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Offspring of Male and Female Parents With Thalidomide Embryopathy: Birth Defects and Functional Anomalies

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ABSTRACT

Background: The aim of the study was to evaluate congenital malformations and functional anomalies in the offspring of Swedish parents with thalidomide embryopathy (TE).

Methods: Sixty-four children (29 girls, 35 boys) with ages ranging from 0–18 years, born to 34 Swedish parents (14 women, 20 men) with TE, were studied. Data on malformations and dysfunction were collected from medical records at maternity and child healthcare units, delivery units, hospitals, outpatient clinics and schools.

Results: Five children had both a mother and father with TE, 23 had a mother suffering from TE, and in 36 children the father had TE. One girl had a major malformation consisting of pulmonary stenosis, and single cases of minor physical features and positional deformities were observed. One boy had autism. Four children were born preterm, all to a TE mother. One child died within 24 hr after birth. Seven spontaneous abortions were registered, five of them in TE mothers. The cesarian section rate was 39% among the TE mothers, compared to 14% among the non-TE mothers.

Conclusions: Malformations or functional anomalies similar to those typical for TE were not found in this group of children born to Swedish parents with TE. Cesarian sections were more frequently performed in TE mothers, partly because of pelvic and uterine malformations.

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INTRODUCTION

Thalidomide (alpha-phthalimido-glutarimide) was used worldwide at the end of the 1950s and beginning of the 1960s for the treatment of anxiety and insomnia. After the recognition of an increasing number of children born with hypoplastic malformations of the limbs in Germany, Lenz ('61) carried out a detailed analysis that confirmed a correlation between the intake of thalidomide during pregnancy and the observed birth defects. At the same time, similar observations were made in England (Smithells, '62) and Australia (McBride, '61). In addition to limb defects, thalidomide may give rise to a wide spectrum of malformations of various organ systems. Among the significant anomalies noted are heart defects, laryngeal and tracheal abnormalities, anotia, microtia and hearing impairment, choanal atresia, microphthalmia, coloboma, intestinal atresia, aplastic or hypoplastic gallbladder, renal anomalies, cryptorchism, vaginal and anal atresia, as well as dysfunction of cranial nerves, notably the sixth and seventh nerve (Lenz, '61; Zetterström, '66; Brent and Holmes, '88; Smithells and Neuman, '92).

The teratogenic period of thalidomide has been defined as 20–21 to 36–40 days post fertilization (Lenz and Knapp, '62; Nowack, '65). The mechanisms of the teratogenic action of thalidomide on the embryo remain unclear, despite many proposed hypotheses (Vaisman, '96; Stephens and Fillmore, '00; Stephens et al., '00). Today, there is a renewed interest in thalidomide, and the drug is prescribed for the treatment of various disorders, such as leprosy, human immunodeficiency virus infections, and some dermatological and autoimmune diseases (D'Arcy and Griffin, '94; Lary et al., '99; Miller and Strömland, '99; Stephens et al., '00). Thalidomide is an angiogenetic inhibitor and has been proposed as a potential therapy for some types of cancer and ocular conditions associated with abnormal angiogenesis, such as macular degeneration and diabetic retinopathy.

After the observation of parents with thalidomide embryopathy (TE) giving birth to children with congenital limb defects (McBride, '94; Tenconi et al., '94; Tenconi and Clementi, '96), the question has arisen of whether thalidomide is not only a teratogen, but may also be a mutagen (McBride, '94; Ashby and Tinwell, '95). This has been contested strongly by Smithells ('94), Read ('94), and Kida ('94). Studies of the possible mutagenicity of thalidomide were made by Jensen ('65) and Roux and Emerit ('71). These studies were contra-

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dicted by Ashby et al. ('97), who could not find any mutagenic activity across phyla and genetic endpoints.

In Sweden, patients with TE are registered in "The Swedish Association of Thalidomide Embryopathy Patients" and receive lifelong yearly monetary compensation. During 1987–1989 the patients participated in a study, mostly focusing on ocular findings (Miller and Strömland, '91; Strömland and Miller, '92) and autism (Strömland et al., '94). The present study was set up to register any birth defects or functional anomalies in vision, hearing and mental ability, and behavior in the offspring of Swedish parents with TE.

SUBJECTS AND METHODS

According to "The Swedish Association of Thalidomide Embryopathy Patients," 88 Swedes (43 women and 45 men) with TE, born between 1959 and 1963, were living in Sweden at the time of the investigation, and 46 individuals (23 women, 23 men) were the biological parents of 86 children. An invitation to participate in the investigation was sent out through the association and 38 parents (82.6%) answered the invitation. Thirty-four parents (74%) agreed to participate and four parents with a total of five children declined. The eight parents who did not answer the invitation had a total of 17 children. Sixty-four children (74%) finally participated in the study. Records from maternity and child healthcare units, delivery units, hospitals, outpatient clinics, and schools were studied. The following data were collected: pregnancy history and prenatal data, including the number of live births, stillbirths and spontaneous abortions; prenatal exposure to alcohol, tobacco and medications, as well as complications in pregnancy; the method of delivery; gestational age, birth weight and length, head circumference and congenital abnormalities of the children. The structural anomalies were recorded according to the inclusion and exclusion criteria described by Holmes ('99). Infancy and childhood data regarding psychophysical development, vision, and hearing were collected from child healthcare units and schools and, when appropriate, from hospitals and outpatient clinics. Additional information on the parents was obtained from the raw data of the study on Swedish thalidomide embryopathy patients (Miller and Strömland, '91; Strömland and Miller, '92, '93). A clinical examination of the children was not performed. The study was approved by the ethical committee at the University of Göteborg.

RESULTS

Sixty-four children (74%), 29 girls and 35 boys, with ages ranging from newborns to 18 years, among them two pair of twins, participated in the study. They were born to 34 parents (14 women, 20 men) with TE. The number and gender of the children born to TE mothers or TE fathers is shown in Figure 1. Both parents of three families had TE, and they had a total of five children. Fourteen mothers had TE and gave birth to 28 children, whereas the 17 non-TE mothers had 36 children. The number of children in each family varied from one to five (mean 2.1).

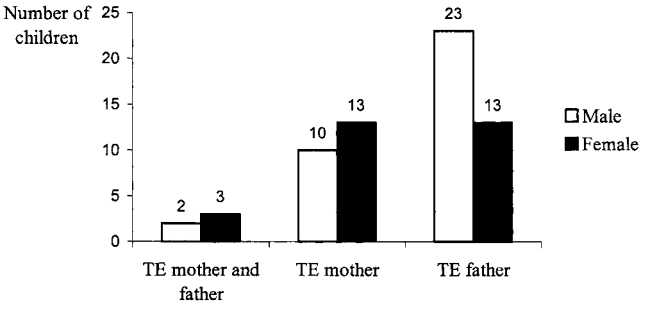

Fig. 1. Sixty-four children born to 34 parents with thalidomide embryopathy specified to mother- or fatherhood.

Children

Complete medical records for all but two of the 64 children were obtained. One child, born in Canada, had no prenatal and delivery records available but, according to the parents, the pregnancy and delivery were normal. The file from the child healthcare unit of another case could not be traced. The mean and range of gestational age, birth weight, length, and head circumference of the 64 children are shown in Table 1.

Fourteen children had one or more abnormal findings, mostly of minor severity, were born preterm or small for gestational age (SGA). Four children (Cases 3, 9, 10, and 14), of which two were twins from different families, were born preterm. Three of them had a subnormal birth weight and associated severe complications, and one girl with fetal asphyxia and infantile respiratory distress syndrome (IRDS) died soon after birth. Another child (Case 9) had fetal asphyxia and IRDS and one girl (Case 3) had IRDS. The major and minor malformations, normal variants, positional defects, functional anomalies, ophthalmological findings, gestational age, birth weight, and length as well as perinatal data of these children are summarized in Table 2. Table 3 shows the gender and malformations of the corresponding TE parents as well as pregnancy history and mode of delivery. Twenty-one of all 64 studied children had experienced one or more episodes of otitis media.

Mothers

Pregnancy. The age of the TE mothers in their 28 pregnancies ranged from 17–38 years (median 27 years) and that of the 36 pregnancies of non-TE mothers from 19–39 years (median 27 years). One non-TE mother had epilepsy and another non-TE mother had insulin-dependent diabetes. Urogenital defects were observed in four TE mothers, of which two had renal defects and two a uterus septum defect. Four TE mothers, including the mother of Case 8, had, altogether, a history of five spontaneous abortions. One of them, the mother of Case 48, who had a uterus septum defect,

TABLE 1. Birth weight and length, head circumference and gestational age of children born to parents with thalidomide embryopathy

	Birth weight (g) $n = 64$	Birth length (cm) $n = 62$	Head circumference (cm) $n = 61$	Gestational age (weeks) $n = 63$
Mean (SD)	3450 (763.33)	50.5 (2.84)	34.2 (2.30)	39 (2.50)
Range	900–4820	39–55.5	31–37.5	28–42

had had two spontaneous abortions. Two non-TE mothers, including the mother of Case 7, had each had one spontaneous abortion.

Five mothers (4 TE, 1 non-TE) developed preeclampsia during pregnancy. Five (4 TE, 1 non-TE) mothers had hypertension and nine (2 TE, 7 non-TE) proteinuria. Single cases of high levels of hepatic enzymes (1 non-TE), prophylaxis of prematurity (1 TE), cervical insufficiency and anemia (1 TE) and urinary tract infection (1 TE) were recorded during pregnancy. Antiarrhythmic drugs, Class II, were taken during three pregnancies (3 TE mothers) due to tachycardia. In eight pregnancies, the mother (4 TE, 4 non-TE) was treated with antibiotics due to pneumonia, urinary tract infections, upper respiratory tract infection and, in one case, for unknown reasons. Smoking during pregnancy was reported in 19 (30%) cases (8 TE, 11 non-TE mothers), alcohol consumption of unknown amount in 18 (29%) (4 TE, 14 non-TE mothers), and in eight of these pregnancies the mother (2 TE, 6 non-TE) was using both alcohol and tobacco.

Delivery. The children were delivered by vaginal birth, vacuum extraction, or cesarian section. The numbers of the different modes of delivery are shown in Table 4. The cause and level of emergency of the cesarian section are listed in Table 5. Cesarian section was performed in seven of a total of 14 TE mothers (50%), compared to a total of 17 in non-TE mothers (18%). Fetal asphyxia occurred in six cases (3 TE, 3 non-TE mothers). No stillbirths were registered.

DISCUSSION

From time to time the public press has drawn attention to children born to parents with TE, who have similar malformations as their parents. Scientific reports, however, are scarce. In a study by Mauoris and Hirsch ('88), 35 mothers with TE answered a questionnaire regarding disabilities, pregnancies and deliveries, and no abnormalities were reported among their 64 children. The aims of our study were to investigate birth defects and functional anomalies of the children born to Swedish parents with TE, using information from their medical records. Sweden offers good opportunities for these types of retrospective studies, having a well-developed system for registering diseases, with most medical records available for investigation. A study of the members of "The Swedish Association of Thalidomide Embryopathy Patients" had earlier been carried out (Strömland and Miller, '93) and the association was favorably disposed to the present study. Sweden is a small country with approximately 8.5 million inhabitants and has a limited number of individuals with TE.

Therefore, even if 74% of both parents and children participated and all required data on them were received, this is a small number of children and it is not possible to draw any conclusions regarding the overall frequency or specificity of anomalies in children born to TE parents. Furthermore, it is impossible to study mutagenic effects of thalidomide on such a small population. This was thoroughly discussed by Neel ('99) in an article comparing the frequency of radiation-induced mutations in humans, mice and Drosophila. Ionizing radiation of high dosages is a known mutagen. The authors were, however, unable to demonstrate a mutagenic effect in the large number ($n = 31150$) of second generation children and their control groups of the atomic bombings in Hiroshima and Nagasaki that were studied. Also, Brent ('99) pointed out that there is a very small risk for potent mutagens in the second generation and that you need very large populations to demonstrate a mutagenic effect. Using small populations does not refute a mutagenic effect, it only tells that there is no support for such an effect in that specific population. Another type of second generation effects are those due to abnormalities in the parents that may change their reproductive performance that our finding of a higher frequency of caesareans in the TE mothers may illustrate. We considered it of interest to report our findings, as we were able to get information on a considerable number of the Swedish children and their parents suffering from TE, data that might be difficult to obtain in other countries.

Most of the children in the present study were healthy, and the observed anomalies were not "typical TE" birth defects, such as limb defects or palsy of the sixth and seventh cranial nerves. There was one malformation of significance, namely pulmonary stenosis. The mean birth weight, length, head circumference, and gestational age of the studied children are all within the normal range compared to the Swedish population (Niklasson, '93). One boy (Case 8) with autism represented a functional anomaly of considerable degree. In the Swedish study on adults with TE (Strömland et al., '94), some patients had autism. Their congenital anomalies consisted of malformed or absent external ears and hearing impairment. In addition they all had Duane syndrome, which is characterized by palsy of the sixth cranial nerve combined with other ocular motility disturbance, and seventh cranial nerve

TABLE 2. Major malformations, minor anomalies, and other data of children born to Swedish parents with thalidomide embryopathy*

Case/ Gender/ Age (yrs)	Major malformations	Minor anomalies	Normal variants	Positional defects	Abnormally small body size	Functional anomalies	Ophthalmology	Gestational age (weeks)	Birth weight (g)	Birth length (cm)	Perinatal data
1/M/16	Retentio testis						Astigmatism	40	3750	53	
2/M/4			Pes planus valgus, hydrocoele testis					38	3110	50	
3[a]/F/18	Pulmonary stenosis, ASD							31	1325	No info	Twin, preterm
4[b]/M/9	Retentio testis		Inguinal hernia, hydrocoele testis				VA 0.7/0.4, myopia	39	2925	48	
5[b]/M/7							VA 0.4/0.5, astigmatism	39	3010	49	
6/F/12		Asymmetry of the thoraco-lumbar back, preauricular fistula	Pes planus valgus				Hyperopia, astigmatism	42–43	3900	54	
7/F/8				Hip luxation				40	3580		
8/M/7						Autism	VA 0.5 binocular	41	4578	55.5	
9/F/7								28	1149	39	Preterm
10[c]/M/16								36	2440	47	Preterm
11[c]/F/10					Growth delay			40	2530	45	SGA
12[c]/F/8								38	2490	45	SGA
13/F/10			Pes calcaneus valgus				VA 0.9/0.9, exotropia	40	3320	50	
14[a]/F	Died within 24 hr post delivery							31	900	No info	Twin, preterm

*ASD, atrial septal defect; preterm, gestational age ≤37 weeks; VA, visual acuity.
[a]Siblings, born to same TE mother.
[b]Siblings, born to same TE mother.
[c]Siblings, born to same TE father.
[d]Died.

TABLE 3. Gender, anomalies, pregnancy history and mode of delivery of parents with TE*

Case/Gender/Age (yrs)	Gender of parents with TE	Anomalies in parents with TE	Pregnancy history	Mode of delivery
1/M/16	Mo	Thumb hypoplasia	Infection of urinary tract (ab)	Vaginal
2/M/4	Fa	Thumb hypoplasia, Duane	Spontaneous abortion	Vaginal
3[a]/F/18	Mo	Anotia, absence of ear canal, preauricular tag	Cervical insufficiency	ECS
4[b]/M/9	Mo	Anotia, ear hypoplasia, 6th (Duane), 7th cranial nerve palsy	Maternal tachycardia (anti-arrythmica class II)	Vaginal
5[b]/M/7	Mo	Anotia, ear hypoplasia, 6th (Duane), 7th cranial nerve palsy	Maternal tachycardia (antiarrythmica class II)	Vaginal
6/F/12	Fa	Thumb aplasia, hearing loss, Duane	Pneumonia (ab)	ECS
7/F/8	Mo	No info		Vaginal
8/M/7	Mo	Anotia, 6th (Duane), 7th cranial nerve palsy, hearing loss, VSD, LVH	Spontaneous abortion	Vaginal
9/F/7	Mo	Uterus septum defect, hearing loss	Two spontaneous abortions	ECS
10[c]/M/16	Fa	No info		Vaginal
11[c]/F/10	Fa	No info		Vaginal
12[c]/F/8	Fa	No info		Vaginal
13/F/10	Fa	Thumb hypoplasia, upper limb malformations	Infection of urinary tract (ab)	Vaginal
14[a,d]/F	Mo	Anotia, abscence of ear canal, preauricular tag	Cervical insufficiency	ECS

*ab, Antibiotics; Duane, Duane syndrome (sixth cranial nerve palsy characterized by a marked limitation or absence of abduction, restriction of adduction, retraction of the globe and narrowing of the palpebral fissure on adduction); ECS, emergency caesarian section; Fa, father; LVH, Left ventricular hypertrophy; Mo, mother; No info, no information; VSD, Ventricular septal defect; TE, Thalidomide embryopathy.
[a]Siblings, born to same TE mother.
[b]Siblings, born to same TE mother.
[c]Siblings, born to same TE father.
[d]Died.

TABLE 4. Mode of delivery of children born to all 31 TE and non-TE mothers*

Mode	Deliveries					
	TE mother (*n*, %)		Non-TE mother (*n*, %)		Total (*n*, %)	
Vaginal	16	57.1	26	72.2	42	65.6
Vacuum extraction	1	3.6	5	13.9	6	9.4
Caesarian section	11	39.3	5	13.9	16	25
Total	28		36		64	

*TE, Thalidomide embryopathy.

palsy. Congenital palsy of the 6th and 7th cranial nerves is usually named Möbius sequence. None of the autistic patients has any children. The mother of the autistic boy in the present study had TE, and her manifestations consisted of Duane syndrome, Möbius sequence, anotia and hearing impairment.

An ophthalmologic study of the patients with TE has previously been performed in Sweden (Miller and Strömland, '91; Strömland and Miller, '92, '93), in which eye abnormalities were the second most frequent finding (after limb defects), occurring in 54% of the patients. The most frequent ocular abnormality in that study was strabismus due to palsy of the sixth cranial nerve. The children in the present study did not show any findings different from the general Swedish population regarding eye morphology, visual acuity, refraction or motility disturbances.

There was no evident difference regarding the number of affected children between the two groups of mothers. The TE mothers had a total of eight children compared to six children among the non-TE mothers, with one or more signs of major malformations, minor anomalies including normal variants, positional deformities, functional anomalies, prematurity or born small for gestational age. Four children were born preterm, all to mothers with TE. Seven TE mothers had signs of an early teratogenic effect of thalidomide, showing thumb hypoplasia, ear anomalies, and Duane syndrome. The ratio between mothers and fathers with TE was 9:6. Prenatal exposure to medications, alcohol and tobacco as well as complications in pregnancy did not differ from those of Swedish mothers in general.

The incidence of caesarian sections was higher among the TE mothers (39%) than among those who were not affected (14%), the latter percentage corresponding to the average rate of caesarian sections being performed in Sweden at the time of the investigation. In the study by Mauoris and Hirsch ('88) of 35 women with TE, 22% had experienced caesarian sec-

TABLE 5. Caesarian sections in TE and non-TE mothers*

Cause	n	Emergency	Planned	TE mother	Non-TE mother
Fetal asphyxia	4	4		2	2
Contracted pelvis	5	1	4	5	
Premature rupture of membranes	2	2		2	
Secondary labor weakness	1	1			1
Herpes genital infection	1		1	1	
Uterus septum defect	1		1	1	
Complicated fetal position	1	1			1
Prolapsis of umbilical cord	1	1			1
Total	16	10	6	11	5

*TE, Thalidomide embryopathy.

tions. The caesarians among the Swedish TE mothers were partly performed because of pelvic and uterine malformations. In the initial Swedish report on TE (Winberg, '64), genital malformations without further specification were noted in some cases. Hoffman et al. ('76) reported single cases of absent or deformed vagina and uterus in females with TE, predominantly in teenaged girls entering menarche. In the Swedish investigation by Strömland and Miller ('93) a few women reported uterine defects or absence of the vagina and uterus. They were about 27 years old at that time and had no children. In the present study, uterus septum defect in another two Swedish TE mothers were noted, and five had pelvic disproportion. This shows that the rate of genital and skeletal malformations is probably higher in the Swedish women suffering from TE than previously reported and that there might still be some undetected cases.

In the present study, 14 TE mothers gave birth to 28 children and four had had a total of five miscarriages (36%). This has to be compared to the 20 non-TE mothers, among whom only two spontaneous abortions (10%) occurred and with the study of Mauoris and Hirsch ('88), who found six miscarriages (9%) among 35 women with TE giving birth to 64 children.

In conclusion, we did not find any "typical" malformations or dysfunction in this group of children born to Swedes with TE. Abnormalities of the uterus and pelvic resulted in an increased incidence of cesarian sections among the TE mothers.

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