this point it is appropriate to mention two important paradoxes. First, although a few mothers may have claimed untruthfully to have taken thalidomide (acting in what they believed to be their child's best interests), a vastly greater number of the mothers of accepted Trust beneficiaries denied any knowledge of any drug consumption during pregnancy. There is a negative drug history in about 50% of accepted cases, and there is unlikely to be any such evidence in the future.

The second paradox is that, bearing in mind that 2 to 3% of all babies born have significant birth defects, and that thalidomide consumption was widespread in 1960 to 1961, some mothers who undoubtedly took the drug when pregnant (though probably outside the sensitive period) gave birth to babies with defects quite unrelated to thalidomide. It is also possible for a baby exposed to thalidomide during the sensitive period to be born with a variety of defects, of which some, but not all, are drug induced. Authorities differ about the possibility that a fetus exposed to thalidomide during the sensitive period might be born without birth defects. If it happens, it is rare.

The last general point to mention is the risk of perpetuating an error. If a clinician accepts as resulting from thalidomide a defect which has not, in fact, been described in cases with strong documentary support, he is more ready to accept that defect the next time he meets it. A defect that has been accepted two or three times becomes built into his repertoire of 'thalidomide defects'. This underlines the necessity to start from those cases with good evidence of drug exposure.

The following comments are based on 148 personally examined cases with good evidence of thalidomide exposure in early pregnancy, with documentary support in 35 cases.

Some general features of thalidomide damage
At birth, many thalidomide babies exhibited a central facial naevus of the 'stork mark' variety in the centre of the forehead (which is common among all babies) but spreading down over the nose and upper lip, and sometimes with a small element on the lower lip just below the vermillion border. These birthmarks disappeared over one to two years and will not be seen in future claimants, but there may be historical or photographic evidence. Some children showed facial features best understood by reference to photographs.

Short stature, over and above the shortness attributable to short leg bones, is seen more often than would be expected by chance, and is accepted as attributable to thalidomide.

SYMmetry
As the two sides of the embryo develop more or less in parallel, and it is difficult to envisage a drug which reaches it via the blood stream being distributed only to one side, one would expect drug induced malformations of bilateral...
structures to be more or less symmetrical. This is, broadly, what is observed in practice, not only with thalidomide, but with other teratogenic drugs and with defects of genetic origin. However, the extent of the symmetry varies according to the nature of the defect, both in the closeness of the match between left and right, and in the proportion of cases which are appreciably asymmetrical. The significance of symmetry will be discussed in relation to each defect group.

![Figure 1 Symmetrical reduction deformities of all limbs with loss of preaxial upper limb digits. Note hypoplastic scrotum.](image)

**UPPER LIMBS**

The most characteristic defects are reduction deformities, that is, the loss of part or the whole of one or more bones. The bones of the upper limb are affected in a remarkably regular order, starting with the thumb, followed by the radius, the humerus, the ulna, and finally the fingers on the ulnar side of the hand (middle, ring, and little fingers). Consequently, the defect which falls just short of complete absence of the arm (upper limb amelia) consists of one or more digits attached directly to the shoulder. If the defect is a little less severe still, there is a lump of bone interposed between the shoulder and the digits, the origin of this lump being impossible to determine on anatomical grounds. If the reduction deformity is less still, it is possible to identify the individual long bones (humerus, ulna).

Not surprisingly, when substantial parts of bones are missing, the muscles normally attached to them are hypoplastic, but the extent of this muscle hypoplasia does not always correspond exactly to the loss of bone. For example, the muscles of the shoulder and upper arm may be markedly hypoplastic even when the humerus is of normal length. The degree of underdevelopment of the thenar eminence does not always reflect the size of the thumb bones.

When the long bones of the arm are affected, their relationships to one another may be disturbed. The radius and ulna may be partly or wholly fused, limiting rotation of the forearm. There may be humeroulnar fusion, preventing movement at the elbow, in which case the humerus and ulna are usually short.

**Thumbs and thenar muscles**

Careful examination and x rays of the thumbs are often extremely informative. The human embryo is thought to be sensitive to thalidomide from approximately 34 to 50 days after the start of the mother's last menstrual period, although individual structures may only be sensitive for part of that time. The thumbs appear to be the first part of the skeleton to be affected, and the last. Early involvement may be associated with a range of facial defects (see below) or more extensive involvement of the upper limbs: late involvement may be associated with anorectal stenosis.

Complete absence of the thumbs is far more common than thumb deformity. Next most common is hypoplasia of the thumb and thenar muscles: these small, thin thumbs are commonly fused in part to the adjacent index finger.

Thumbs affected by thalidomide quite often contain three phalanges (which may only be shown on x ray), and may resemble, in size and position, a fifth finger rather than a thumb, a problem which often necessitated an operation to create an opposable digit. If the thumb is affected early by a short exposure to thalidomide, the radius may escape intact. Equally, if the thumb is affected late, the radius may be unaffected. However, on the basis of cases with sound evidence of thalidomide exposure, it seems likely that the thumb is never completely normal if the radius is abnormal. If the radial defect is very slight, so may the thumb defect be, but the combination of a severely abnormal or absent radius with a normal thumb militates strongly against thalidomide as a cause.

**Radius**

Reduction deformities of the radius tend to start at the distal end and extend towards the elbow. In addition to being short, a thalidomide damaged radius tends to be bowed, and may be thicker than normal. It is occasionally fused to some degree with the ulna. If the radius is shorter than the ulna, which is common, the wrist and hand cannot be in normal alignment with the forearm but are rotated towards the radial side (radial club hand).
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Humerus
The humerus also tends to be affected from the distal to the proximal end. However, the shoulder joint is often weak and liable to recurrent dislocation, even with a normal length humerus, because of hypoplasia of the muscles surrounding the shoulder. A weak shoulder is therefore common even though the humeral head and glenoid cavity are both present. The lower end of the humerus is sometimes fused to the upper end of the ulna.

Ulna
The characteristic shape of the proximal end of the ulna is retained in less severe defects and makes the ulna identifiable. In extreme cases, it loses its shape, and the residual knob of bone which is often seen on x rays can only be assumed to be of ulnar origin because of the sequence of events already described.

Fingers
The thumb develops in association with the radius; the middle, ring, and little fingers with the ulna; and the index finger usually, but more variably, with the radius. Consequently, if the radius is affected, the thumb, and often the index finger, will be affected, but the other three fingers are usually present if there is any part of the ulna present. They may be thin, flexed, and weak. If the ulna is absent, there may be three (exceptionally four), two, one, or no fingers at the shoulder.

Scapula and clavicle
The scapula and clavicle are not subject to deformity as the arm bones are, but where the arm is small or absent and the muscles correspondingly defective, the scapula and clavicle are of little or no use and may therefore be smaller than normal. The scapula in particular may be grossly underdeveloped, and when the humerus is severely deficient, the glenoid cavity is underdeveloped or absent.

Not infrequently x rays show bones of curious shapes which do not closely resemble any of the three long bones of the arm. These may represent aggregates derived from more than one primitive bone (radius + ulna, humerus + ulna).

Symmetry of upper limb defects
Bilateral symmetry is more marked with defects of the upper limbs than it is with lower limb or non-limb defects. Nevertheless, there is almost invariably a small difference between the two sides, often confined to the digits. Commonly, for example, there are three digits on one side and four on the other, or there may be the same number on both sides, but the size of one, or the degree of fusion between adjacent digits, differs. There may be complete amelia on one side and a single digit on the other. It is unusual to find the number of digits on the two sides differing by more than one (bearing in mind that some very rudimentary thumbs either necrosed and dropped off spontaneously or were surgically removed soon after birth).

When the long bones of the arms are involved, there is usually a small difference in the extent of the reduction deformity. The greater the difference between the two sides, the less likely are the defects to be of drug or genetic origin, but it is not possible to draw rigid lines. Complete amelia on one side with a normal upper limb on the other is, at the least, highly unlikely to be attributable to any drug.

LOWER LIMBS
The majority of people with thalidomide defects of the upper limbs have normal lower limbs. A minority have defects of all limbs. Defects of the lower limbs with normal upper limbs are uncommon.

Symmetry of lower limb defects
The pattern of lower limb defects is more variable than in the upper limbs, and the degree of bilateral symmetry is less marked; symmetry is most frequently seen with the most severe defects. The long bones are the first to be affected, although talipes (club foot) and congenital dislocation of the hip may both occur without reduction deformities. Complete lower limb amelia is rare, especially in survivors. In the most severe cases commonly seen, the feet (usually abnormal) arise from the hip areas, often with one or more unidentifiable small bony lumps shown on x rays.
between the pelvis and the feet. Lesser degrees of reduction deformity show much more variable patterns, as described below.

**Femur**

The femur is quite often the only long bone to be affected, although the tibia or tibia + fibula may be affected as well, or with a normal femur. The upper end is the first to go, which inevitably prevents the formation of a normal hip joint. The lower end is usually the last part to be preserved. In addition to shortening, the femur may be bowed or angulated. Early fracture of its upper end, which may not ossify for some years after birth, may result in separated or angulated portions appearing on x ray after mid-childhood.

**Tibia**

The tibia may be the only long bone to be affected, but the femur is often affected as well, and if the tibia is significantly shorter than normal, the fibula has no option but to be short or bent. In contrast to the femur, the tibia tends to be affected first at its lower end, compromising the integrity of the ankle joint. Like the femur, it may be bowed as well as short, in which case the fibula is almost bound to be bowed as well.

**Fibula**

When a single long bone remains visible on x ray (with or without additional bony lumps) it tends to be slender and straight, with ends little thicker than the shaft, that is, it resembles a fibula much more closely than it does a femur or tibia. It therefore appears to be analogous to the ulna in the upper limb in being the last long bone to disappear.

**Feet and toes**

Talipes (club foot) can occur without any limb reduction deformity. It is, of course, a very common birth defect, but it occurs more commonly in people exposed to thalidomide in utero than would be expected by chance. Talipes is virtually constant if the tibia or fibula or both are affected, or if all three long bones are affected. It may also be seen when the femur is affected but the tibia and fibula are normal. When there is virtually no structure between the feet and the hips, the feet are inevitably in an abnormal posture.

In contrast to fingers, where the general rule is 'five or fewer', the rule for toes is 'five or more'. Supernumerary and bifid toes are usually on the side of the big toes. There may be as many as eight (possibly more) toes on each foot, and the number on the two feet rarely differs by more than one. Supernumerary toes were often removed surgically soon after birth.

**Hips, knees, and ankles**

Hips may be dislocated or unstable at birth, and may develop Perthes' disease later. Knees may be unstable at birth or develop arthritis later or both. There may be recurrent dislocation of the patellae. Ankles may be deformed or unstable.

**SPINE**

Congenital absence of part of the sacrum is thought rarely to be a manifestation of thalidomide damage. Later changes in the spine (loss of joint space, anterior fusion of vertebral bodies) affect principally the low thoracic and lumbar spine.

**EARS, EYES, AND ASSOCIATED DEFECTS**

The second most common group of defects, grouped because of their tendency to occur in a variety of combinations and permutations, involves developmental abnormalities of the ear and eye, and abnormalities of innervation of the external ocular muscles, the facial muscles, and the tear glands. Other thalidomide defects in this anatomical region include cleft palate, bifid uvula (which may be thought of as a minimal degree of cleft palate), and choanal atresia. The overall facial features which characterise a number of affected subjects are better illustrated than described.

**Ears**

Ear defects tend to be bilateral and fairly symmetrical. In the most extreme cases, the pinna is completely absent (anotia) and the external auditory meatus is a blind pit. Such an ear is inevitably profoundly deaf. There may be fleshy skin tags (accessory auricles) where the ear should be. Less severe is microtia, in which there is an attempt to form an ear: here again there may be accessory auricles. It is often easy to decide that one pinna is smaller than the other, but less easy to decide whether the difference is any greater than the normal asymmetry of ears, and whether a pair of pinnae of the same size are smaller than they should be. If the pinnae are normal, the external auditory meati (usually both) may be narrow or tortuous or both. These narrow meati readily become obstructed by wax or, less commonly, cholesteatomata, leading to recurrent deafness.

**Facial palsy**

Weakness of the facial muscles (usually affecting the whole face, but occasionally only part) is much more often unilateral than bilateral, and is almost invariably associated with anotia or microtia on the same side. It is also commonly associated with the other defects of innervation described below.

**Eyes**

The most common structural defects of the eyes are coloboma of the iris, with or without coloboma of the retina, and underdevelopment of the globe leading to anophthalmos or micro-
phalamos. Coloboma and microphthalmos are quite often associated. Both defects are predominantly bilateral.

Dermoid cysts on the surface of the eye are less common and tend to occur in association with anotia or microtia (which may lead to diagnostic difficulties: see Differential diagnosis below). Abnormal eyes are, for obvious reasons, associated with poor visual acuity, but vision may also be poor in structurally normal eyes.

Defects of eye movements are nearly always associated with ear defects, often with facial weakness, and tend to be bilateral. Most commonly, abduction of the eye is restricted or entirely absent, sometimes wrongly described as a VIth nerve palsy, the fault being in the brain stem connections, not in the lower motor neurone. Next most commonly, both abduction and adduction are affected. Rarely, eye movements may be even more restricted, or aberrant eye movements may occur (for example, when looking to the right, the left eye deviates upwards). Defects of eye movement may also present diagnostic difficulties (see Differential diagnosis below).

In the tear-saliva syndrome (crocodile tears), tears are secreted rather than saliva when food is eaten, and tears may not be secreted in association with crying. This results from wrong nerve connections, probably in the brain stem. It may be bilateral or unilateral. Affected subjects usually also have defects of eye movements and abnormalities of the ears. Crocodile tears are not unique to thalidomide.

Squint
Not surprisingly, squint is common in association with any of the eye abnormalities described above although not, as a rule, if there is only a defect of eye movements. It also appears to be more common in children affected by thalidomide than in the general population, although there is nothing specific about their squints.

Structural defects of the ears and eyes can scarcely be missed, and facial weakness is unlikely to be overlooked unless it is very slight. In contrast, defects of eye movements, even when quite extensive, can easily be missed if the range of movement is not fully tested. Similarly, crocodile tears cannot be observed and are only recognised by asking the right question.

Cleft lip and palate
These occur among persons affected by thalidomide more often than in the general population. The deformities appear not to differ from other facial clefts.

Summary of external defects associated with thalidomide (figs 1 to 4)

**Upper limbs**
Shoulder: hypoplasia of shoulder muscles, scapula, clavicle.

Arm: total absence, prominent acromioclavicular joint.
Upper arm: reduction deformity of humerus (upper end).
Elbow: humeroulnar, radioulnar fusion.
Forearm: reduction deformities of radius > ulna.
Hand: deformities usually related to those of forearm (preaxial emphasis, for example, radial club hand).
Fingers: absence, hypoplasia, fixed flexion, syndactyly (preaxial emphasis).
Thumb: absence, hypoplasia, triphalangy, non-opposable.

**Lower limbs**
Hip: congenital dislocation.
Thigh: reduction deformity of femur (upper end).
Knee: patellar dislocation.
Lower leg: reduction deformity of tibia > fibula.
Foot: deformities usually related to those of leg (for example, club foot).
Toes: polydactyly, bifid toes (preaxial emphasis).

Craniofacial
Characteristic facies in some cases.
Central facial naevus, fading over one to two years.
Eyes: anophthalmia, microphthalmia, coloboma of iris retina, conjunctival dermoid cyst.
Ears: anotia, microtia, accessory auricles; atresia, stenosis, tortuosity of external auditory meatus.
Neurology: facial palsy, restricted eye movements, tear-saliva syndrome.

Stature
Often short because of poor growth/osteochondritis of spine/progressive kyphosis.

External genitalia
Hypoplasia of scrotum/labia with severe lower limb deficiency.

**Functional problems**
A number of thalidomide damaged persons exhibit a variety of neurodevelopmental problems: mental handicap, dyslexia, autism, or epilepsy. These problems appear indistinguishable from the same conditions in people not affected by thalidomide, but they have occurred more often than would be expected by chance and have therefore generally been accepted as attributable to the drug when associated with more characteristic features.

Summary of internal defects associated with thalidomide
Heart: patent ductus arteriosus, VSD, ASD, and pulmonary stenosis in survivors. Complex, especially conotruncal, lesions were seen among early deaths.
Urinary tract: absent, horseshoe, ectopic, hypoplastic, rotated kidney; hydronephrosis, megaretter, ectopic ureter, vesicoureteric reflux, inert bladder.

Genital tract: undescended, small, or absent testis, hypospadias, cyst of hydatid of Morgagni; vaginal atresia, interruption of the Fallopian tube, bicornuate uterus.

Alimentary tract: duodenal atresia, pyloric stenosis, inguinal hernia, imperforate anus with fistula, anorectal stenosis, anteriorly displaced anus. (Congenital absence of appendix and gall bladder have been noted at necropsy.)

Orofacial: cleft palate, high arched palate, bifid uvula, palatal palsy, cleft lip, choanal atresia, small mandible, conjunctival dermoids; absent, overcrowded, or maloccluded teeth.

Skeletal: sacral agenesis, hemivertebrae, rib anomalies.

Neurodevelopmental problems: mental handicap, epilepsy, dyslexia, receptive dysphasia, behaviour disorder (including autistic and hyperkinetic), involuntary movements. Some of these defects have been recorded only once or twice, and the association with thalidomide may be coincidental, but most of the defects listed have been seen more frequently than would be expected by chance.

A number of acquired diseases (for example, coeliac disease, diabetes, multiple sclerosis) have been seen, but no more frequently than expected by chance. A causal relationship is unlikely.

Differential diagnosis

Limb defects

Some of the conditions which have caused problems in the past will not do so in the future because they are associated with perinatal or early childhood death. These include short limbed dwarfism, which should not present diagnostic difficulty (for example, achondrogenesis, thanatophoric dwarfism, severe osteogenesis imperfecta), and pseudohalidamide syndrome (Roberts syndrome, SC syndrome), an autosomal recessive disorder which includes limb reduction deformities.

Life expectancy is more variable in the TAR (thrombocytopenia-absent radius) syndrome, an autosomal recessive disorder in which thrombocytopenia tends to improve and may not be evident after the neonatal period, and in which absent radii are associated with normal thumbs, and in the Cornelia de Lange syndrome, in which the limb defects are bizarre and asymmetrical, and other features often suggest the diagnosis at birth.

Radial aplasia is a feature of Fanconi's pancytopenia, but the blood changes indicate the diagnosis. The family history may indicate autosomal dominant radial aplasia (though not, of course, new mutations). Radial and external ear defects may be associated with deafness, eye, cardiac, and dental defects in the lacrimo-auriculo-dento-digital (LADD) syndrome. The maternal history will help to identify diabetic embryopathy (which does not closely resemble thalidomide embryopathy).

Amniotic band lesions most often affect a single limb, are rarely symmetrical, and resemble 'congenital amputations'. Ring constrictions may be present on one or more limbs.

Poland anomaly is unilateral, the hand defect being associated with agenesis of part of the pectoralis major muscle. There may be homolateral deficiency of the breast, nipple, or ribs.

In the femur-fibula-ulna (FFU) syndrome, the named bones are principally affected, contrasting with thalidomide which affects the radius and humerus before the ulna, and the tibia before the fibula. The defects may be very asymmetrical.

The major difficulty is presented by the Holt-Oram syndrome, an autosomal dominant disorder usually affecting the hands and forearms symmetrically, and associated in almost all cases with congenital heart disease, principally atrial septal defect. The family history often helps, but new mutations occur.

Eyes, Ears, Etc

Five syndromes need to be considered here, one of which can cause considerable difficulty. Goldenhar syndrome (oculoauriculovertebral dysplasia), which merges with hemifacial microsomia, is characterised by microtia, accessory auricles, epibulbar dermoids, and abnormalities of the cervical spine.

Wildervank syndrome (seen predominantly in girls) is characterised by malformed ears, deafness, and defects of the cervical spine. Thalidomide rarely affects the cervical spine.

Möbius syndrome may manifest as facial/ocular palsy.

Duane syndrome is a disorder of ocular movements characterised by (1) decreased abduction, (2) decreased adduction, (3) retraction of the globe on adduction, (4) oblique rise or depression on adduction, (5) partial closure of the eyelids on adduction, (6) deficient convergence. It may be bilateral or unilateral. An association with other defects, especially of the hands and ears, was described as long ago as

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_Figure 5_ Postaxial reduction deformities of hand and foot (different people), not caused by thalidomide.
1918. Some or all of these features, together with the Marcus Gunn 'jaw winking' phenomenon, occasionally accompany thalidomide facial defects.

The LADD syndrome has been considered above.

To confuse the picture still further, medical publications contain examples of children who appear to show a mixture of features of more than one syndrome, for example Möbius syndrome and Poland anomaly. Whether these children are manifesting two separate syndromes, an entirely different syndrome, or some unusual 'intermediate' manifestation can only be a matter for speculation and further research.

Selected bibliography (in chronological order)