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What can we learn from the thalidomide experience: an ophthalmologic perspective

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Abstract

Purpose of review—The thalidomide tragedy of the early 1960s resulted in a great number of studies and reports involving many specialties of medicine. Because of the estimated large number of affected children (5000+) worldwide exposed to this potent teratogen, and the many informative cases in which the exposure time was known, a teratogenic timetable was constructed relating affected structures to the time of exposure. This demonstrated that thalidomide had a teratogenic effect between approximately 20 to 36 days after fertilization.

Recent findings—We found that Duane syndrome and its variants were prominent in individuals who were exposed to thalidomide early in the sensitive period (days 20 to 26±). Other anomalies associated with this early effect were aberrant tearing, facial nerve palsy, ear malformations, and autism. Structural eye malformations were less frequent in this early phase, appearing slightly later in the sensitive period.

Summary—This study summarizes the ophthalmologic findings from a number of studies and compares them with respect to the implications of time of exposure. Because the timing of anomalies such as external ear and limb malformations are well established in the thalidomide literature, correlation with associated eye anomalies gives insight into the approximate timing of the causative teratogen exposure.

Keywords

aberrant tearing; Duane syndrome; facial nerve palsy; thalidomide embryopathy

Introduction

Thalidomide is an extremely potent teratogenic drug capable of causing severe systemic malformations to an exposed fetus during the sensitive period. Thalidomide [α -(*N*-phthalimido)-glutarimide] was synthesized in 1954 by Chemie Grünenthal under the brand name of Contergan and later licensed in more than 40 countries worldwide [1]. One exception to the general availability of thalidomide occurred in the USA. The United States Food and Drug Administration (FDA) had not approved the drug for unrestricted use because of concerns raised by Francis Kelsey [2], an FDA physician. The ensuing delay was

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Conflicts of interest

There are no conflicts of interest.

long enough to have the teratogenic effects recognized worldwide. Thus the number of cases of thalidomide embryopathy in the USA was very small. Manufactured under several trade names, thalidomide was a popular treatment for anxiety, insomnia, gastritis, and hyperemesis and advertised as safe and harmless for pregnant women even in high doses. Its teratogenicity in humans and higher mammals was not anticipated [1,3]. The severe teratogenic effects of thalidomide led to passage of new regulatory legislation for pharmaceuticals [4].

In the late 1950s and early 1960s, Lenz [5] noted that in Germany there was an alarming increase in the number of infants born with hypoplastic and aplastic malformations of the extremities. This observation was also noted in other countries [6,7]. In addition to limb anomalies, many other structural and functional anomalies were reported [1,8–11]. Ocular motility dysfunction and structural eye malformations, along with craniofacial anomalies, were prominent [12–20]. Within a few months of the initially reported cases, the drug was withdrawn from commercial sale in most European countries, but not before approximately 5000 cases of malformed live births occurred worldwide. As the survival rate of thalidomide-exposed embryos is estimated to be between 40 and 50%; more than 10 000 pregnancies may have been affected [1].

The literature suggested that exposure to thalidomide caused malformations primarily between 20 and 36 days after fertilization (34–50 days after the last menstrual cycle) [1,5,10]. Thalidomide differs from some teratogens in that the clinical dosage seems not to be as significant as the time of intake of the drug. It is quite rapidly hydrolyzed and because of this short action time, extreme potency, and the large number of women who took thalidomide, informative histories could be ascertained [20]. Many women knew the exact date of intake and the number of pills they took, and a correlation between time of drug intake and resultant malformations could be made [8,9,12,15,21]. From this information, summary timetables of the causation of various malformations were developed (Fig. 1) [10,21].

Swedish thalidomide study (1987–1989)

During the 1960s there had been litigation against the drug company in Sweden and about 100 children were identified as meeting the criteria for thalidomide embryopathy. From 1987 to 1989, a total of 86 of these patients were examined [22–24]. The patients were 27–30 years old, although the diagnosis of thalidomide embryopathy had been made when they were children. The purpose of this study was to describe the ophthalmologic findings and then compare them with the associated limb and ear anomalies in which the teratogenic susceptibility timetables were well documented. Table 1 summarizes the ophthalmologic findings and Table 2 summarizes the limb and systemic anomalies. There was a surprisingly large number of patients with incomitant strabismus, usually of the Duane type [22–25], but variations, such as abduction deficits without palpebral fissure change, were also noted [22,25]. Each case was then analyzed as to their associated limb or ear anomalies. An example of this analysis with Duane type ocular motility abnormality can be seen in Fig. 2. It is convincing that exposure was early in the thalidomide sensitive period, from days 24 to 26 after fertilization, although it was difficult to refine this timeline further since there were no distinguishing characteristics of associated anomalies between days 24 and 26. There were some patients who had exposure throughout the sensitive period, but most fall into the early group with associated anomalies limited to ear, thumb, and upper limb. It is unknown whether there were more mothers who took thalidomide for a longer period, but one might speculate that many of those with more severe systemic anomalies in the later period had spontaneous abortions.

The other frequent ocular-related abnormalities included aberrant tearing in 17 (20%) and coloboma and/or microphthalmia in five. Facial nerve palsy was noted in 17 patients (20%) and, like aberrant tearing, was associated with early exposure, while the structural anomalies of coloboma and microphthalmia seemed to occur slightly later. A surprising observation not previously noted in the literature was that at least four individuals in the early-effect group had severe autism [26]. This was of considerable interest to researchers in autism as it suggests that an early insult in embryogenesis could lead to a functional disturbance involving higher brain centers [26,27]. A summary of these associations has been shown in Fig. 3.

Congenital aberrant tearing

Congenital aberrant (anomalous) tearing includes tearing when eating, absence of emotional (psychic) lacrimation, or an unusual late onset of tearing. Inappropriate tearing associated with eating or sucking is often referred to as paradoxical gustolacrimal tearing or 'crocodile tears'. Bogorad [28] suggested the term 'crocodile tears' came from the myth that crocodiles cried when eating their prey.

Although the number of patients with Duane syndrome who also have anomalous tearing are few, the association of anomalous tearing with Duane syndrome is exceedingly strong. There are many case reports and small series that support this observation [29–31]. Although reported in connection with other teratogens and syndromes, these two examples of anomalous innervation are usually isolated findings [31]. A congenital lack of emotional tearing, with a normal cornea, suggests adequate basal tearing. Lack of emotional tearing is also often associated with crocodile tears and Duane syndrome.

A book summarizing the Japanese experience of a large number of individuals with thalidomide embryopathy was edited by Kida [10] in 1987. Thalidomide was on the market in Japan for 5 years (1958–1963) and was sold without a prescription. Arimoto [19] conducted detailed ocular examinations and reported Duane syndrome in 31 (23%), crocodile tears syndrome in 24 (18%), and facial nerve palsy in 38 patients (28%). Arimoto [19] also postulated that the susceptible period was approximately 20–24 days after fertilization for these malformations.

It is noteworthy that the tearing findings in the Japanese study are similar to those of the Swedish thalidomide study and aberrant tearing has also been reported with thalidomide embryopathy in a number of other studies [17,32–35]. Table 3 summarizes these studies. Other reports on thalidomide investigations often do not even mention tearing symptoms or findings. One wonders whether the appropriate questions were asked. This lack of investigation of these symptoms may also exist with reports of the nonsyndromic Duane patients.

Zhang [29], in an article from China in 1997, summarized 201 cases of Duane retraction syndrome, in which crocodile tears were noted in 26 cases (13%). In 2002, he reported 25 cases of gustatory tearing associated with Duane syndrome [30].

Lack of emotional (psychic) tearing is another unusual form of anomalous tearing. This information will rarely be volunteered by the patient unless specific questions are asked. In our thalidomide series, lack of psychic tearing was always associated with Duane syndrome and usually, but not always, with tearing when eating.

A recent second Swedish thalidomide study by the authors was a multidisciplinary design [31]. Because many members of the original cohort of Swedish patients with thalidomide embryopathy declined to participate in the new comprehensive study, our results are only for

a subset of the Swedish patients plus a few new cases, and thus there may be some bias in the results. One goal was to add more information on tearing symptoms in these thalidomide survivors (44–46 years old) by adding a baseline Schirmer I test and repeating the test while the patient is chewing. Although there may be reservations about the accuracy and reproducibility of the Schirmer tests, certain findings were very interesting. Eleven individuals complained of anomalous tearing. Nine of 11 individuals had Duane syndrome and seven of these showed increased tearing greater than 10 mm in the Schirmer test after chewing. All individuals with lack of emotional tears in this group (seven) had Duane syndrome. Eight with Duane syndrome and a very low Schirmer score but no history of dry eyes. Seven of these showed a 10 mm or greater increased Schirmer score on eating.

These findings lead to several considerations beyond the thalidomide population. Do our routine adult patients with Duane syndrome have a greater prevalence of 'dry eyes' with or without symptoms? Do some have increased tearing during eating that gives an overall total adequate tearing? Jacklin [36] mentioned a patient with unilateral dry eye and crocodile tears who carried an apple to eat to relieve his low tearing symptoms. Is there a connection between these two forms of aberrant innervation? Cells destined to form the sixth and seventh nerve nucleus and the superior lacrimal nucleus in the brain stem, are felt to be in close proximity in early embryogenesis. Ramsay and Taylor [37] proposed that there was nuclear damage or dysgenesis in the vicinity of the abducens nucleus, with the lacrimal finding being the result of innervation of the lacrimal gland by fibers subserving salivation. The observations in thalidomide embryopathy of an overwhelming association between facial nerve palsy, Duane syndrome, and aberrant tearing strongly support a theory of a common nuclear location during embryogenesis. There may also be some damage in the lacrimal nucleus to cells that are destined to be connected with higher centers that would normally be responsible for emotional tearing.

Möbius sequence

There is a resemblance between some individuals with anomalies connected with early exposure to thalidomide and those with Möbius sequence [38,39]. Möbius sequence is classically described as a condition characterized by involvement of the sixth and seventh cranial nerves frequently associated with limb and facial anomalies. This constellation of cranial nerve anomalies is similar to some individuals with thalidomide embryopathy due to early exposure in the sensitive period. In 1995, a multidiscipline, prospective study was done in Sweden involving 25 patients exposed to thalidomide who had Möbius sequence [40,41]. One of the motivating factors for this study was to investigate functional issues such as autism and tearing abnormalities, which had been observed in the thalidomide early exposure group. There had been few articles in the older literature that reported autism in individuals with Möbius sequence [42]. In this 1995 study, there were 21 patients old enough to have a psychiatric examination and eight met the diagnostic findings of autism disorder [43]. Six patients in the study were noted to have some tearing abnormality. These comparisons became more interesting with the reports from South America, especially Brazil, that children were born with findings compatible with the diagnosis of Möbius sequence whose mothers had unsuccessfully attempted abortion with a drug, misoprostol [44]. In a study in Recife, Brazil, of 28 patients with Möbius sequence, there was a history of misoprostol exposure early in pregnancy in 17 [39]. Autism was present in seven patients and was represented in both groups. Abnormal tearing was also reported in some [31,39,45].

What has been learned?

The potent teratogenicity appropriately discouraged other uses of thalidomide, although the drug has subsequently been tried for many diseases and medical problems. At present the

FDA has approved its use for erythema nodosum leprosum (ENL) and multiple myeloma. Other uses are off label or on an experimental protocol [46–48]. The effectiveness of thalidomide in any particular condition will depend on its mechanism of action and at this time these mechanisms are only understood in a few situations [24,46–49]. It has been shown to have some sedative, anti-inflammatory, immunomodulatory, and antiangiogenic activity [24,40,46]. Nonetheless, it should not be used during pregnancy or in women of child bearing age who are fertile and not using contraception.

1. Thalidomide is a potent teratogen capable of causing severe ocular and systemic malformations when the fetus is exposed during the early 4th week of pregnancy (days 20–26±).
2. The most frequent ocular manifestation is incomitant strabismus, mostly of the Duane type syndrome type, but also including isolated abduction deficit with no palpebral fissure changes (exposure days 20–24±). Associated nonocular anomalies include external ear malformations, hearing deficits, facial nerve palsy, and thumb anomalies. As shown in Fig. 4, more severe upper limb, lower limb, and inner ear malformations occurred later in the sensitive period. Systemic anomalies involving the heart, kidney, and gastrointestinal system were not easy to associate with a particular exposure time but seemed to involve the mid to late periods.
3. There were no cases of comitant strabismus associated with early exposure, but in the cases observed (7) all had limb anomalies, suggesting a later exposure. The seven cases of concomitant strabismus noted in the thalidomide study had associated anomalies characteristic of later exposure to thalidomide (Fig. 5).
4. The association of Duane syndrome and facial nerve palsy is similar to characteristic findings in Möbius sequence, which can at times be caused by a teratogen, although the exposure time by history seems later.
5. Aberrant tearing, either inappropriate lacrimation with eating or lack of emotional tearing, is rare but frequently noted in individuals with embryopathy from early exposure to thalidomide. Most cases are associated with Duane syndrome.
6. Structural anomalies of the eye such as microphthalmos and/or uveal colobomas occur infrequently and suggest a slightly later, but abutting, exposure time. This later period is thought to be the thalidomide exposure time for many systemic malformations that might result in a spontaneous abortion. When eye malformations occur with serious systemic malformations, the fetus is more likely to be spontaneously aborted and the eye anomalies may never be noted.

Conclusion

There have been many inspiring examples of the individuals with thalidomide embryopathy coping and overcoming their major handicaps. Many of these survivors agreed to the multiple studies done on thalidomide embryopathy. We owe much to these patients. Although the drug was only on the market in most countries for a few years in the early 1960s, these studies have given information on the time and location of the developmental insult that results in specific malformations and functional defects. There is overwhelming evidence that a disturbance in development at a very early time (days 20–26±), probably in the area of the sixth nerve nucleus, can result in Duane syndrome in association with aberrant tearing and facial nerve palsy. Möbius sequence and colobomatous microphthalmia appear to be manifestations of slightly later exposure.

Acknowledgments

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Key points

- The thalidomide tragedy resulted in an increased awareness of possible teratogenic causes of ocular malformations.
- The well established timetable of the period of sensitivity of this drug for some limb and ear anomalies allowed comparison with the associated ocular malformation and therefore speculation as to the sensitive period for these ophthalmologic malformations.
- The high frequency of Duane syndrome noted in affected individuals was associated with early exposure to thalidomide (days 20 to ± 24).

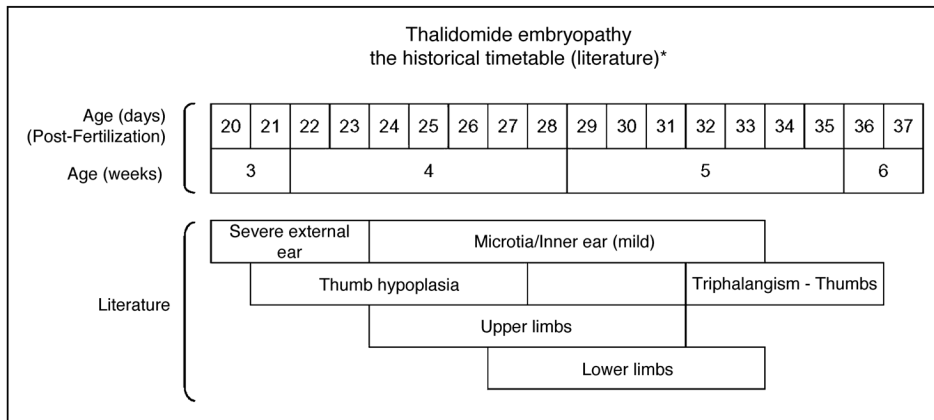


Figure 1. Summary timetable of thalidomide embryopathy based on observations in the literature

The sensitive period is 20–36 days after fertilization. If calculated from the last menstrual period, it would be approximately days 34–50 [5,10,21].

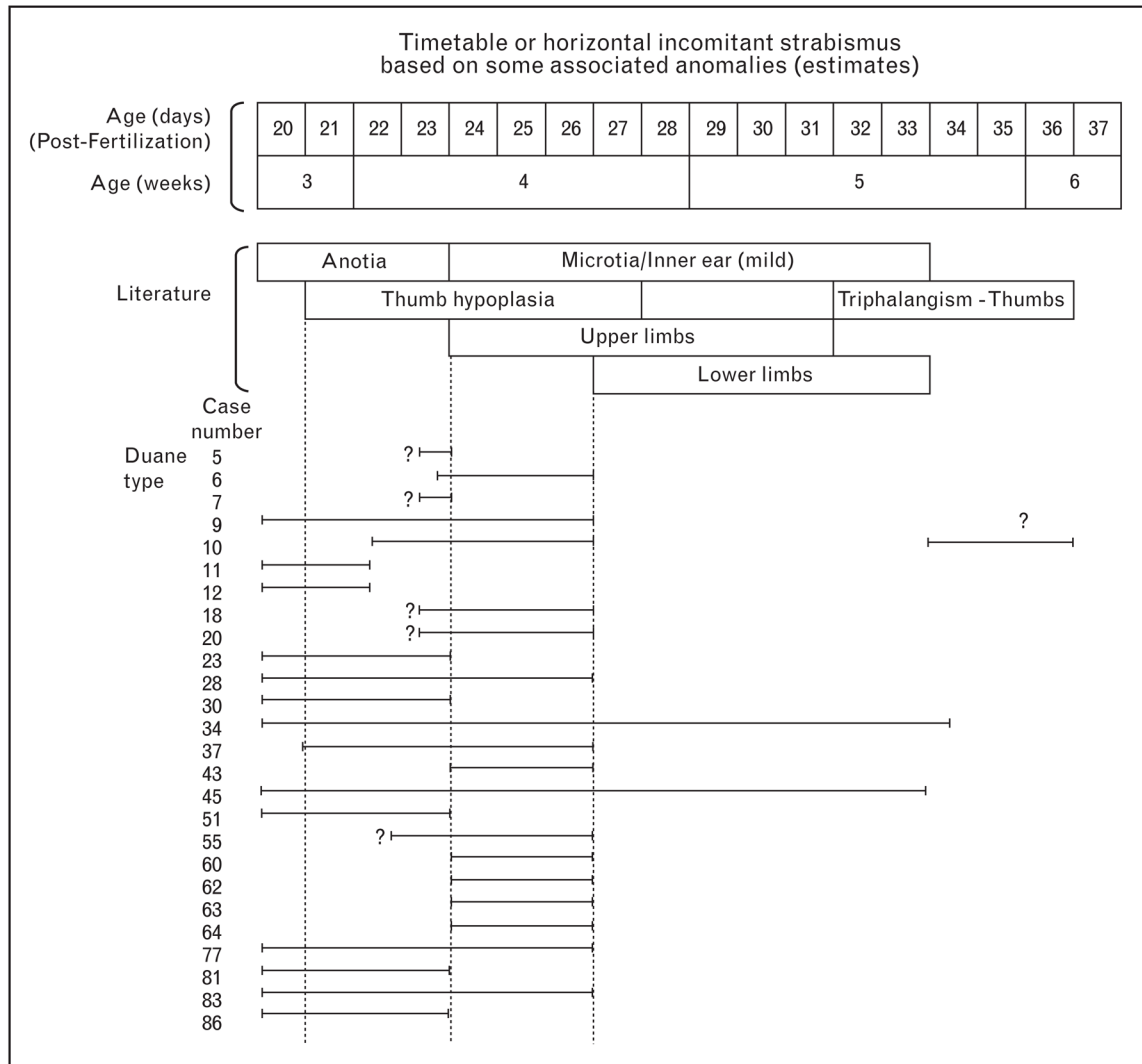


Figure 2. Timetable of Duane syndrome based on associated ear and limb anomalies of each patient compared with the thalidomide timetable established from studies conducted in Sweden For example, patient 9, who had moderate ear anomalies, upper limb but no lower limb malformations suggests that thalidomide was taken in the early to middle phase of the sensitive period. Some of the beginning and end points are estimates (e.g., the difficulty in separating anotia from microtia and how to plot the few patients with very mild or questionable limb anomalies). Other problem patients include patients 5 and 7, who only had a few malformations. Even with the less clear examples, there was no question that Duane syndrome was associated with an early thalidomide effect within the 20–36 day overall sensitive period. Data for other types of incomitant strabismus, facial nerve palsy, and aberrant lacrimation were also consistent with an early thalidomide effect [22].

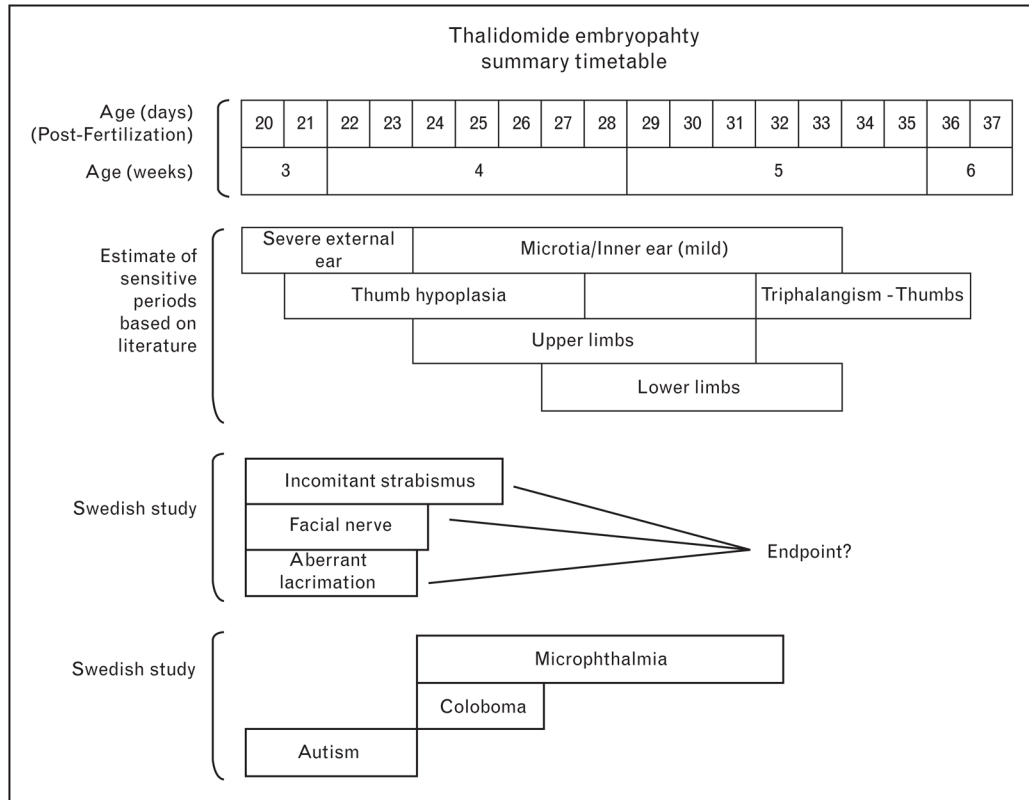


Figure 3. Summary estimates of sensitive periods for ophthalmic malformations based on associated anomalies manifested by most patients (see Figure 2 for Duane syndrome, the most frequent incomitant strabismus)
 All clinical forms of incomitant strabismus had similar associated anomalies. These blocks of sensitive periods for the development of eye anomalies and autism are estimations and may be shorter or slightly longer than indicated. The thalidomide timetable for the ear, thumb, and limb anomalies was derived from the literature [8,10,21,22].



Figure 4. Malformations of shoulders, upper limbs and hands in thalidomide embryopathy
Reproduced from [22,23].

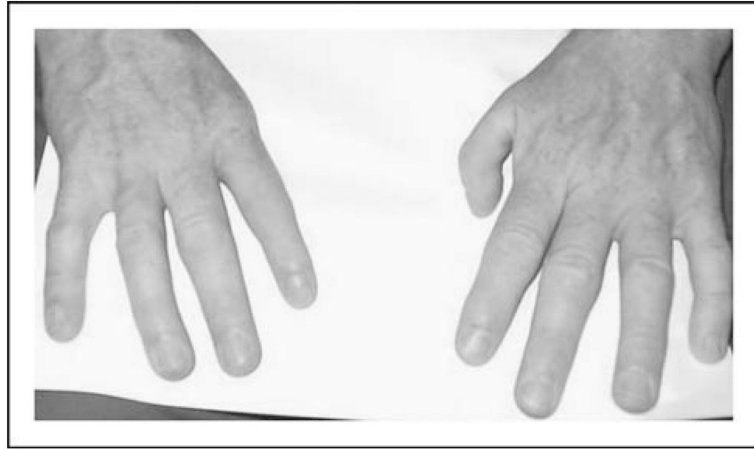


Figure 5. Hand malformations in thalidomide embryopathy, showing aplasia of the right and hypoplasia of the left thumb
Reproduced from [22,23].

Table 1Ocular anomalies documented in the Swedish Thalidomide Study (1987–1989)^a

Anomaly	No. of (%) affected ^a
Strabismus – incomitant	37 (44%)
Typical Duane syndrome with pronounced limitation abduction and fissure change on adduction [26]	
Marked limitation abduction and adduction [7]	
Abduction deficit only [4]	
Strabismus – comitant (all esotropia)	6 (7%)
Aberrant lacrimation	17 (20%)
Coloboma (uveal or optic disc)	3
Microphthalmos	2
Glaucoma	1
Lipodermoid of conjunctiva	1
Hypertelorism	1
Retinal myelinated nerve fibers	2
Ptosis	2

Reproduced with permission [24].

^a*N* = 86, except strabismus *N* = 84.

Table 2

Limb and systemic anomalies in Swedish Thalidomide Study (1987–1989) (N=86)

Limb and systemic anomalies in Swedish Thalidomide Study (1987–1989) (N = 86)	
<u>Anomalies/site of anomaly</u>	<u>No. (%) affected</u>
Thumbs	70 (81%)
Upper limb (excluding thumb)	59 (69%)
Lower limb	21 (24%)
Ears/hearing	33 (38%)
Facial nerve palsy	17 (20%)
Kidney	12 (14%)
Cardiovascular	7 (8%)
Chest/lung	4 (5%)
Genitalia	3 (3%)
Anal atresia	4 (5%)
Choanal atresia	2 (2%)
Dental anomalies	4 (5%)
Mental retardation (moderate to severe)	5 (6%)
	By history or medical record
Severe autism **	4 (5%)

Reproduced with permission [24].

^aUnable to comment on possible milder cases of autism as protocol did not include a formal psychiatric evaluation. However, for these four patients, there was a later formal evaluation by psychiatrists.

Table 3
Thalidomide embryopathy associated with congenital aberrant tearing in some or all cases

Author	Series type	No. of cases with aberrant tearing	Age/sex	Motility	Crocodile tears	Emotional tearing	Seventh nerve palsy	Comments
Arimoto [19]	138 cases of thalidomide	23	NI	23 DS	23 cases	NI	20	
Maruo <i>et al.</i> [32]	266 cases of DS including 23 cases of thalidomide	27	NI/121 M; 145 F	23 bilateral DS; 4 unilateral DS	27 cases	NI	NI	18 of 23 cases with history of thalidomide had aberrant tearing
Miller [31]	86 cases of thalidomide	17	NI/12 M; 15 F	16 bilateral DS; 1 abduction ↓	15 cases	Absent	10	Hearing loss 7; autism 2
Trieschmann [33]	All 3 cases of thalidomide	3	1) 10 mo 2) 9 y/F 3) 11 y/F	1) DS OU 2) Abduction ↓ OU 3) NI	1) OU 2) OU 3) OD worse than OS	NI	1) R/L 2) R/L 3) R	Schirmer test scores (mm) 8 OD/5 OS → eating 20/16 deaf; tearing ↑ with eating apple
Uemura and Tamura [34]	4 cases of thalidomide HX	10	3–6 y/3 F 7 M	Bilateral 9; 1 OD	7 cases OU; 3 cases OS	NI	6	4 thalidomide history; 3 CNS malformations; 1 deaf; Schirmer after eating on 2 cases, both ↑
Takemori <i>et al.</i> [35]	Thalidomide series of 18 cases with ear anomalies	7	NI/12 M; 6 F	11 abduction ↓ OU; 1 abduction ↓ unilateral	7 cases	NI	3 OU; 3 unilateral	11 external ears; absence of stapes; inner ear 15; vestibular hypoplasia 15; 4 limb anomalies; Schirmer 11/8 mm → 34/28 mm after eating sour apple

CNS, central nervous system; DS, Duane syndrome; NI, no information; OD, right eye; OS, left eye; OU, both eyes; ↑, increased; ↓, decreased. Reproduced with permission from [31].