Recognition of the phenotype of thalidomide embryopathy in countries endemic for leprosy: new cases and review of the main dysmorphological findings

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Thalidomide is the best-known teratogen worldwide. It was first marketed as a sedative in the late 1950s, but the birth of ~10 000 children with birth defects resulted in the withdrawal of thalidomide from the market in 1962. Thalidomide embryopathy affects almost all organs but the main defects are concentrated in the limbs, eyes, ears, and heart. Shortly after the withdrawal of thalidomide from the market, its effectiveness in the treatment of erythema nodosum leprosum, an inflammatory condition resulting from leprosy, was reported and since the mid-1990s, the drug has been used widely in the treatment of cancers and autoimmune diseases, among other conditions. 40 000 new cases of leprosy are diagnosed every year in Brazil. Although there is a strict legislation for the prescription and use of thalidomide in Brazil, cases of thalidomide embryopathy have continued to be reported. Here, we present two new cases of thalidomide embryopathy identified in 2011 and review the major clinical findings in the literature that can aid the identification of the embryopathy. *Clin Dysmorphol*

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Introduction

Thalidomide is the best-known teratogen worldwide. It was first marketed as a sedative in the late 1950s almost worldwide, but the birth of ~10 000 children with birth defects resulted in the withdrawal of thalidomide from the market in 1962 (Lenz, 1988). Through evaluations carried out with a large number of patients, it was possible to describe thalidomide embryopathy. Almost all organs may be affected, but the main defects are concentrated in the limbs, eyes, ears, and heart (Lenz, 1988; Smithells and Newman, 1992).

Shortly after the withdrawal of thalidomide from the market, Sheskin (1965) reported its effectiveness in the treatment of erythema nodosum leprosum (ENL), an inflammatory condition resulting from leprosy. He prescribed this drug to a leprosy patient as a sedative, and observed a complete improvement in symptoms and skin lesions within 3 days. Subsequently, clinical trials supported the efficacy of thalidomide in the treatment of ENL and it is currently one of the most effective treatments (Sheskin and Convit, 1969; Penna *et al.*, 2005; Kaur *et al.*, 2009). Also as a consequence of the efficacy in ENL, thalidomide's anti-inflammatory (Sampaio *et al.*, 1991) and antiangiogenic properties (D'Amato *et al.*, 1994) were discovered, and since the mid-1990s, the drug has been used widely in the treatment of cancers and autoimmune diseases, among other conditions (Matthews and McCoy, 2003), and its use has expanded.

Leprosy is a neglected disease in some countries, especially in Brazil, where 40 000 new cases are diagnosed every year (Duppre *et al.*, 2012). Since 1965, thalidomide has been used for the treatment of ENL (Oliveira *et al.*, 1999). Although there is a strict legislation for the prescription and use of thalidomide in Brazil (Resolution RDC N1-11 March 22, 2011. National Health Surveillance Agency of Brazil (ANVISA), cases of thalidomide embryopathy have continued to be reported over the decades (Castilla *et al.*, 1996; Schuler-Faccini *et al.*, 2007).

Here, we present two new cases of thalidomide embryopathy identified in 2011 and review the major clinical findings that can aid the identification of the embryo-

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pathy. This study has been carried out with informed consent of the patients.

Cases reports

Case 1

Patient 1 was referred for evaluation because of congenital malformations. As she was born in a leprosy-endemic area and the mother had a past history of the illness and was currently under treatment for ENL, she was asked directly about the use of thalidomide.

The female baby was the fifth child of a nonconsanguineous young couple; she presented with reduction defects of the upper and lower limbs bilaterally; bilateral absence of the radius and ulna; a single bone appearing to be the humerus; she had no thumbs on either side and two digits on the right hand and three digits on the left hand; a hypoplastic scapular girdle; bilateral femoral hypoplasia and clubfeet; bilateral bifid hallux; a large umbilical hernia (Fig. 1a); right microphthalmia (Fig. 2a); and a nevus on her face that was especially apparent on her nose (Fig. 1). Echocardiography, abdominal and pelvic ultrasound, and hearing screening were normal. Eye examination was requested, but no information is available.

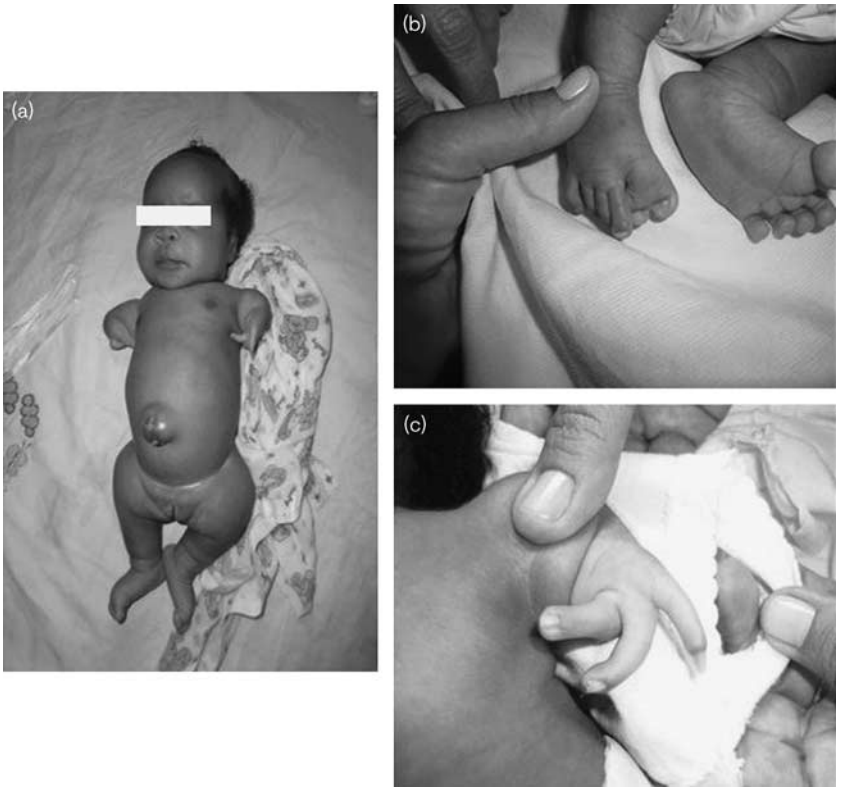
The patient's mother had leprosy in the past and was treated with antibiotic therapies (rifampicin, dapsone, and clofazimine) over a 1-year period. Eventually, she developed ENL, for which she received thalidomide 100 mg/day, and was advised to follow a contraception program because of the risk of teratogenesis. As she did not use contraceptives, further thalidomide treatment was denied. However, she took some leftover pills before realizing that she was pregnant. The exact dose and period of use of thalidomide during pregnancy was not recalled.

Case 2

The second case was ascertained during the interview of the mother of case 1. She reported another child with a similar phenotype in the same town.

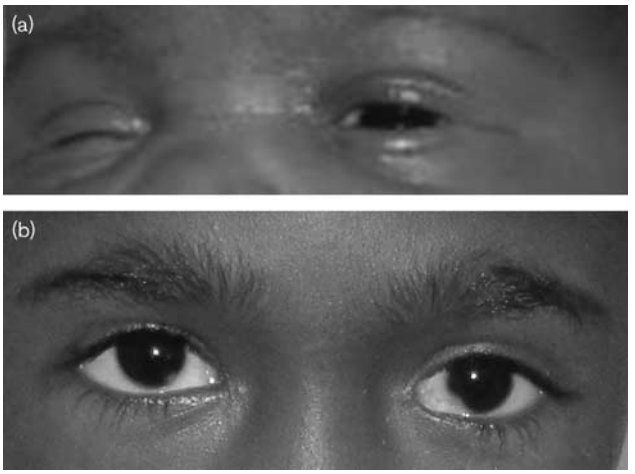
Patient 2 is a male who was born in 1998. He was the fifth of six children of a nonconsanguineous young couple. He presented with bilateral absence of the upper limbs and pedunculated structures bilaterally (probably corresponding to digits); the structure on the left was larger, but calcification was not seen on a radiograph. He also had a

Fig. 1



Case 1: (a) photograph of a patient showing intercalary limb reduction defects in the upper and lower limbs and microphthalmia of the right eye. (b) Right foot showing duplication of the hallux. (c) Right hand with three fingers.

Fig. 2

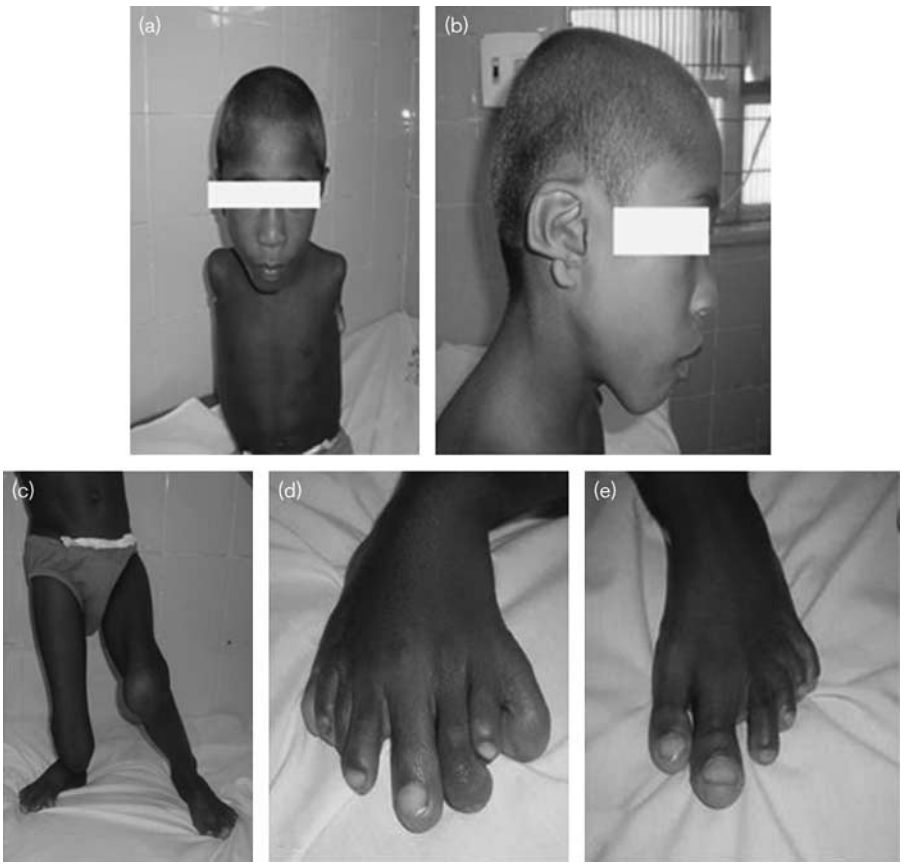


(a) Patient 1, right microphthalmia. (b) Patient 2, opacification in the left cornea.

hypoplastic scapular girdle; asymmetric lower limbs with apparent shortening of the legs, more pronounced on the right; clubfeet with bilateral but asymmetric preaxial polydactyly (six toes on the left foot and eight toes on the right foot); hip dislocation; advanced opacification in the left iris (Fig. 2b); impaired adduction and abduction in both eyes; dysplastic ears; ear canal stenosis; and ear lobes with a cleft and prominent helix bilaterally (Fig. 2). The abdominal ultrasound indicated unilateral renal agenesis. Echocardiographic examination showed an atrial septal defect. Neurodevelopment was normal.

During the interview, the patient's mother reported that she had had leprosy in 1995 and described the symptoms of ENL. She was treated for 5 years in different clinics until she became pregnant with Case 2. She could not recall the exact dose or period of use of thalidomide during pregnancy. Many members of her family were also affected by leprosy and reported having ENL. They live in an isolated area under very poor conditions (Fig. 3).

Fig. 3



Case 2: (a) upper body showing the absence of upper limbs, with only one digit on each side and scapular girdle hypoplasia. (b) Right ear tag. (c) Asymmetric lower limbs, with the right side more affected than the left. (d) Right foot with preaxial polydactyly. (e) Left foot with hallux duplication.

Table 1 Clinical features of thalidomide embryopathy observed in the 1960s and in recent cases identified in Brazil

Expected clinical features in thalidomide embryopathy[a]	Frequency in published thalidomide embryopathy cases	Case 1	Case 2
Upper limbs	+ + +		
Shoulder			
Hypoplasia of shoulder muscles, scapula, clavicle	+ + +	✓	✓
Arms			
Total absent	+ +		
Prominent acromioclavicular joint	+ + +	✓	✓
Upper arm			
Reduction deformity of humerus (upper end)	+ + +	✓	
Elbow			
Humeroulnar fusion	+ +		
Radioulnar fusion	+ +		
Forearm			
Reduction deformities of radius>ulna	+ +		
Hand			
Deformities usually related to those of the forearm (preaxial and intercalary)	+ +	✓	
Fingers			
Absence	+ + +	✓	✓
Hypoplasia	+ +		
Thumb			
Absence	+ + +	✓	✓
Hypoplasia	+ +		
Triphalangy	+ +		
Nonopposable	+		
Lower limbs	+ +		
Hip			
Congenital dislocation	+		✓
Thigh			
Reduction deformity of the femur (upper end)	+ +	✓	✓
Knee			
Patellar dislocation	+		
Lower leg			
Reduction deformity of tibia>fibula	+ +	✓	✓
Foot			
Deformities usually related to those of the leg (for example, club foot)	+ +		✓
Toes			
Polydactyly	+ + +		✓
Bifid toes (preaxial)	+ + +	✓	✓
Craniofacial			
Asymmetric face	+ + +	✓	✓
Central facial nevus, fading over 1–2 years	+ +	✓	NE
Cleft upper lip	+		
Cleft palate	+		
High arched palate	+		
Bifid uvula	+		
Palatal palsy	+		
Small mandible	+		
Eyes			
Overcrowded or malocclusion teeth	+		
Anophthalmia	+ + +		
Microphthalmia	+ + +	✓	
Coloboma of iris/retina	+ +		
Ears			
Conjunctival dermoid cyst	+ +		
Anotia	+ + +		
Microtia	+ + +		
Tag auricles	+ +		✓
Atresia	+		
Stenosis	+		
Neurology			
Tortuosity of external auditory meatus	+		
Facial palsy	+ +		✓
Restricted eye movements	+ +		✓
Aberrant tearing	+ +		✓
Deafness			
Internal defects	+ +		
Heart			
Patent ductus arteriosus	+ +		
Ventricular septal defect	+ +		✓
Atrial septal defect	+ +		
Pulmonary stenosis	+ +		
Conotruncal lesions were seen among early deaths	+ +		
Urinary tract			
Absent	+ +		✓
Horseshoe	+		
Ectopic	+		
Hypoplastic	+		
Rotated kidney	+		
Hydronephrosis	+		
Megaureter	+		
Ectopic ureter	+		
Vesicoureteric reflux	+		
Inert bladder	+		
Genital tract			
Absent testis	+		
Undescended testis	+		
Small 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	+		
Skeletal			
Sacral agenesis	+		
Hemivertebrae, rib anomalies	+		
Spina bifida	+ + +		

NE, not evaluated; + + +, very frequent; + +, frequent; +, infrequently.
[a]Cases reported in Schmidt and Salzano (1983), Lenz (1988), Smithells and Newman (1992), Shardein (1993).

Discussion

Thalidomide embryopathy is an ongoing public health problem in Brazil as the identification of cases with this syndrome was not restricted to the 1960s (Castilla *et al.*, 1996; Oliveira *et al.*, 1999; Schuler-Faccini *et al.*, 2007). Although the legislation has become more rigid in recent years (limiting access to thalidomide only at government facilities) and there is an established surveillance system for the identification of thalidomide embryopathy (Vianna *et al.*, 2011), we continue to identify new cases.

The phenotype of thalidomide embryopathy is well described in the literature (Schmidt and Salzano, 1983; Lenz, 1988; Smithells and Newman, 1992; Shardein, 1993), but there are still huge challenges in its diagnosis because of the

difficulty in confirming maternal medication intake and the diversity of the associated birth defects. On the basis of previous cases, we show that the presence of intercalary and preaxial limb reduction defects is a strong indicator of this syndrome (Table 1), as well as bilateral symmetry. The upper limbs are more frequently affected than the lower limbs. Our evaluation also corroborates the finding that microphthalmia, congenital heart disease, defects in the urinary tract, ear malformation, and duplication of the hallux are also common in thalidomide embryopathy (Schmidt and Salzano, 1983; Lenz, 1988; Smithells and Newman, 1992; Shardein, 1993; Miller and Stromland, 2011). Preaxial polydactyly of the toes is described and was present in both new cases. The upper limbs are mainly affected by loss of digits, whereas in the lower limbs, preaxial polydactyly is frequent (Smithells and Newman, 1992).

Many different causes of limb reduction defects have been identified (Gold *et al.*, 2011); thus, these should be ruled out before establishing the diagnosis of thalidomide embryopathy. The main differential diagnoses are genetic conditions that cause limb defects affecting mainly the radial axis, for example Fanconi pancytopenia and Holt–Oram syndromes. For other genetic syndromes associated with limb reduction defects such as Roberts SC syndrome, the family history and the other features suggest the diagnosis (Smithells and Newman, 1992).

Brazil has the second-highest prevalence of leprosy in the world and thalidomide is available for ENL treatment. The most common reason for exposure to thalidomide was treatment of ENL (Table 1), and sharing medication is a very common habit. However, this problem is not restricted to Brazil and remains a worldwide issue.

Our study draws attention to the possibility of thalidomide embryopathy in any country that uses thalidomide for clinical conditions, and shows the importance of detailed evaluation of the phenotype to establish a diagnosis of thalidomide embryopathy.

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Conflicts of interest

There are no conflicts of interest.

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