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Thalidomide, a Current Teratogen in South America

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ABSTRACT Thalidomide, mainly used for the treatment of leprosy, is a current teratogen in South America, and it is reasonable to assume that at present this situation is affecting many births in underdeveloped countries. Moreover, the potential re-marketing of thalidomide for the treatment of a large variety of diseases may extend the problem to the developed world. When the drug is available, the control of its intake during early pregnancy is very difficult since most pregnancies are unintended. The ongoing occurrence of thalidomide embryopathy cases went undetected by the ECLAMC, due to several factors: (1) low populational coverage through this monitoring system; (2) pre-existence of the teratogen with its effects present in both baseline (expected) and monitored (observed) materials; and (3) lack of a defined phenotype to be monitored. Thus, if thalidomide re-enters the market throughout the world, due to the wide range of new applications, occurrence of phocomelia alone might not be sufficient to detect its effects. By a case-reference approach, the ECLAMC registered 34 thalidomide embryopathy cases born in South America after 1965 whose birthplaces correspond to endemic areas for leprosy. Phocomelia was found in five of eleven fully described cases. Thus, phocomelia alone is neither specific nor sufficient to serve as a suitable phenotype to survey the teratogenic effects of thalidomide. Therefore, a thalidomide-like phenotype, defined as any bilateral upper and/or lower limb reduction defect of the preaxial and/or phocomelia types, should be included in the routine surveillance of birth defects in all programmes. *Teratology 54:273–277, 1996.* © 1997 Wiley-Liss, Inc.

The thalidomide tragedy occurred between 1959 and 1964, and in most countries the drug had been removed from the market by 1965. Nevertheless, thalidomide continued in use for the treatment of leprosy, and in recent years its indications were extended to a wide variety of medical conditions (D'Amato et al., '94). This situation prompted the *Teratology Society Newsletter* to publish a warning regarding the possibility that thalidomide would reappear on the market with an expected increase in the frequency of certain types of birth defects. The note calls for birth defects monitoring systems to anticipate increases in the frequency of phocomelia (Erickson, '95).

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TABLE 1. Availability of thalidomide by country[1]

Country	Leprosy	TE	Thalidomide available		Registered name/Laboratory/ Country of origin
			Comm	Offic	
Argentina	Yes	Yes	No	Yes	Talidomida/Cassara/Argentina Talidomide/Lazar/Argentina Tarisolin/Alet/Argentina
Brazil	Yes	Yes	Yes	Yes	Talidomida/Brasifa/Brazil Talidomida/FUNED/Brazil
Bolivia	Yes	No	No	Yes	Talidomida/FUNED/Brazil
Chile	No	No	No	No	
Colombia	Yes	No	No	Yes	Talidomida/Brasifa/Brazil
Ecuador	Yes	No	No	No	
Paraguay	Yes	No	No	Yes	Talidomide/Lazar/Argentina
Peru	Yes	No	No	Yes	Provided by PAHO
Uruguay	Yes	No	No	Yes	Talidomide/Lazar/Argentina
Venezuela	Yes	No	No	Yes	Talidomida/Brasifa/Brazil Talidomida/Pediat. Pharm./USA

[1]TE, thalidomide embryopathy cases reported after 1965. Comm, commercially; Offic, officially.

Even though the media (Gorman, '94) and a correspondent's note (Rocha, '94) have reported on the availability of thalidomide to women of reproductive age, as well as on the current occurrence of thalidomide embryopathy cases in South America, the only information on this subject to reach the scientific literature was a prenatal case report from Sao Paulo, Brazil (Gollop et al., '87). This paper adds to this literature by reporting on the ongoing occurrence of birth defects caused by thalidomide in South America.

MATERIALS AND METHODS

This study was based on information provided by the network of reporting maternity hospitals collaborating with the ECLAMC (Latin American Collaborative Study of Congenital Malformations). ECLAMC is a hospital-based birth defects surveillance system, extending over all ten South American countries (Castilla and Lopez-Camelo, '90). The availability of thalidomide in each country was investigated through local ECLAMC representatives. The requested information included: availability of thalidomide; names and addresses of manufacturer and distributor; means of obtaining the drug; brand name; pharmaceutical form and dose. This direct inquiry was considered to be more reliable than an official inquiry addressed to local health authorities.

Case reference call

A request for information on thalidomide embryopathy cases born after 1965 was sent to all medical geneticists and pediatricians in the ECLAMC network, as well as to the ABVT (Brazilian Association of Thalidomide Victims) (Schmidt and Salzano, '83).

RESULTS

Thalidomide was found to be available in eight of the ten South American countries, except Chile and Ecuador, through leprosy treatment centers depending on their ministries of health. In Brazil the drug may also be obtained commercially at some pharmacies. Thalidomide is manufactured in Argentina and in Brazil, and exported to other countries (Table 1).

Thirty-four cases of thalidomide embryopathy born after 1965 were ascertained by a case reference approach. These 34 cases were born between the years 1969 and 1995. One case was born in 1969, 7 cases in the 1970s, 20 in the 1980s, and 6 in the 1990s. One case was born in Argentina (city of Córdoba), and the remaining 33 cases in 21 cities of 9 different states in Brazil. Their birthplaces are here specified by city, state (standard two-letter abbreviation), and number of cases (in parentheses): Belém, PA (2); Manaus, AM (1); Paulista, PE (2); Salvador, BA (1); Belo Horizonte, MG (4); Itaúna, MG (1); Itaú de Minas, MG (1); Pompeu, MG (3); Ubá, MG (1); Nova Iguazú, RJ (1); Niteroi, RJ (1); Sao Paulo, SP (2); Tatuí, SP (1); Campinas, SP (3); Sao José dos Campos, SP (1); Sertaozinho, SP (1); Ribeirao Preto, SP (1); Piraguara, PR (1); Marandero, PR (1); Curitiba, PR (2); Bagé, RS (1). These birthplaces are plotted on a map of South America shaded according to their published prevalence rates for leprosy (OPS/OMS, '94) (Fig. 1).

Full descriptions are available only for the ten cases reported by ECLAMC centers, plus the one fetus published by Gollop et al. in 1987. Their summaries follow.

Case 1. Female, born 1971, in Sao José dos Campos, Brazil, from a lepromatous mother, medicated with thalidomide during pregnancy. Limbs: upper right: amelia with remnants of one digit; upper left: hypoplastic hand, with two three-phalangeal digits, articulated on shoulder. No other anomalies.

Case 2. Female, born 1978, in Córdoba, Argentina, from a 36-year-old mother lepromatous, medicated with thalidomide for 2 years, until the 8th month of pregnancy. Limbs: upper: symmetrical bilateral defect

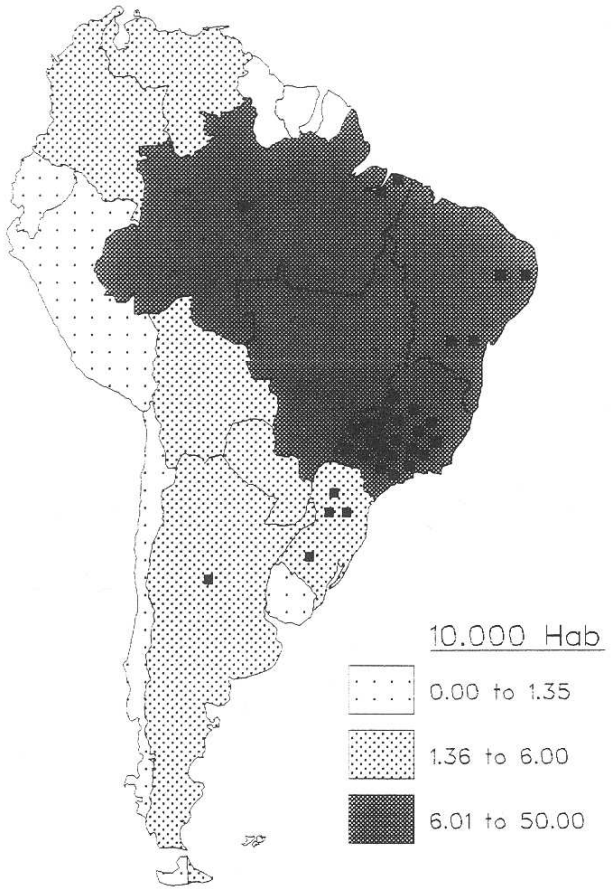

Fig. 1. Birthplaces for the 34 thalidomide embryopathy cases born after 1965 are plotted on a map where South America is subdivided by country, while Brazil is further partitioned into five regions. These 17 geographic areas are shaded according to their published prevalence rates for leprosy.

with hypoplastic humeri, absent radia and ulnae, hands with three three-phalangeal digits; lower left: hypoplastic femur and tibia. Other anomalies: frontal flat hemangioma, IVSD with pulmonic hypertension. Died at 7 months of age due to cardiac insufficiency.

Case 3. Male, born 1980, in Manaus, Brazil, from a lepromatous mother, medicated with thalidomide during pregnancy. Limbs: upper: bilateral hypoplastic shoulder girdle with hypoplastic glenoids, subluxated ulnas, agenesis of radius and thumbs, syndactyly of fingers 2 and 3, clinodactyly of 5th. No other anomalies.

Case 4. Male, born 1980, in Sertaozinho, Brazil, from a 32-year-old lepromatous mother, medicated with thalidomide for 8 years and throughout pregnancy. Limbs: upper: hypoplastic glenoids, stiff shoulders, bilateral absent radia, and thumbs. Other anomalies: flat hemangioma on glabela.

Case 5. Unknown sex, born 1986, in Sao Paulo, Brazil, from a 24-year-old lepromatous mother, medicated with thalidomide for 1 year preconception until the 35th day of pregnancy. After ultrasonographic diagnosis, pregnancy was interrupted at 17th weeks of gestation. Limbs: upper: bilateral phocomelia; lower: bilateral absent tibia and fibula. Other anomalies: bilateral anotia (Gollop et al., '87).

Case 6. Male, born 1988, in Sao Paulo, Brazil, from a lepromatous mother, medicated with thalidomide until the 2nd month of pregnancy, when she realized she was pregnant and stopped medication. Limbs: upper: symmetrical bilateral defect with absent radia, short ulnae; lower right: short femur, dislocated knee, absent tibia, duplicated hallux; lower left: absent femur, hypoplastic tibia. Other anomalies: Bulging philtrum; fused C1-C2 vertebrae.

Case 7. Female, born 1988, in Itaú de Minas, Brazil from a lepromatous mother, medicated with thalidomide for 2 years and throughout gestation. Limbs: upper: bilateral absent thumbs and small pedunculated tag on proximal phalanx of 2nd right finger. Other anomalies: bilateral microtia grade III, A-V canal, gastroesophageal reflux.

Case 8. Female, born 1991, in Campinas, Brazil, from a 32-year-old lepromatous mother, medicated during first trimester of pregnancy, presumably with thalidomide. Limbs: upper left: hypoplastic radius; bilateral triphalangeal thumbs. Other anomalies: flat hemangiomas on eyelids, face, and glabella; A-V canal; septated cysts in right lobe of liver, hamartoma of bile ducts.

Case 9. Male, born 1994, in Bagé, Brazil, from a 28-year-old lepromatous mother, medicated with thalidomide during 7 years, and in the first trimester of pregnancy. Limbs: bilateral tetra-phocomelia, oligodactyly of both hands, preaxial polydactyly (7 toes) of left foot; duplicated hallux of right foot. Other anomalies: bilateral undescended testes.

Case 10. Male, born 1994, in Campinas, Brazil, from a 22-year-old lepromatous mother, medicated with thalidomide preconceptionally and during the first 16 weeks of pregnancy: 300 mg, 3 times a week. Limbs: tetramelic preaxial defect. Upper: radius absent at right and hypoplastic at left; both thumbs pedunculated with absent metacarpals; lower: bilateral absent tibiae. Other anomalies: bilateral transverse grooves on ear lobes; right hydrocele.

Case 11. Female, born 1995, in Campinas, Brazil from a 22-year-old lepromatous mother, medicated with thalidomide and dapsona on alternate days for 5 years, at the time of conception she was taking thalidomide "prn" for pain relief. Fetus with bilateral renal agenesis diagnosed by ultrasonography at 16 gestational weeks, interrupted at week 21. Autopsy revealed a 16–18-week female fetus with partial agenesis of left tibia, curved fibula, duplication of right thumb. Other anomalies: bilateral renal agenesis, bilateral talipes equinovarus.

Figure 1 displays the geographical distribution of the 34 reported cases by their birthplace. South America is subdivided by country, while Brazil, representing about

half of its territory and population, is further partitioned into five regions. These geographical areas are shaded according to their published prevalence rates for leprosy.

DISCUSSION

As is the case with many other birth defect monitoring systems and registries, ECLAMC (Castilla and Lopez-Camelo, '90) was founded as an aftermath to the thalidomide pandemic, starting data collection in 1967. Nevertheless, thalidomide itself was used more as a model than as an actual issue, since this teratogen had supposedly been removed from the market before the ECLAMC system started. In spite of this, thalidomide continued in use in South America, unnoticeably causing severely malformed babies.

Several factors may be invoked to explain the failure of the ECLAMC monitoring system to identify this teratogen in the population. One is that thalidomide was already present when the system started, so that its effects were included in the expected prevalence rates and thus went unnoticed. Another more important factor is that ECLAMC is a hospital-based and not a population-based system. Thus the system covers less than 1% of all births in South America by excluding rural areas, including those in which leprosy is endemic. A third factor contributing to this failure in monitoring, which is not limited to South America, is the lack of an appropriate type of birth defect to be monitored.

Phocomelia may be neither sensitive nor specific enough to identify the effect of thalidomide. Phocomelia is an ill-defined condition not to mention that some cases of thalidomide embryopathy did not present with phocomelia, but instead were characterized by preaxial limb defects or other anomalies (Smithells and Newman, '92). Phocomelia has not been precisely defined in most published epidemiological studies of limb reduction defects (Källén et al., '84; Froster-Iskenius and Baird, '89; Calzolari et al., '90; Lin et al., '93; Castilla et al., '95) and reported birth prevalence rates differ greatly, suggesting differences in case definition.

The clinical delineation of the thalidomide embryopathy syndrome seems to be so difficult that Smithells and Newman ('92) estimated that the number of experts on the subject totalled 3 in the U.K. Furthermore, now that the victims of the 1950s epidemic have entered the reproductive age, cases with similarly affected offspring are known, suggesting that some of the original cases had been misdiagnosed and actually represented autosomal dominant traits such as Holt-Oram syndrome (McBride, '94; Read, '94; Kida, '94).

The ongoing occurrence of thalidomide embryopathy cases is limited to the underdeveloped world, where leprosy is more common, and drug control measures are more relaxed. In South America, thalidomide accessibility is proportional to the frequency of leprosy, which has a maximum prevalence in Brazil (14 per 10,000 inhabitants), intermediate in Colombia, Venezuela, and Paraguay (3 to 5 per 10,000), minimal in Argentina, Bolivia, Ecuador, Peru, and Uruguay (around 1 per 10,000), and close to zero in Chile (OPS/OMS, '94). This South American situation could also be true for other underdeveloped areas where proper information is missing, if they are not covered by birth defect surveillance systems.

However, new applications for thalidomide are being tested in clinical trials, for a variety of diseases, from ocular complications of AIDS to common aphthae (D'Amato et al., '94), and it is reasonable to suspect that permission requests to commercialize thalidomide may be on their way in various developed countries. Thus, with the difficulties inherent in enforcing drug control regulations in many countries, as shown by the leprosy-thalidomide-malformation chain of events in South America, the high rate of unintended pregnancies in many countries, the low commercial cost of thalidomide, and the drug's potential for widespread use for other more common diseases, the stage may be set for a new catastrophe as great as that of the early sixties.

Therefore, if a new epidemic is anticipated, there is a need for birth defects monitoring systems to ascertain increases in the frequency of congenital anomalies attributable to thalidomide. However, we first need to define what to look for. Based on published data (Smithells and Newman, '92), and on the observation that only five of the eleven cases reported here presented phocomelia or some type of intercalary transverse limb reduction defect, the following definition is proposed for a thalidomide-like phenotype to be included in the routine surveillance of birth defects: any bilateral upper and/or lower limb reduction defect of the preaxial and/or phocomelia types.

In spite of all the progress made in birth defects surveillance during the past 30 years, in the case of thalidomide we are still in the same situation as we were in the early sixties. Thus, the clinical case-reference approach provides more information to the present report than the epidemiologic monitoring of a still undefined thalidomide-like phenotype.

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