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A clinical review and introduction of the diagnostic algorithm for thalidomide embryopathy (DATE)

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Abstract

Thalidomide embryopathy results from the ingestion of thalidomide in the first trimester during pregnancy, causing multiple forms of congenital abnormalities of variable severity that involve all systems. The skeletal findings most frequently affect the limbs, particularly the upper limbs and hands. Increasingly, several genetic disorders with similar birth defects have been identified. New cases of malformations owing to possible exposure to thalidomide continue to present through both historical and current usage. However, inadequate proof of ingestion, marked phenotypic variation and the possibility of an alternative genetic condition, hinder the diagnosis of thalidomide embryopathy. We introduce a 'diagnostic algorithm for thalidomide embryopathy' (DATE) diagnostic software that can potentially provide a numerical score for the likelihood of birth defects in an individual as being caused by exposure to thalidomide and to provide a differential diagnosis based on the pattern of malformation.

Keywords

Thalidomide embryopathy, teratogen, limb defects, congenital, birth defects

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Background

The teratogenic effects of thalidomide (α-(N-phthalimido) glutarimide) were first recognized over 50 years ago. The scale and severity of the human birth defects caused by thalidomide in the late 1950s and early 1960s were, and remain, unprecedented. The lessons learned led to much stricter control of the release of new drugs and more stringent preclinical testing.

Thalidomide was developed by the pharmaceutical company Chemie Grunenthal in West Germany and first marketed in 1957. It was licensed as a sedative and hypnotic drug and quickly became widely prescribed. This popularity was partly because other sedatives of the time (especially barbiturates) were lethal on overdose. In contrast, 100 times the usual dose of thalidomide caused no more than a deep sleep without overt complications on recovery. These properties were thought to make it a suitable treatment for nausea and vomiting in pregnancy. When marketed, thalidomide had not been tested for prenatal toxicity, for which there was no regulatory requirement at that time, nor were there any established protocols for such testing. The extent to which the manufacturers were aware of other aspects of thalidomide toxicity at the time of marketing remains contentious. The drug was licensed in Australia, Canada, Japan, Brazil and several European countries. In West Germany, it could be bought over the counter as part of a cold remedy. In the United Kingdom (UK), it was accessible

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predominantly by prescription only, but was still widely available and a component of many drug preparations. The drug was not licensed in the United States of America (USA) because of concerns during the regulatory processes about the potential side effect of peripheral neuropathy.

Between 1958 and late 1961, a few obstetricians and paediatricians in different countries noted an increase in the prevalence of babies born with unusual congenital abnormalities, particularly affecting the limbs. Wiedemann (1961) first suggested that the cause was an exogenous factor, although he could not identify it. He noted that the phenomenon was confined by the West German border, did not affect East Germany, and that the increase started at the same time in many locations. Several other West German doctors also studied the epidemic, but Lenz (1961) conducted extensive investigations, including visiting and questioning affected families. His work finally identified the cause of these birth defects as being early exposure to thalidomide and in the very same month McBride (1961), an obstetrician in Australia, reached the same conclusion. In most countries, the drug was withdrawn in late 1961, but in some, not until mid-1962 or later. Following withdrawal, there was a subsequent dramatic decrease in the incidence of these congenital defects, returning to the background rate (Smithells, 1963).

Thalidomide was marketed in the UK between April 1958 and November 1961 and most affected children were born between January 1959 and August 1962. However, some tablets remained in circulation and subsequent cases were reported as late as May 1963. Thalidomide was available during slightly different time periods in different countries. For example, it was not withdrawn from use in Spain until 1969. Teratogenic effects have been reported to occur after a single dose of 100 mg (UK Teratology Information Service, 2015). Over 2000 infants were born in the UK with related defects, half of whom died in the first few months. At the time of writing, 468 identified affected individuals are still alive. There was almost complete certainty of the causative teratogenic effect of the drug in those infants of mothers with a positive history of thalidomide intake during the sensitive period. However, for up to 50% of the UK Thalidomide Trust beneficiaries, the mothers have denied knowledge of thalidomide intake (Smithells and Newman, 1992). Retrospective analysis in Germany conducted soon after the event found either positive or negative recollections to be often unreliable (Lenz and Knapp, 1962).

Despite concerns over thalidomide embryopathy (TE), the drug was reintroduced onto the market in 1965 in several countries for the treatment of erythema nodosum leprosum because of its significant immuno-modulatory properties. Thalidomide is currently being used in the treatment of oncological, dermatological, gastrointestinal and infectious conditions in many countries worldwide. In the UK, it is currently licensed for the treatment of multiple myeloma in patients >65 years old who are unsuitable for chemotherapy, and for the treatment of the cutaneous lesions of erythema nodosum leprosum. All UK patients, prescribers and pharmacies must be registered before prescription of the drug and patients of either gender must comply with the drug companies' pregnancy prevention programmes (UK Teratology Information Service, 2015). This resurgence of thalidomide use in medical practice has led to new reports of TE, particularly from Brazil, despite the distribution of the drug being tightly regulated. As before, there is often a lack of evidence of intake of the drug during early pregnancy to convincingly attribute birth defects to TE (Castilla et al., 1996; Schuler-Faccini et al., 2007; Vianna et al., 2011).

In the minority, with a proven maternal history of thalidomide intake during the critical period of embryonic development, a pattern of birth malformations typical for that exposure time and no associated family history of similar malformations, there can be little doubt about the diagnosis of TE. It is in those cases that do not meet these criteria where potential diagnostic difficulties arise. Defining the effects of thalidomide has been difficult because many of the structural abnormalities have similar presentations to other genetic or teratogenic disorders. Even for definite cases of TE, the manifestations of exposure remain varied, partly depending upon the time of exposure (Figure 1), and also because there are likely to be stochastic effects from other genetic and environmental influences.

Adding to the confusion, it has been reported that some individuals that were diagnosed with TE have gone on to have children with similar congenital defects and this led to speculation that thalidomide may be mutagenic (McBride, 1994). However, experimental evidence has shown convincingly that thalidomide does not have mutagenic action (Ashby et al., 1997) and more recent human genetic data endorse the conclusion that there is no evidence of a transgenerational effect. Cases of suspected 'familial thalidomide syndrome' have been found to be phenocopies (a similar pattern of malformations) due to other genetic conditions, such as Holt-Oram syndrome or Okihiro syndrome (Kohlhase et al., 2003; Van Regemorter et al., 1982).

This review describes the clinical and radiographic features of TE and the development of a diagnostic software based on its salient features, and also

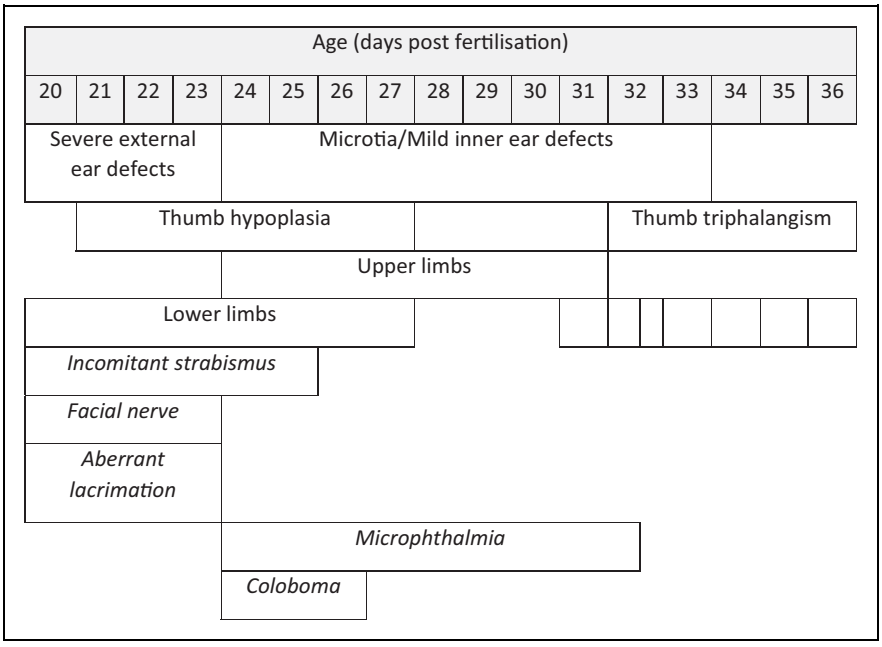

Figure 1. The gestational timing for thalidomide sensitivity for limb and craniofacial defects. The findings of numerous studies are summarized (modified from Lenz and Knapp, 1962). The critical time for the teratogenic effects of thalidomide is between days 34–50 after the first day of the last menstrual period (20–36 days post-fertilization). Defects affecting the eyes and facial nerve (shown in italics) relate to the findings of the Swedish Thalidomide Study (1987–1989) published in Miller and Stromland in Tetralogy 1999.

discusses genetic syndromes with similar malformations. It is hoped that this will help to refine the diagnostic criteria and remove some of the uncertainty surrounding diagnosis in some individuals and their families. This review does not attempt to address the potential mechanisms of thalidomide teratogenicity as these are discussed in another article (Vargesson et al. 2015, 2018).

Clinical and radiographic features of TE

The typical congenital malformations associated with prenatal exposure to thalidomide, are described here.

The upper limb and hand are most frequently affected (87% of which 94% are bilateral). The most severe malformations are amelia (total absence of the limb) or phocomelia (absence of intermediate parts of the limb, but with some digits present). Any remaining long bones may assume bizarre shapes, with hypoplasia or absence of the proximal humerus associated with corresponding hypoplastic changes in the glenoid fossa. Typically, the clavicle and acromion process appear long and give rise to the appearance of a 'pointed' shoulder. This is an important finding as it contrasts with other syndromes associated with congenital upper limb malformations, such as Holt-Oram syndrome, in which the shoulders are typically sloping. Occasionally, fusions may be present in the elbow joint, which are either longitudinal (humeroradial or humeroulnar) or transverse (radioulnar). In the forearm, there are predominately preaxial abnormalities with hypoplasia or absence of the radius giving rise to a radial longitudinal deficiency. The ulna may show some deformity secondary to the radial deficit, resulting in thickening and bowing. Primary postaxial defects are not typically a feature of TE (Figures 2 and 3).

At the wrist, the carpal bones may be absent on the radial side (trapezium and scaphoid) or there may be fusions either transversely across the proximal or distal rows, or longitudinally between the rows; this longitudinal fusion is rarely seen in other conditions. The hand may show preaxial deficiency with hypoplasia or absence of the thumb and thenar hypoplasia, or it may also be triphalangeal, but is rarely duplicated (Figures 2 and 4).

The findings in the lower limbs are analogous to those seen in the upper limbs, but changes are less common with about 40% of patients affected, of which 84% are bilateral. Lower limb involvement is usually associated with malformations of the upper limbs, and the presentations are usually lower limb amelia or phocomelia. Similar to the upper limb, proximal femoral hypoplasia is associated with hypoplasia of the acetabulum and rarely there are fusions

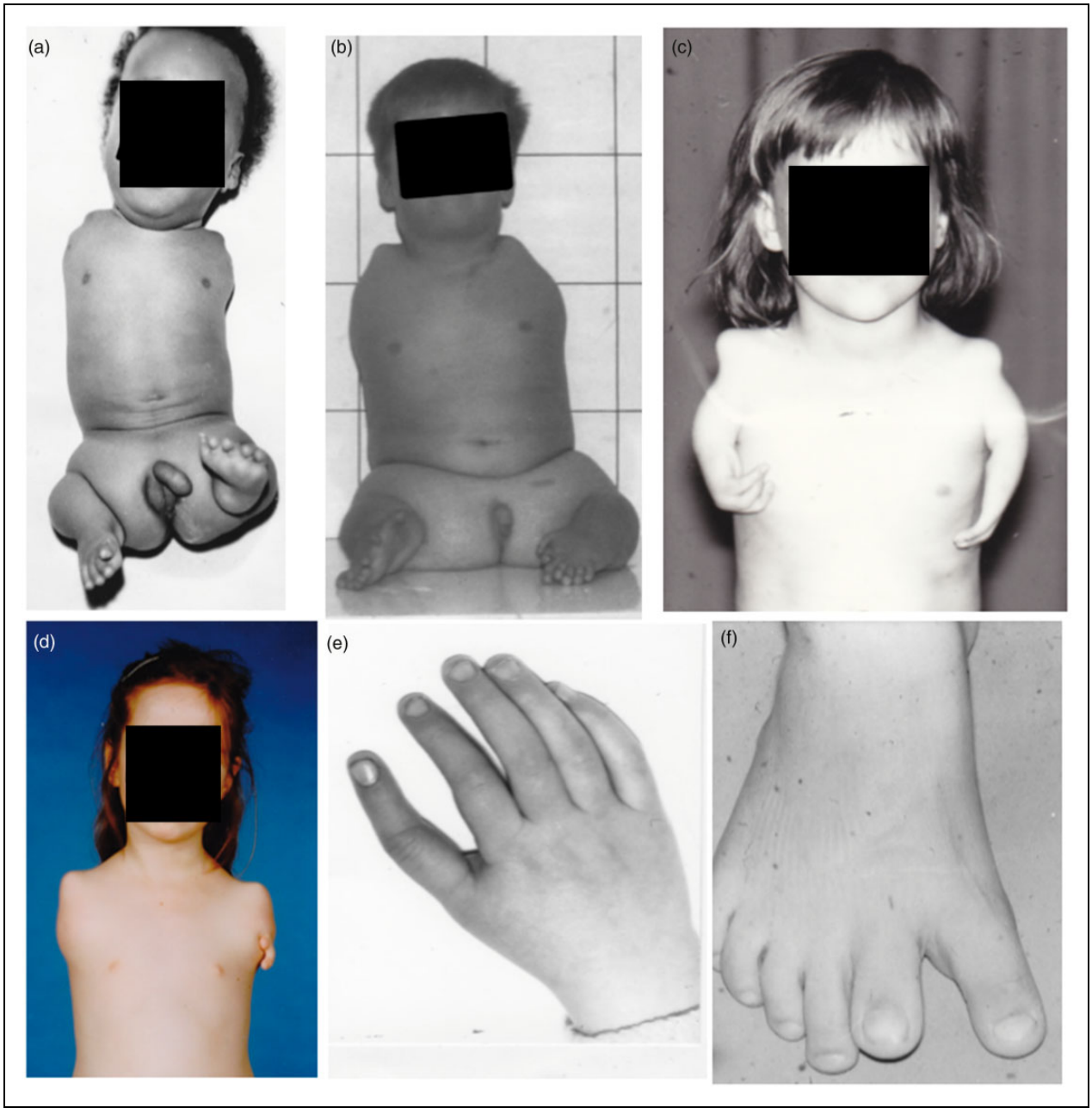

Figure 2. (a) Bilateral upper limb amelia and lower limb phocomelia. There is left microphthalmos. (b) Bilateral upper limb amelia and lower limb phocomelia with preaxial polydactyly. There is cryptorchidism. (c) Bilateral pointed shoulders and phocomelia with absent thumbs. There is left-sided microtia. (d) Right upper limb amelia and left phocomelia. (e) Triphalangeal thumb. (f) Preaxial polydactyly of a hypoplastic hallux.

at the knee joint. Preaxial hypoplasia or absence of the tibia occurs with relative sparing of the fibula, although this may be bowed and dislocated upwards. Tibial hypoplasia results in talipes equinovarus analogous to the radial longitudinal deficiency in the upper limbs. Tarsal fusions may be present, but unlike the hands, the feet show preaxial polydactyly rather than hypoplasia or absence of the hallux (Figures 2). The other associations of TE includes craniofacial, cardiac, gastrointestinal and renal malformations, as summarized in Tables 1 and 2.

Development of the diagnostic software

The presentation of TE is diverse. Earlier reports, although very extensive, are not comprehensive in the description of the clinical features or radiological findings in each individual case (Smithells and

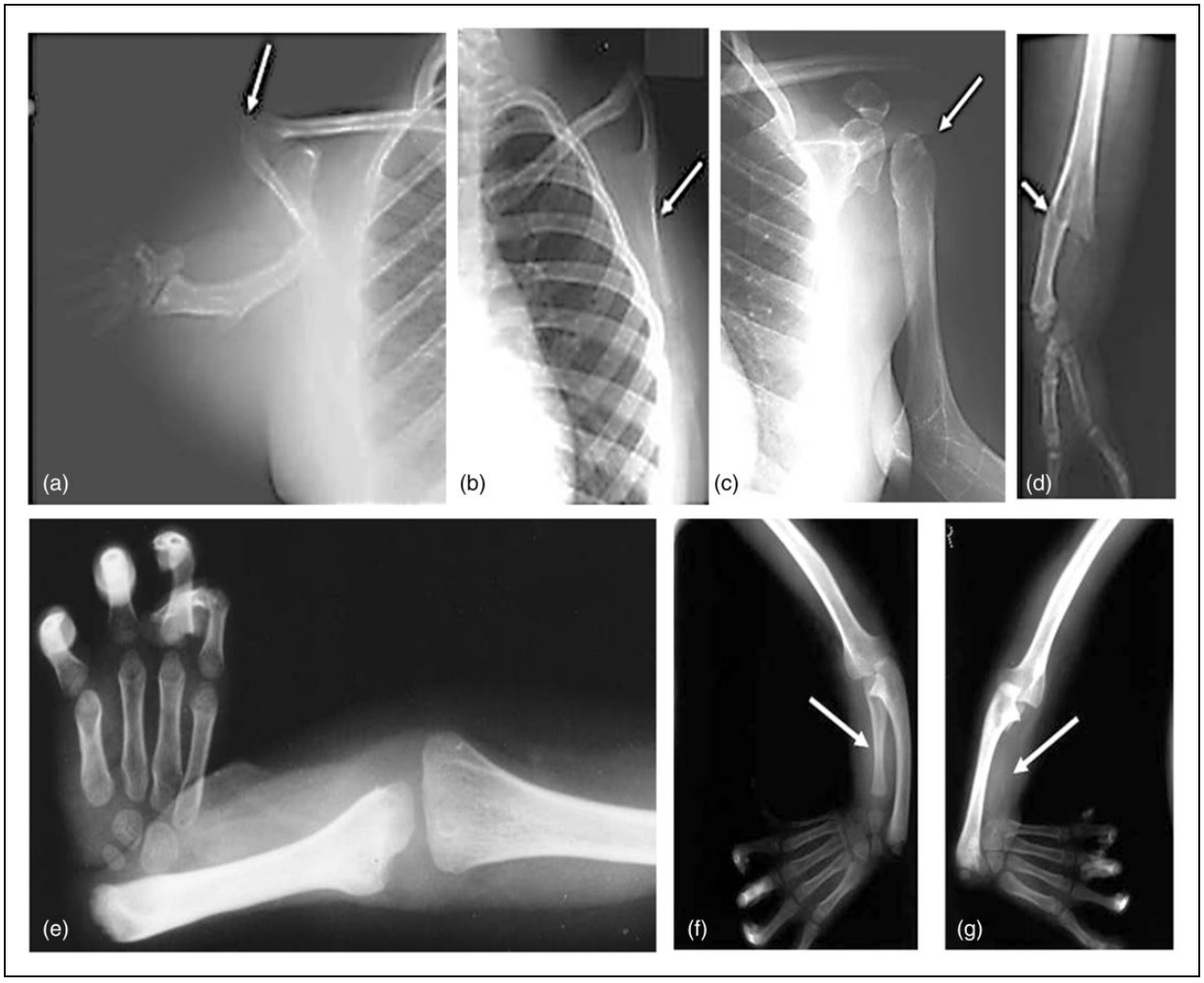

Figure 3. (a) The clavicle and relatively long acromion form the typical pointed shoulder. There is phocomelia with only one fused long bone (arrow). (b) There is amelia. The glenoid fossa of the scapula is absent/hypoplastic (arrow). (c) The proximal humerus is hypoplastic (arrow). The neck of the scapula is narrow and there is an abnormal, separate coracoid process. There is fusion at the elbow. (d) There is humeroulnar fusion with and absent radius and oligodactyly. (e) The radius is absent with a radial longitudinal deficiency. The thumb and several carpal bones are absent. (f) The radius is hypoplastic and the ulna curved (arrow). The thumb is absent. (g) The radius is absent and the thumb missing.

Newman, 1992). Inevitably, some of the cases described as TE probably have an alternative diagnosis. In the preparation of the diagnostic algorithm for thalidomide embryopathy (DATE), historical and current publications have been reviewed, as well as a number of radiographs from some of the UK cases of presumed TE. Three early German articles, in which there was documented ingestion of thalidomide in the first trimester resulting in affected infants, a total of 142 cases have been analysed (Kreipe, 1967; Lenz and Knapp, 1962; Nowack,1965). In these articles, the individual cases were described in some detail with close documentations of the clinical findings. Additional data from further studies have been used; notably the specialized eye and facial malformations identified by the Swedish studies (Miller and Stromland, 1999, 2011; Stromland and Miller, 1993) and ear abnormalities (Tanaka, 1987; Reports on Public Health and Medical Subjects, 1964). Integrating this information, a list of the clinical and radiological features associated with known TE was devised and assigned to four categories as follows (further explained in Table 1).

- Typical and highly suggestive of TE (i.e. the cardinal features). (These findings are rarely seen in either the background population or in genetic malformation syndromes.)

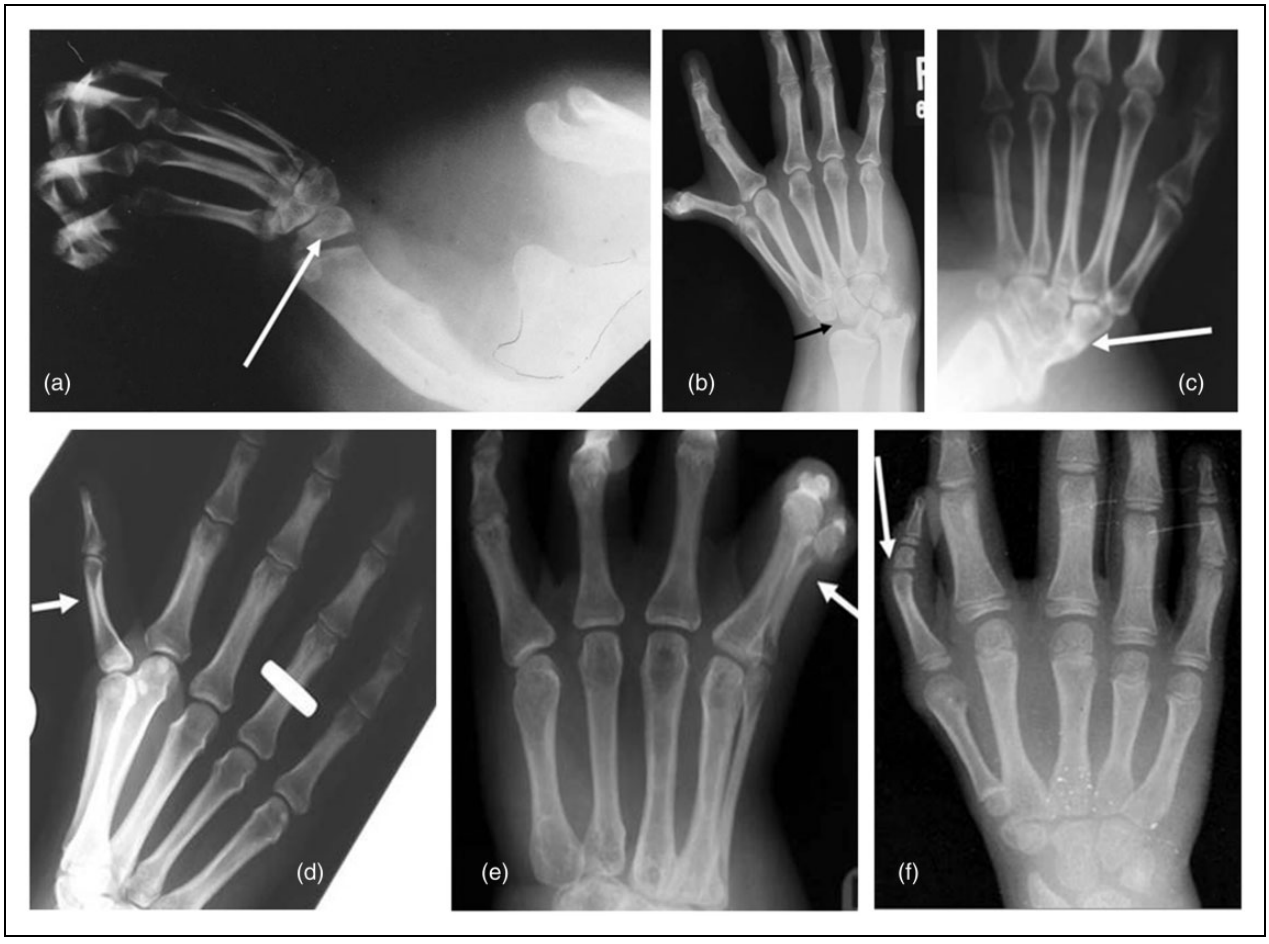

Figure 4. (a) Fusion of the proximal row of carpal bones (arrow). Pointed, prominent shoulder (acromion and clavicle) and abnormally shaped humerus. There is partial fusion of the radius and ulna. The thumb is absent. (b) Missing scaphoid bone (arrow). The distal end of the radius is short and the thumb hypoplastic. (c) Fusion of the proximal row of carpal bones and between the scaphoid, trapezium and trapezoid (arrow). (d) Hypoplastic thumb (arrow). (e) and (f) Hypoplastic triphalangeal thumbs (arrows).

- Typical but not specific for TE (i.e. seen frequently in patients with TE but also seen in other genetic malformation syndromes).
- Common malformation and occasionally associated with TE (i.e. malformations that are fairly frequent in the general population and other syndromes, but also seen in TE).
- Features not associated with TE.

The first criteria for inclusion into the analysis depend on country of residence during the pregnancy and appropriate year of birth (where thalidomide exposure was possible, for example, 1959 to 1962 in the UK) and a negative family history for similar problems. Based on the clinical and radiographic findings, a numerical weighted scoring system has been devised for each feature of TE based on the above categories and the score attributed to each patient. In addition, several features may be expected to occur together and when seen in this grouping would attract an enhanced score (for example, there was a strong association between facial palsy and Duane anomaly of the eyes). Any findings in the group 'Features not associated with TE', would indicate that a DATE consultation was inappropriate for this patient and TE was unlikely to be the diagnosis. Each patient achieves an individual score based on the combination of weighted scores of all the abnormal findings. This final score is indicative of the likelihood of a patient suffering from TE and these may be grouped into one of three categories:

- probable;
- possible; or
- unlikely.

Table 1. Features of TE.

Site/organ	Classical TE Typical and highly suggestive of TE (occurs rarely otherwise)	Nonspecific features of TE (Occurs both in TE and in other conditions)	Common malformation and occasionally associated with TE	Not associated with TE
Upper limb	Amelia Phocomelia Humerus proximal deficiency Humerus abnormal bone shape	Preaxial limb defects/radial ray defect Oligodactyly		Isolated post axial limb defects Isolated unilateral limb defects Terminal transverse limb defects Phocomelia with normal hand ectrodactyly
Thumbs		Absent, hypoplastic thumb/triphalangeal thumb Hypoplastic thenar eminence		
Shoulder girdle	Dislocatable shoulder Abnormal pectoral girdle Pointed shoulder – projecting acromioclavicular joint			
Radiological features	Fusion of long bones – longitudinal humeroradial; humeroulnar Radius: abnormal bone shape Carpal bones; fusion; abnormal shape; reduced number Long acromion process Glenoid deficiency	Fusion of long bones transversely Radio-ulnar synostosis		
Lower limb	Proximal focal femoral deficiency Lower limb amelia Phocomelia	Preaxial polydactyly Tibia short/absent/bowed Fibula dislocation at knee	Hip dislocation Dislocatable knees congenital deficiency of cruciate ligaments Unstable ankles Talipes	Isolated fibula abnormalities (short absent, bowed (post-axial defect))
Radiological features		Fusion of talus and calcaneum Abnormalities of big toe-absent/hypoplastic/short Triphalangic; duplication Facial haemangioma Facial palsy (unilateral > bilateral)		

(continued)

Table 1. Continued

Site/organ	Classical TE Typical and highly suggestive of TE (occurs rarely otherwise)	Nonspecific features of TE (Occurs both in TE and in other conditions)	Common malformation and occasionally associated with TE	Not associated with TE
Ears	Anotia Microtia	Deafness Semi-circular canal abnormality/ auditory canal atresia or narrow		
Eyes	Duane anomaly/	Coloboma Crocodile tears Anophthalmos/microphthalmos	Myopia; poor vision; ptosis; squint/amblyopia	
Oral region			Cleft lip and palate Bifid uvula Small mandible Paralysis of soft palate Absent teeth/overcrowded teeth	
Thorax		Bilobed right lung Oesophageal atresia	Rib abnormalities	
Spine			Spondylolysis/listhesis L5	Spina bifida Sacral agenesis
CNS			Speech delay Epilepsy	
Heart		Patent ductus arteriosus Ventricular septal defect Atrial septal defect Fallot tetralogy Situs inversus/conotruncal abnormalities		
Urinary tract		Renal malformation (any) Megaureter; VUR; inert bladder RV fistula, UV fistula		
Genitalia – internal		Gonadal absence Septate vagina/atresia	Interrupted vas deferens, fallopian tube Bicornate *uterus*	
Genitalia – external		Micropenis; hypospadias scrotal/ labial hypoplasia		
GI tract	Duodenal atresia/stenosis Absent gall bladder	Oesophageal atresia/TOF Anal atresia/stenosis	Pyloric stenosis Meckel's diverticulum Absent appendix Inguinal hernia	

TE: thalidomide embryopathy; VUR: vesicoureteric reflus; RV: rectovaginal; UV: urethrovaginal; TOF: tracheo-oesophageal fistula.

Table 2. Summary of differential diagnoses and recommended investigations.

Site/organ	Abnormality	Differential diagnosis	Additional features	Recommended investigations
Upper limb malformations				
Upper limb	Radial ray defect	Holt-Oram	Atrial septal defects/conduction defects	*TBX5*
		Townes-Brocks	Anal stenosis/atresia/deafness/renal	*SALL1/SALL4*
		Okihiro syndrome	Duane anomaly	*SALL1/SALL4*
		TAR syndrome	Thrombocytopenia/cow's milk intolerance	Array CGH (1q2 Deletion)
		VACTERL association	Congenital heart disease; vertebral segmentation defects; anal atresia; renal malformations	No specific tests available
		Triphalangeal thumb		ZRS mutations
	Amelia/phocomelia	Roberts syndrome		Premature centromere separation/*ESCO2*
		TAR syndrome		Array CGH (1q2 Deletion)
		Femur-fibula-ulna		None
		Holt-Oram		*TBX5*
		Limb pelvis hypoplasia/aplasia syndrome	Family history/consanguinity	*WNT7a*
	Fusion of long bones – longitudinal/Fusion of carpal bones	WL-symphalangism-brachydactyly		*NOGGIN* *GDF5*
Shoulders	Dislocatable shoulder/abnormal pectoral girdle/glenoid deficiency/pointed shoulder – projecting acromioclavicular joint/long acromion process	Specific to TE (Holt-Oram have narrow, sloping shoulders)		
Other		Poland anomaly	Hypoplastic pectoralis unilateral	none
Lower limb malformations				
Lower limb	Focal femoral deficiency	Femur-fibula-ulna	Difficult to differentiate, but usually very asymmetrical	None
		Proximal femoral focal deficiency		None

(continued)

Table 2. Continued

Site/organ	Abnormality	Differential diagnosis	Additional features	Recommended investigations
		Femoral hypoplasia, unusual facies		None
		Maternal diabetes	Maternal history	None
	Lower limb amelia	Roberts syndrome		Premature centromere separation/*ESCO2*
		Cornelia de-Lange	Hypertelorism/cleft lip and palate Typical facies, microcephaly severe growth retardation	*NIPBL/SMC1A/HDAC8*
	Fibula aplasia/hypoplasia	Okihiro syndrome	Duane anomaly	*SALL1/SALL4*
		Femur-fibula-ulna	Asymmetrical	None
		Fetal valproate	Maternal ingestion	
	Abnormalities of big toe-absent/hypoplastic, triphalangic, duplication/preaxial polydactyly	Greig syndrome	Macrocephaly	*GLI3*
		Tibial hemimelia-polydactyly-clubfoot	Predominantly lower limb	*PITX1*
		Werner syndrome		
	Fusion of talus and calcaneum	WL-Symphalangism-brachydactyly		*NOGGIN* *GDF5*
Facial features				
Face/head	Facial haemangioma	Many syndromes		
	Facial palsy (unilateral >bilateral)	OVAS/Goldenhar/hemifacial microsomia	Vertebral abnormalities Epibulbar dermoid Ear tags	Array CGH
		CHARGE syndrome	Choanal atresia; deafness Genital/renal abnormalities Intellectual disability	*CHD7*
		22q11 microdeletion	Cleft palate Congenital heart disease	FISH 22q11
	Anotia/microtia	OVAS/Goldenhar/hemifacial microsomia	As above	None
		Branchio-oto-renal syndrome	Branchial fistulae/cysts Renal abnormalities	*SIX1/EYA1/SIX5*
		Chromosomal abnormality		Array CGH
	Anophthalmos/ microphthalmos	Anopthalmia Microphthalmia	Often isolated, no limb abnormalities	*SOX2, OTX2, CHX10*
		OVAS/Goldenhar	As above	None
		Chromosomal abnormality		Array CGH

(continued)

Table 2. Continued

Site/organ	Abnormality	Differential diagnosis	Additional features	Recommended investigations
	Coloboma			
	Crocodile tears	Branchio-oto-renal syndrome	Renal abnormalities deafness	*EYA1/SIX1/SIX5*
	Duane anomaly	Okihiro syndrome		*SALL1/SALL4*
Internal malformations				
Thorax	Oesophageal atresia/trachea-oesophageal fistula	VACTERL association	Vertebral abnormalities Radial ray defects Anal atresia/stenosis	None
		CHARGE syndrome	Choanal atresia Deafness Genital abnormalities Renal abnormalities Intellectual disability	CHD7
		Fetal alcohol	Maternal ingestion	None
		Fetal carbimazole	Maternal ingestion	None
		TAR syndrome	Thrombocytopenia/cow's milk allergy	Array CGH (1q2 Deletion)
		Limb/pelvis-hypoplasia/aplasia syndrome	Difficult to differentiate	*WNT7a*
Spine	Sacral agenesis	Maternal diabetes	History of maternal diabetes	
Heart	Congenital heart disease	Multiple syndromes		
Urinary tract	Renal malformation (any)	Multiple syndromes		
GI tract	Duodenal atresia/stenosis anal atresia/stenosis	Maternal diabetes	History of maternal diabetes	
		VACTERL association	As before	No specific test
		CHARGE syndrome	As before	*CHD7*

TAR: thrombocytopenia absent radius syndrome; VACTERL: vertebral, anorectal atresia, cardiac, tracho-esophageal atresia, radial/renal, limb/lung defect; ZRS: sonic hedgehog regulatory sequence; TE: thalidomide embryopathy; OVAS: oculo-vertebro-auriculo syndrome; CGH: comparative genomic hybridisation; CHARGE: coloboma, heart defect, anal atresia, renal/retardation, genital and ear syndrome; FISH: fluorescent in situ hybridisation.
Reference to conditions: Genetics Home Reference, US National Library of Medicine (NLM) http://ghr.nlm.nih.gov/

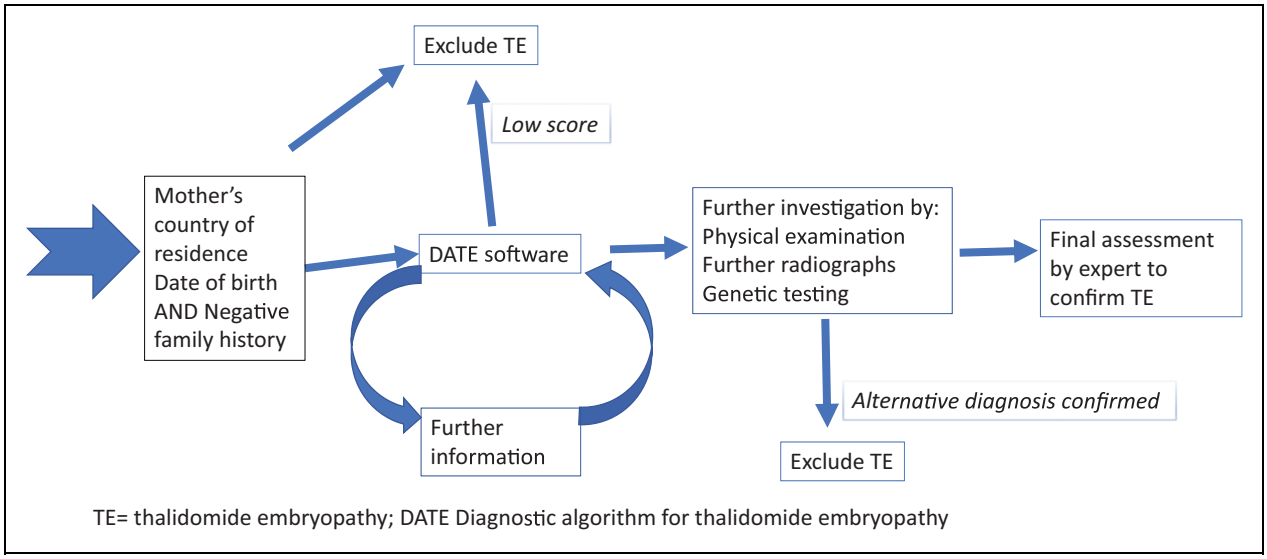

Figure 5. Pathway for the assessment of a patient with possible TE.

Based on these three categories, further investigation of the 'probable' or 'possible' in the form of genetic testing may be indicated before final diagnostic conclusions (Figure 5).

Differential diagnosis

Many syndromes have now been recognized as potential phenocopies (a similar pattern of malformations) of TE. Some of these malformation syndromes can now be accurately diagnosed by genetic testing. Table 2 summarizes the main clinical and radiological features of TE, the other conditions with the same birth defects and the diagnostic tests available for the specific condition.

In the DATE software, each feature of TE identifies the genetic and congenital conditions with the most phenotypic overlap and describes the features that help to differentiate them. The software and scoring thresholds for DATE are currently under development and will be made available for consultation on the web.

Discussion

Despite 50 years of research, the mechanism by which thalidomide disturbs human embryonic development remains largely speculative. Several possibilities have significant experimental evidence, but none are conclusive and overall, current mechanistic information is not informative nor helpful for the diagnosis of TE. The medical information on thalidomide is vast, but most reports on those congenitally affected have limited clinical and radiological details and sadly much of the radiological evidence is now no longer available. Even the large and comprehensive studies, for example from Japan (Kida, 1987) are of limited contemporary value. In many studies, ingestion of thalidomide is often presumed, whereas actual evidence of intake is rare. There is no doubt that genetic and environmentally induced malformations occurred at their usual rate during the 1956–1963 period and some of these will have been reported as TE, affecting the accuracy of previous reports. Some abnormalities present in TE are not rare in the background population. It is thus extremely difficult to determine causation when these defects occur in isolation.

Clear progress has been made in identifying the genes that, when mutated, give rise to syndromes displaying phenotypic overlap with TE (Table 2). These genetic mutations are likely to account for a significant proportion of cases historically misclassified as TE. Hypothetically, critical knowledge would be gained if all living, thalidomide-affected individuals were to undergo full clinical, radiological and genetic assessment, but this is obviously impractical and ethically debateable. In any event, radiological and other features will be obscured by surgery, ageing and wear and tear. However, for newly presenting cases, comprehensive investigations should be possible. As illustrated in this article, there is a pattern of malformation in TE that is characteristic. A few of the malformations, for example the 'pointed shoulder', are rarely seen in other disorders. Some features, for example isolated post-axial defects, are never seen in TE. Clear definitions of the phenotype will aid accurate diagnosis and may eventually lead to a better understanding of the underlying mechanism.

In practice, a clinician will be able to enter the clinical details of their patient and the DATE software will determine the probability of the patient's malformations as being caused by thalidomide. Clearly, the accuracy of this assessment will be dependent on the information provided by the clinician. The software therefore functions as an aid to diagnosis rather than a 'stand-alone' test (Figure 5).

The use of DATE, together with targeted genetic analysis, will result in more confidence in the accurate diagnosis of TE and the exclusion of other phenotypically similar conditions. This will be helpful in terms of determining financial compensation for these individuals, supplying accurate information about the recurrence risk for offspring and understanding the natural history of this disorder.

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