CONGENITAL ABERRANT TEARING: A RE-LOOK

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ABSTRACT

Purpose: Congenital aberrant tearing is characterized by tearing when eating ("crocodile tears"), lack of emotional tearing, or both. Most reported cases are associated with Duane syndrome. In our previous studies we observed aberrant tearing in individuals with thalidomide embryopathy and Möbius sequence. This report summarizes the literature on the subject and adds 3 new studies that give information on this unusual condition.

Methods: Twenty-eight individuals with Möbius sequence were interviewed about tearing symptoms at a support group meeting in Italy. In Sweden 30 adults primarily from the original thalidomide series were reexamined. In this latter study, a Schirmer test was done at baseline and repeated 5 minutes after eating. Twenty families in Brazil who have children with Möbius sequence were questioned about tearing symptoms and exposure to misoprostol during pregnancy.

Results: In the 28 Italian individuals, either "crocodile tears" or lack of emotional tearing was noted in 7 cases. In the thalidomide study, 10 of 30 patients had tearing when eating and 7 had no emotional tearing. Low Schirmer scores or increased tearing after eating was noted in a few asymptomatic individuals. Among the 20 Brazilian children with Möbius sequence, 10 had some tearing abnormality.

Conclusion: Congenital anomalous lacrimation is rare but usually associated with Duane syndrome or abduction deficits, as in Möbius sequence and, less frequently, facial nerve palsy. Studies implicate an early insult in development at 4 to 6 weeks. At that time the facial nerve, sixth nerve, and lacrimal nucleus are in close proximity in the embryo.

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INTRODUCTION

Congenital aberrant (anomalous) tearing describes unexpected alteration in lacrimation, such as tearing when eating, absence of emotional (psychic) lacrimation, or an unusual late onset in tearing. When this inappropriate tearing is associated with eating or sucking, it is often referred to as paradoxical gustolacrimal tearing or *crocodile tears*, so named by Bogorad,[1] who said "crocodiles cried when eating their prey." However, the term *crocodile tears* also refers to feigned or misleading hypocritical tearing.[2,3] Murube[2] reviewed a large body of historical literature on the use of the term and points out that although crocodiles have lacrimal glands, the secretion seems more directed to glands of eating than to ocular structures, so the implication may be inappropriate. Darwin[4] believed that very few animals shed tears, with the possible exception of the India elephant and, questionably, some monkeys.

The condition of crocodile tears most often occurs as a complication of acquired facial nerve palsy.[2,3,5] This report confines the discussion primarily to congenital forms, since the explanations of the neurologic implications are probably different.

Although the number of patients with both Duane syndrome and aberrant tearing is rare, the corollary of the association of anomalous tearing with Duane syndrome is exceedingly strong, even when this combination is not part of a specific syndrome or caused by a known teratogen (Table 1, Figure 1).[6-30] Another type of anomaly of lacrimation is the congenital lack of emotional tearing in the presence of a normal cornea on examination. This finding is also often associated with crocodile tears and Duane syndrome. Congenital facial nerve palsy is reported with both aberrant neurologic conditions, but the linkage is not as strong. These combinations of malformations occur very rarely except in a few conditions: thalidomide embryopathy[31-41] (Table 2), Möbius syndrome,[42-45] and, to a lesser extent, Wildervanck syndrome[46-48] (Table 3). There are a few isolated unusual associations[49-51] (Table 3).

Duane syndrome is a common example of congenital aberrant innervation in which there is miswiring between the cranial nerves to the extraocular muscles, most commonly a branch of the medial rectus to the lateral rectus muscles. In addition to aberrant lacrimation, there are a few examples of less frequent congenital miswiring conditions, such as Marcus Gunn syndrome (occasionally noted with Duane syndrome) and a case of an abnormal innervation of motor branch of trigeminal to the medial rectus muscle.[52,53]

This report summarizes the literature on tearing aberrations, including the 2 Swedish studies previously reported by the authors, which were associated with thalidomide embryopathy and Möbius sequence.[34-36,43-45] Additionally, the results of a new Swedish thalidomide study are reported, along with the findings of a questionnaire obtained at an Italian Möbius support group, a Brazilian Möbius study, and an informal discussion at the Möbius Foundation meeting, which is a support group for patients with Möbius sequence and their families that is located primarily in the United States.

METHODS AND MATERIALS

The first Swedish thalidomide study was conducted to focus on the ocular motility findings in patients (age range, 26 to 29 years) with known thalidomide embryopathy. Following a legal trial against the drug company, about 100 children were identified as meeting the

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Bold type indicates AOS member.

TABLE 1. CONGENITAL ABERRANT TEARING REPORTED WITH DUANE SYNDROME BUT NO OTHER SYNDROME

SOURCE	SERIES TYPE	NO. OF CASES WITH ABERRANT TEARING	AGE (YR) /SEX	MOTILITY	CROCODILE TEARS	EMOTIONAL TEARING	7TH NERVE PALSY	COMMENTS
Agarwal[6]	Aberrant tearing	1	15/M	DS OU	OU	NI	0	Tearing with most sour foods, not sweet taste
Antonelli[7]	Aberrant tearing	1	NI	NI	OD	Absent	NI	
Biedner and associates[8]	Aberrant tearing	1	6/M	DS OU	OU	NI	0	Mastication movements alone did not cause tearing
Cricchi[9]	Aberrant tearing	1	16/NI	DS OU	OU	Absent	0	
D'Ermo[10]	Aberrant tearing	2	NI	DS OU	OU	Absent	0	Facial asymmetry; oxycephaly
			NI	DS OD	OD	Absent	0	Facial asymmetry
Ehlers[11]	Aberrant tearing	1	5/F	Abduction deficit OU	OU (sour)	Absent OU	Weakness	Schirmer test (mm) 7 OD/23 OS → 19/35 with vinegar; no change with sweet
Hartwig and Kaufmann[12]	Aberrant tearing	1	NI	DS OU	OU	NI	NI	
Jacklin[13]	Aberrant tearing	1	42/NI	Normal	OS	NI	L	↓ Hearing; birth trauma L; Schirmer 3/12 mm; used chewing to treat dry eye OS
Jampel and Titone[14]	Aberrant tearing	1	6/F	DS OD	OD	Normal	R	Normal reaction to ammonia; tearing primarily to sucking and chewing; scoliosis; syndactyly; arachnodactylia; microstomia; leg anomaly
Karsenti and associates[15]	Aberrant tearing	1	4/NI	DS + Brown syndrome	Yes	NI	NI	Internal and external ear
Komoto[16]	Aberrant tearing	2	2/F	Normal	OD	Absent OD	0	
			5/M	Normal	OU	Normal	0	
Lillie[17]	Aberrant tearing	1	NI	Lateral rectus palsy	Yes	NI	NI	
Lutman[18]	Aberrant tearing	2	NI	Limited abduction deficit	Unilateral	NI	NI	
			NI	Limited abduction OU	OU	NI	NI	
Magni and associates[19]	Aberrant tearing	1	5/F	DS OU	OU	NI	NI	
Molinari[20]	Aberrant tearing	1	29/M	DS OD	OD	Absent OD	0	
Nair[21]	Aberrant tearing	1	30/M	DS OU	OU	NI	0	Tearing with chewing spicy food
Pereira and Arts[22]	Aberrant tearing	1	Infant/M	NI	OU	NI	NI	
Ramsay and Taylor[23]	Aberrant tearing	2	3/M	DS OU	OU	Absent	Bilateral weakness	No lacrimation to irritants but ↑ to chewing; normal corneal sensation; finger anomaly; no stapedial reflex
			3/M	DS OU	OU	Absent	Bilateral weakness	Deaf, external ear; normal corneal sensation; no tearing to irritants
Regenbogen and Stein[24]	Aberrant tearing	1	7/F	DS OS	OS	Normal	0	Lacrimation with chewing, especially sour but not tasteless substances; ammonia fumes and corneal irritation stimulate tearing; Schirmer scores equal between eyes
Sannohe and associates[25]	Aberrant tearing	1	13/F	DS OU	OU	NI	0	Sensorineural hearing loss due to failed cochlear development
Sarda and associates[26]	Aberrant tearing	1	14/M	Abduction deficit OD	OD	Absent OD	0	Normal cornea response to irritation and ammonia fumes; equal normal Schirmer scores
Tachibana and associates[27]	Aberrant tearing	1	19/F	DS OU	OU	Absent OU	0	Adopted; internal and external ear; scoliosis; hearing ↓, absence of oval window
Walsh and associates[28]	Aberrant tearing	1	1/NI	Abduction deficit	OU	NI	NI	
Zhang[29]	201 cases of DS	26 (12%)	ɹI*/ 99 M; 102 F	All DS	26 (13%)	NI	NI	No pregnancy history given
Zhang[30]	Aberrant tearing	25	NI/8 M NI/17 F	15 DS OU 10 monocular	15 cases OU; 10 monocular	NI	NI	DS usually bilateral with bilateral tearing and unilateral DS with unilateral tearing

DS, Duane syndrome; OD, right eye; OS, left eye; OU, both eyes; L, left side; NI, no information; R, right side; ↑, increased; ↓, decreased.

*Age in series was 1-32 years, but no information was given on the 26 patients with crocodile tears.

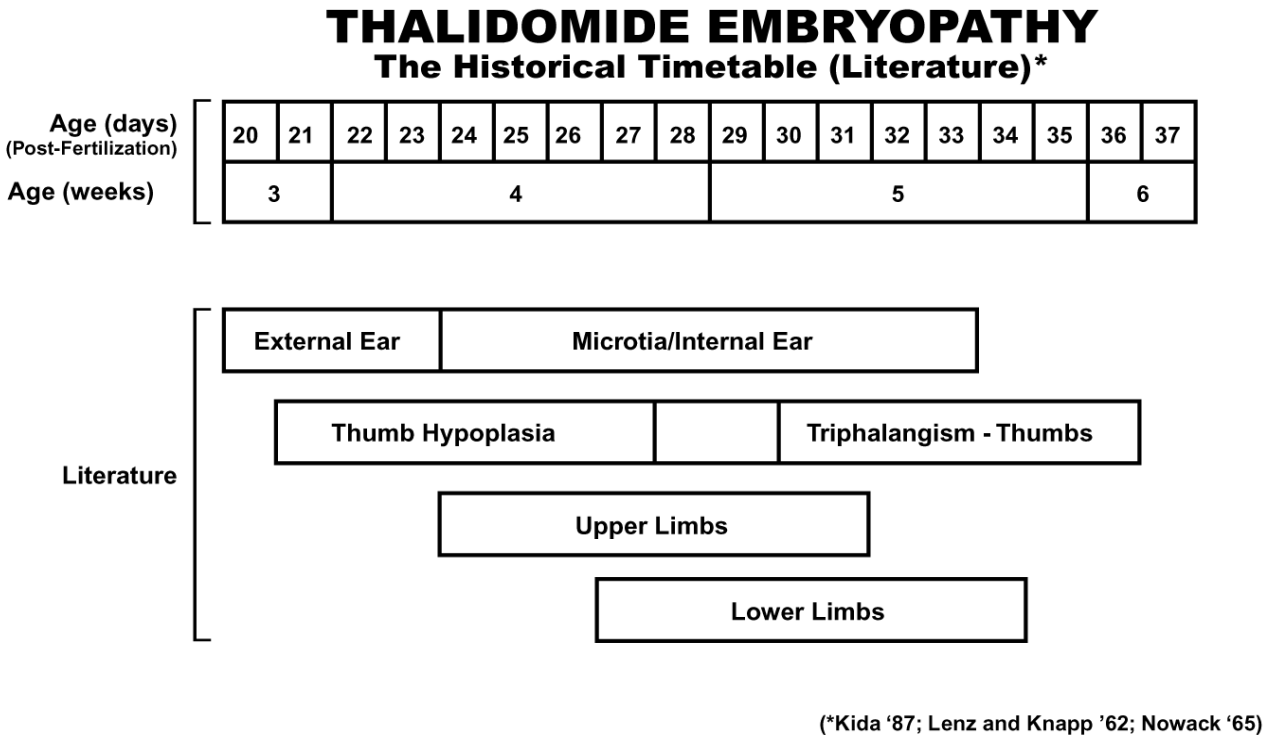

FIGURE 1

Summary timetable of thalidomide embryopathy. Timetable is based on observations in the literature. Sensitive period in pregnancy is 20 to 36 days after fertilization. If calculated from the last menstrual period, it would be approximately days 34 to 50 (Kida,[55] Lenz[56]).

criteria for thalidomide embryopathy, and in 1987 to 1989 a total of 86 patients were previously reported by 2 of the authors (K.S., M.M.),[34-36] but the tearing data are reanalyzed for this report. Aberrant tearing, although mentioned in the literature, was a surprisingly frequent finding. Another unexpected finding was autism in 4 of the patients. Both of these functional disturbances were often accompanied by Duane syndrome, facial nerve palsy, and ear and thumb malformations that were the hallmark of the early effect (days 20 to 24 after fertilization) from thalidomide ingestion in pregnancy (Figure 2). Because of the similarity to the characteristic findings of Möbius sequence, it was decided to do a prospective multidisciplinary study of individuals in whom Möbius sequence had been diagnosed.[43,44] This Swedish study (1995 to 1998) evaluated 25 cases of Möbius sequence, targeting not only the ocular findings but also the associated systemic and functional problems, with special attention to the autism spectrum disorders that had been reported in a few cases of Möbius sequence.

Our tearing data, collected during the previous Swedish thalidomide study of 86 patients and from the Swedish Möbius Study, were analyzed more closely and are summarized in Table 4. In these studies the diagnosis of abnormal lacrimation was made by history alone, with only a few patients tested with a Schirmer test.[34,36,43,44] Fifteen years later, a multidisciplinary group decided to perform a more detailed examination of as many patients as possible from the original Swedish thalidomide cohort.

The study described in this article was conducted in 2006 and 2007 and involved individuals with thalidomide embryopathy, now 45 to 47 years of age, who are registered in the Swedish Association of Thalidomide Embryopathy. This study was approved by the Sahlgrenska Academy at Göteborg University in Sweden, and each individual signed a consent form for photographs and participation in the study. All members were invited to participate in this study, but many did not agree to be examined, so this new prospective study was done on a subset of individuals from the original cohort of Swedish patients with thalidomide embryopathy. The multidisciplinary study included orthopedics, speech and language pathology, dentistry, psychiatry, and ophthalmology. Although in the 1989 study there were estimated to be 100 individuals affected with thalidomide embryopathy in Sweden, 4 new patients had been identified more recently, and these were also examined. Two patients from the original group of 86 are deceased. Only 27 members of the original group plus the 4 new patients agreed to participate. The allotted time for the ophthalmologic examination was 1½ hours. This included a routine general ophthalmologic evaluation (eg, slit lamp, dilated fundus evaluation, ocular motility [motor and sensory], refraction, intraocular tensions). The additional ophthalmologic information added in this study was a more detailed history of tearing symptoms and a 5-minute Schirmer test without anesthetic, followed by a 5-minute Schirmer test (also without anesthetic)

TABLE 2. THALIDOMIDE EMBRYOPATHY ASSOCIATED WITH CONGENITAL ABERRANT TEARING IN SOME OR ALL CASES

SOURCE	SERIES TYPE	NO. OF CASES WITH ABERRANT TEARING	AGE/ SEX	MOTILITY	CROCODILE TEARS	EMOTIONAL TEARING	7TH NERVE PALSY	COMMENTS
Arimoto[32]	138 cases of thalidomide	23	NI	23 DS	23 cases	NI	20	
Maruo and associates[33]	266 cases of DS	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[34]	86 cases of thalidomide	17	NI/12 M; 15 F	16 bilateral DS; 1 abduction ↓	15 cases	Absent 10	12	Hearing 7; autism 2
Trieschmann[37]	Thalidomide	3	(1) 10 mo (2) 9 yr/F (3) 11 yr/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
Uemara and associates[38]	Aberrant tearing	10	3-6 yr/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 and associates[39]	Thalidomide	18	NI/12 M; 6 F	11 abduction deficits OU; 1 abduction deficit 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
Zetterstrom[41]	Thalidomide	4	NI	3 abduction deficit	NI	NI	NI	17 of 38 had abduction deficits; no details on type of tearing symptoms

CNS, central nervous system; DS, Duane syndrome; NI, no information; OD, right eye; OS, left eye; OU, both eyes; ↑, increased; ↓, decreased.

TABLE 3. OTHER SYNDROMES REPORTED IN CASES OF CONGENITAL ABERRANT TEARING (NOT THALIDOMIDE)

SOURCE	SYNDROME	NO. OF CASES WITH ABERRANT TEARING	AGE/SEX	MOTILITY	CROCODILE TEARS	EMOTIONAL TEARING	7TH NERVE PALSY	COMMENTS
Amaya and associates[42]	18 cases of Möbius sequence	3	(1) 3 mo/NI (2) 6 mo/NI (3) 3½ yr/NI	Abduction deficit OU all*	3	NI	All*	(1) Microglossia (2) Cerebellum hypoplasia (3) Foot and tongue; keratitis
Miller and Strömland[43]	25 cases of Möbius sequence	6-7	2-7 yr/all M	Abduction deficit all*	4 cases (3 with no emotional tearing)	Absent 5* (3 with crocodile)	All*	
Brik and Athayde[46]	Wildervanck	1	13 ½ yr/F	DS OU	OU	NI	0	Klippel-Feil; DS
Haciyakupoglu and associates[47]	Wildervanck	1	13 yr/NI	DS OU	OU	NI	NI	Developmental delay; Dandy-Walker; Klippel-Feil; deaf
Brodsky[48]	Wildervanck	1	5 mo/NI	DS OU	OS	Absent OU	L	Klippel-Feil; deaf; brain stem hypoplasia; kyphosis hyperreflexia
Guirgis and associates[49]	Isotretinoin (Accutane)	1	10 mo/NI	Ophthalmoplegia (restrictive)	OU	Absent OU	NI	Mother used isotretinoin early in pregnancy; middle and external ear anomalies; micrognathia; preauricular skin tags
Nigam[50]	Treacher-Collins	1	11½ yr/M	Normal	OU	NI	NI	Microtia; deaf
Preisch and associates[51]	BOR	2	32 yr/M		OD	NI	NI	Schirmer test negative OD, positive OS; patients are father and daughter
			4 yr/F		OD	NI	NI	BOR syndrome; hearing

BOR, branchio-oto-renal; DS, Duane syndrome; OU, both eyes; OD, right eye; OS, left eye; NI, no information; L, left side; ↑, increased; ↓, decreased

*Inclusion criteria for Möbius sequence.

while the subject was eating "chewy" cookies (Figures 3 and 4).

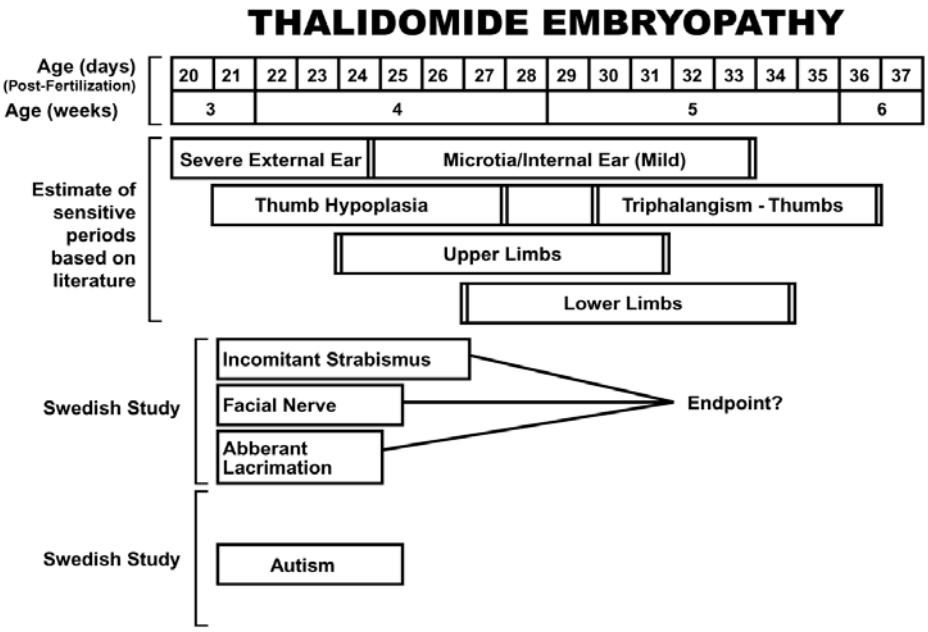

FIGURE 2

Summary estimates of sensitive periods for ophthalmic malformations. Estimates are based on associated anomalies manifested by most patients with Duane syndrome, the most frequent incomitant strabismus. These sensitive time blocks for development of eye anomalies, facial nerve, and autism are estimations, and they may be shorter or slightly longer than indicated (Kida,[55] Lenz[56]).

TABLE 4. SUMMARY OF DATA FROM SWEDISH STUDIES

STUDY, YEAR	NO. (%) OF CASES WITH ABERRANT TEARING	AGE (yr) /SEX	ABDUCTION DEFICITS	CROCODILE TEARS SYMPTOMS + NO EMOTIONAL TEARING	CROCODILE TEARS ONLY	LACK OF EMOTIONAL TEARING ONLY	LATE-ONSET TEARING	7TH NERVE PALSY	AUTISM (TOTAL NO. IN STUDY)
First Swedish thalidomide study, 1987-1989 (n = 84)	17 (20%)	26-29/ 12 M; 5 F	17 (16 DS OU; 1 abduction only OD)†	8	7	2	NI	12 (5 bilateral; 5 R; 2 L)	2‡ (n = 4)
Swedish Möbius study, 1997-1998 (n = 25)	6-7* (24%)	2-17/ All M	All by inclusion criteria	3	1	2	3	All by inclusion criteria	4‡ (n = 6)

DS, Duane syndrome; L, left side; OD, right eye; OU, both eyes; R, right side.
*Some patients had minimal symptoms.
†This patient had crocodile tears OD and no emotional tearing OD.
‡Full autistic disorder and aberrant tearing.

Two of the authors (M.M., L.V.) attended the 2007 meeting of Italy's Möbius Support Group, which meets every 2 years. In 2007 the meeting was held in Piacenza, Italy; the organizing committee agreed that the investigators could ask families of children with Möbius sequence and a few adults participating in the program if they would like to respond to a questionnaire. After signing consent forms, the participants answered some questions about ocular and systemic problems, with special attention to tearing characteristics

(eg, dry eyes, anomalous tearing, corneal complications). No ophthalmologic examinations were performed, except a basic ocular motility evaluation.

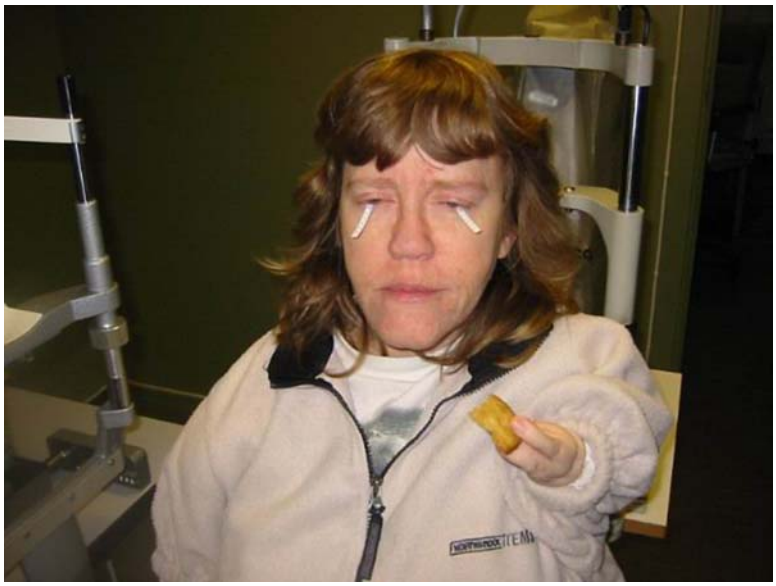

FIGURE 3

Baseline Schirmer I test. Patient was just beginning to chew. Note limb anomalies.

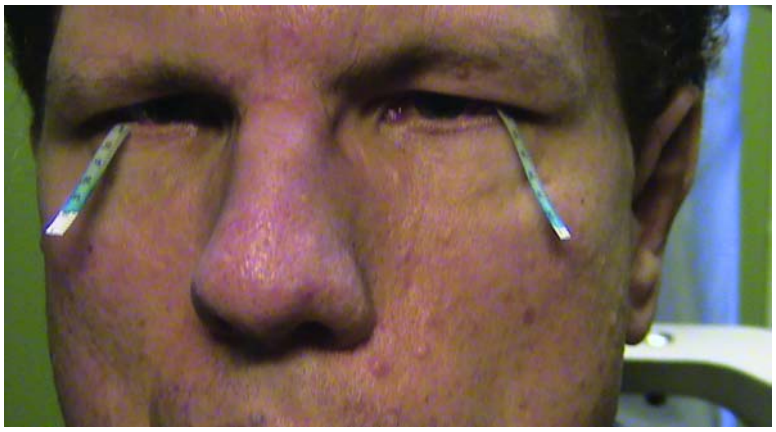

FIGURE 4

Positive response (>10-mm increase) on Schirmer test. Response occurred after chewing in patient with Duane syndrome.

Informal discussions and queries about lack of tearing and anomalous tearing took place at a US Möbius Foundation meeting in San Francisco in 2006, led by one of the investigators (M.M.). The respondents verbalized more tearing problems than previously appreciated and precipitated further investigation. Many of the adults complained of dry eyes requiring treatment, and a number of patients reported having crocodile tears.

In 2008 in Recife, Brazil, the organizers of the Permanbuco Möbius Support Group agreed that a questionnaire be given to families of children with known Möbius sequence while they attended a Möbius Support Group party. After signing an appropriate consent form, those that volunteered to participate answered a few questions on tearing. The information sought was simple, asking only age and whether the children had decreased tearing, tearing when eating, and normal or absent emotional tears. Later, the investigator (L.V.) supplied the data on misoprostol exposure by the mother in early pregnancy from information obtained in previous studies.

RESULTS

Table 4 (first row) summarizes the original Swedish thalidomide study. Seventeen patients (17 of 86) had a history of anomalous tearing, with 15 individuals giving a history of crocodile tears (8 patients with both crocodile tears and lack of emotional tearing) and 2 having only lack of emotional tearing.[34] All patients with abnormal tearing also demonstrated Duane syndrome or abduction deficit. Facial nerve palsy was present in 12 of the patients (total 17 of 86 in the study with seventh nerve palsy). Another surprise at the time of the study was the presence of obvious autism spectrum in 4 patients in the study, of which 2 had anomalous tearing.

Table 4 (second row) summarizes the Swedish study in 1997 and 1998 that evaluated 25 cases of Möbius sequence.[43,44] A more detailed history of tearing symptoms was taken. The abnormal tearing symptoms were not as severe as in the thalidomide cases, but there were 3 cases of crocodile tears and no emotional tearing, 1 case of crocodile tearing only, and 2 cases of absent or reduced emotional tearing. Additionally, there were a few cases of late-onset tearing. The patient with the most extreme case gave a history of

no tearing until age 8 years.

In the recent Swedish thalidomide study done in 2007 to 2008, it was decided to concentrate on the history of tearing characteristics and obtain more detailed data by doing a Schirmer I test before and after eating. Table 5 summarizes the findings from these patients. Although 31 individuals were recruited, one refused most of the ophthalmologic examination (patient 14), which made the final number 30. Also one (patient 18) was monocular because of an enucleated right eye. The Schirmer test seemed imprecise at times. There were a number of variables that could not be easily controlled, such as intolerance of irritation of the filter paper, movement of filter paper, and the amount of blinking of individuals. It would have been desirable to repeat the tests a few times to better control these variables, but that was impossible, as this group of patients are "research fatigued." But even with these limitations, there were some very interesting findings in this recent Swedish thalidomide study:

1. Duane syndrome was present in 11 patients, or 37% (44% in the original study).
2. Almost all of the individuals with a history of crocodile tears (9 of 11) were associated with Duane syndrome.
3. All patients with lack of emotional tears also had crocodile tears (7 of 7).
4. Facial nerve palsy was an associated finding in some patients (6 of 31).
5. If less than 10 mm of wetting on the first Schirmer test was chosen to indicate a low amount of tearing, there were 15 cases, of which 8 had Duane syndrome.
6. If 10 mm or more increase in tearing between the first and second Schirmer tests was taken as a measure of an abnormal response, 13 cases (21 eyes) were positive, of which 7 had Duane syndrome (14 eyes).
7. Of the patients with Duane syndrome and low initial tearing, 7 showed increased tearing on eating (≥10 mm of wetting) and most gave a history of crocodile tears.

It was interesting that a number of patients described specific food items, such as sour or sweet, that result in the phenomenon of crocodile tears. One patient said that green apples were the prime inciting factor of the reflex, and we observed this to be true after we gave her an apple to eat.

Table 6 summarizes the results of the interviews at the Italian Möbius support group meeting. Anomalous tearing was present in 7 of 28 patients interviewed; both tearing when eating and lack of emotional tears were present in some patients, but these were not always combined.

The recent questionnaire from a Möbius support group in Brazil shows again a high number of some tearing anomaly (10 of 20). Additionally, it was known from previous research by Ventura and associates[45,54] that 5 of 9 individuals with a history of misoprostol exposure during their mother's pregnancy had anomalous tearing. In 4 individuals there was no information on the exposure to this drug.

DISCUSSION

Axelsson and Laage-Hellman[5] in 1962 reported 62 cases of crocodile tears in the literature and added 16 cases of their own. All but a few followed acquired known facial nerve palsy. By comparison, congenital anomalous tearing is a rarer condition, with the older literature usually consisting of 1 or 2 cases in each report (Table 1). Most cases of aberrant tearing are associated with Duane syndrome (Figure 5). Regenbogen and Stein[24] in 1968 could identify only 10 reported cases of anomalous tearing in a Duane syndrome series. All cases were associated with involvement of the abducens nerve, usually Duane syndrome; a few were associated with facial nerve palsy, and none were associated with known syndromes. A few exceptions to a small number of case reports are 2 large Chinese series of Duane syndrome, by Zhang,[29,30] indicating a significant number of cases with aberrant tearing, but there was no mention of any association with specific syndromes (Table 1). Reports of the combination of these 2 aberrant neurologic conditions have significantly increased following the thalidomide tragedy and with the publication of a few Möbius sequence studies.[42-45]

Thalidomide (a-[N-phthalmido]-glutarimide) was introduced in the late 1950s in Europe to treat anxiety, morning sickness, and insomnia. It was a popular drug, and its usage spread worldwide with the notable exception of the United States, where it was not approved at that time by the Food and Drug Administration. It has been estimated that greater than 10,000 pregnancies and at least 6000 live births may have been affected by this drug, resulting in major malformations. This large number with many informative cases with narrow exposure history allowed the establishment of a teratogenic timetable of sensitivity for certain malformations, such as limb anomalies, craniofacial structures, and cranial nerves.[55-60] An increased number of limb defects were noted in 1959 by doctors in Germany, Austria, and Great Britain.[56-57,59-62] The drug was removed from the market in Europe starting in early 1961 and later in Japan. It is an extremely potent teratogenic agent, causing a wide variety of serious malformations during the known sensitive period of 21 to 36 days after fertilization. Since it is rapidly hydrolyzed, it has an effect in a very narrow time frame in embryogenesis. It is recognized that the early exposure to thalidomide is associated with cranial nerve malformations, thumb, ear, and upper limb malformations. Thalidomide has proven to be a strong risk factor for the association of Duane syndrome, facial nerve palsy, and anomalous tearing occurring from exposure also in the early sensitive period—days 20 to 24±.[32,34] In the first Swedish thalidomide study, of 86 of the known 100 affected individuals, 44% had Duane syndrome, more than 20% had aberrant lacrimation, and 20% had facial palsy (see Table 4, first row).[34,35] All cases of aberrant tearing were associated with Duane syndrome, and many were associated with facial nerve palsy. Two of the 4 patients with autism in this series also had aberrant tearing (Figure 2).

A book summarizing the Japanese experience of a large number of individuals with thalidomide embryopathy was edited by Dr Mitsuhiro Kida.[55] Thalidomide was on the market in Japan for 5 years (1958 to 1963), but virtually no comprehensive research was conducted until 1974. It was sold without a prescription. There were 309 cases registered as victims of thalidomide embryopathy, of which 137 (44%) were involved in the study.[55] A detailed eye examination was performed by Arimoto[32] on this subgroup. He reported

TABLE 5. FINDINGS FROM SECOND SWEDISH THALIDOMIDE STUDY (n = 30)

CASE NO.	SEX	OCULAR MOTILITY	TEARING WHEN EATING	EMOTIONAL TEARING	7TH NERVE PALSY	SCHIRMER TEST SCORES (MM, OD/OS)			COMMENTS/DEFORMITIES
						INITIAL	5 MIN AFTER EATING	≥10-MM DIFFERENCE	
1	M	DS OU	OU	Normal	0	2/2	12/12	OU	Hearing ↓, external ear, thumb
2	M	DS OU	0	Normal	0	2/2	19/28	OU	Left upper limb, thumbs
3	M	Comitant ET	OU	Normal	0	22/35	35/30	OD	Hearing ↓; upper limbs; lower limb thumbs
4	F	Normal	0	Normal	0	7/28	23/14	OD	Upper limbs, hands and thumbs
5	M	Normal	0	Normal	0	5/5	5/5	—	Right hand and thumb
6	F	Normal	0	Normal	0	16/13	32/30	OU	Thumbs; lower limbs, hands
7	M	Normal	0	Normal	R	5/7	8/10	—	Hands; acquired 7th nerve palsy
8	M	Normal	0	Normal	0	34/16	24/20	—	Upper limbs, thumbs
9	M	DS OU	OU	Absent OU	0	27/20	35/26	—	Thumb
10	M	DS OU	OU	Absent OU	R/L	5/10	30/35	OU	—
11	F	Normal	0	Normal	R/L	5/18	12/17	—	Acquired 7th nerve palsy left, upper limbs, hands, thumbs
12	M	Normal	0	Normal	0	7/8	15/20	OS	Choanal atresia; hand, thumb**,** upper limbs, hypoplasia
13	F	Normal	0	Normal	0	18/22	19/20	—	Double vagina, upper and lower limbs, severe hands, thumbs
14	F								Refused examination
15	F	DS OU	OD	Absent OU	0	1/7	17/24	OU	Right inner ear, upper limbs and thumbs
16	F	DS OU	OD	Normal	L	15/25	24/31	—	—
17	M	↓ Abduction Normal OS Enucleated	0	Normal	0	35/35	35/35	—	↓ Hearing, upper limbs, thumbs
18	M	OD	0	Normal	0	NA/28	NA/16	—	Upper limbs, thumbs
19	F	DS OU	OU	Absent OS	0	8/2	23/16	OU	External ears, cataract OD
20	M	Normal	0	Normal		7/11	9/13	—	Hands, thumbs
21	F	Normal	0	Normal	0	15/20	17/22	—	Hands, thumb, missing uterus and vagina
22	M	Normal	0	Normal	0	0/0	0/13	OS	Thumb; kidney

TABLE 5 (CONTINUED). FINDINGS FROM SECOND SWEDISH THALIDOMIDE STUDY (n = 30)

CASE NO.	SEX	OCULAR MOTILITY	TEARING WHEN EATING	EMOTIONAL TEARING	7TH NERVE PALSY	SCHIRMER TEST SCORES (MM, OD/OS)			COMMENTS/DEFORMITIES
						INITIAL	5 MIN AFTER EATING	≥10-MM DIFFERENCE	
23	M	Normal	0	Normal	0	35/35	35/35	—	Thumb
24	M	DS OU	OU	Absent OU	R	5/5	35/35	OU	↓ Hearing, hands, thumb
25	F	DS OU	OD	Absent OD	R	0/2	17/30	OU	↓ Hearing left ear
26	M	DS OU	0	Normal	0	19/35	35/35	OD	Craniosynostosis, hand, thumbs
27	M	Normal	0	Normal	0	15/25	12/35	—	Upper limbs, hands, thumbs, foot
28	M	Brown S	0	Normal	0	35/25	21/35	—	Nystagmus, upper limb, hand, thumbs
29	F	Normal	0	Normal	0	27/29	25/34	—	Hands
30	M	DS OU	OU	Absent OU	0	8/13	15/17	—	Upper limbs, hands, left foot, triphalangeal thumbs
31	F	Normal	0	Normal	0	14/30	9/9	—	Thumbs, foot
Total									
19 M, 12 F, age 44-46 y		DS = 11; ↓ abduction = 1; Brown S = 1; 1 comitant ET	10 of 30	7 absent	6				

Brown S, Brown syndrome; DS, Duane syndrome; ET, esotropia; NA, not applicable. 0, no tearing when eating or no 7th nerve palsy; +, positive finding; ↓, decreased; —, <10-mm.

TABLE 6. RESULTS OF 2007 INTERVIEWS WITH THE ITALIAN MÖBIUS SUPPORT GROUP(n = 28)

TYPE OF ANOMALOUS TEARING	NO.
Crocodile tears and absent emotional tearing	2
Crocodile tears only	3/28
Lack of emotional tearing only	2/25
Complaints of dry eyes	11/28
Use of artificial tears	9/28
Onset >6 mo	6/12

Duane syndrome in 31 (23%), crocodile tear syndrome in 24 (18%), and facial nerve palsy in 38 patients (28%). All but one of the patients with the aberrant tearing had an associated Duane syndrome. Arimoto also postulated that the susceptible period was approximately 20 to 24 days after fertilization for these malformations. Table 2 summarizes a number of studies involving thalidomide and anomalous tearing.

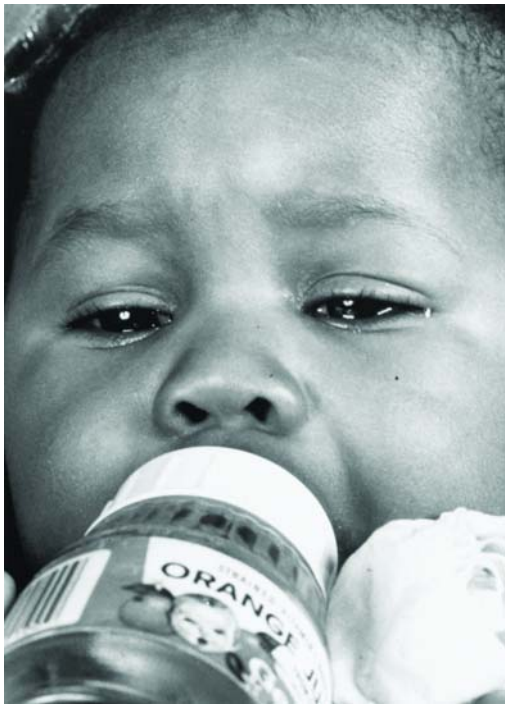

FIGURE 5

Child with exotropic-type Duane syndrome and tearing when eating. (Reprinted with permission from *Trans Am Ophthalmol Soc.*[34])

It is interesting that Arimoto's findings are similar to those of the Swedish thalidomide study. However, other reports on thalidomide investigations often do not even mention tearing symptoms or findings. One wonders whether the questions were asked. This absence of negative or positive history may also exist with the nonsyndromic Duane patients worldwide.

A further study of the Japanese experience was the report by Maruo and colleagues[33] of 266 cases of Duane syndrome between 1963 and 1979. Gustatory-lacrimal reflex was observed in 27 cases (10%). In this Duane series, there were 23 cases of thalidomide embryopathy.[33] Eighteen of the 23 cases of thalidomide embryopathy showed this type of aberrant tearing. The study by Uemura and associates[38] of congenital gustatory-lacrimal syndrome described 10 patients with the association of aberrant tearing, with Duane syndrome in all cases. Six of these individuals had seventh nerve involvement, and in 4 there was a history of thalidomide intake by the mother. There are some other cases from Japan reporting this association, and there may be some overlap of patients from the different studies.[31]

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%). The ratio of males to females in the total number was nearly 1:1. Although thalidomide may have been available in China during the time period of the report, there is no mention of thalidomide intake by the mother. In 2002 Zhang[30] reported 25 cases of tearing when eating that were associated with Duane syndrome. It is unclear how many were from the 1997 cohort. It was also noted that 15 cases were binocular. In general, if it was monocular tearing, it was associated with monocular Duane syndrome (Table 1).

Wildervanck syndrome (cervico-oculo-acoustic syndrome) is a rare syndrome characterized by Klippel-Feil malformation, sensorineural deafness, and Duane syndrome.63 Inheritance has not been clearly established but is seen predominantly in females, and the presence of only 2 parts of the triad may exist. Brik and Athayde46 reported a case of bilateral Duane syndrome, Klippel-Feil anomaly, and crocodile tears. A girl with the full triad and aberrant tearing while chewing was described by Haciyakupoglu and associates.47 Brodsky48 described a young girl also with the triad, who had no emotional tearing in either eye, crocodile tears in the left eye, and brain stem hypoplasia (Table 3).

It would certainly be intriguing and may be informative to study some of the unusual conditions associated with anomalous tearing, albeit a few may be a chance occurrence (Table 3). Branchio-oto-renal (BOR) syndrome is an autosomal inherited developmental complex characterized by branchial cleft cysts, renal anomalies, hearing deficits, and ear pits. Preisch and associates[51] reported a family of 3 cases of BOR syndrome, with 2 of the patients (father, daughter) having gustatory lacrimation with normal reflex tearing on Schirmer test. They alluded to other families with this syndrome in the literature with excessive but not classic

gustatory lacrimal tearing.[51] They noted no abnormal ocular motility in the family. However, in a report of BOR syndrome by Vincent and associates[64] of a case with 8q deletion, there was an association with Duane syndrome, but not abnormal tearing.

A teratogen, isotretinoin (Accutane), a vitamin A analogue used in the treatment of acne, has been frequently noted to have caused craniofacial and other malformations. Guirgis and associates[49] described a boy with restrictive external ophthalmoplegia, crocodile tear syndrome, and no emotional lacrimation. Karsenti and associates[15] also described a case of Duane syndrome, Brown syndrome, and crocodile tears. Nigan[50] reported a patient with Treacher-Collins syndrome (findings similar to Goldenhar syndrome), also with anomalous tearing.

Lack of emotional (psychic) tearing is another unusual form of anomalous tearing. It was present in some patients in our thalidomide and Möbius series. 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 (Table 4, first row). There was no mention of the presence or absence of emotional tearing in the large series by Maruo and associates[33] and Zhang.[29] However, the lack of emotional tearing has been noted in many cases in the literature.[7,9-11,23,43,48,49]

The recent Swedish thalidomide study (Table 5) was a multidisciplinary study with multiple areas of research interest. Because many members of the original cohort of Swedish patients with thalidomide embryopathy declined to participate in the new comprehensive study, our results are for only a subset of the patients, and thus there may be some bias in the results. One goal of the ophthalmologic aspects of the study was to add more information on tearing symptoms in the older age-group and to document in more detail tear function by doing a baseline Schirmer I test and repeating the test while the patient is chewing. Although there were some reservations about the accuracy and reproducibility of the numbers obtained in the Schirmer tests, certain findings were very interesting. Nine of 11 individuals with symptoms of tearing when eating had Duane syndrome; the findings in the Schirmer test of increased tearing greater than 10 mm after chewing was not as strong, yet still very suggestive. There were 7 patients with lack of emotional tears in this group, all of whom had Duane syndrome. Since our patients were aged 44 to 46 years, it would not be unusual to have some individuals with decreased tearing, but the surprise was that there seemed to be a greater number of individuals with Duane syndrome with a very low Schirmer score but no history of dry eyes. Of the 15 patients with decreased tearing, 8 patients had Duane syndrome, but 7 of these with Duane syndrome showed a 10-mm or greater increase on eating.

These observations raise interesting but unanswered questions. Do our routine adult patients with Duane syndrome have a greater prevalence of "dry eyes" with or without symptoms, and do some have increased tearing during eating that gives an overall total adequate tearing? Jacklin13 mentioned a patient with unilateral dry eye and crocodile tears who carried an apple to eat to relieve his low tearing symptoms. None of the patients without Duane syndrome who had 10 mm or more of wetting on the second Schirmer test had symptoms of tearing when eating. Many pediatric ophthalmologists stop seeing their patients with Duane syndrome as they grow older, because these patients come to accept their condition and believe there is no reason to be seen regularly, so we have little knowledge of their tearing characteristics.

The Möbius literature has little mention of tearing anomalies. One exception is an article by Amaya and associates,[42] in which they noted crocodile tears in 3 of 18 patients in their series on Möbius syndrome, but there was no mention of the status of emotional tears. However, the association of Möbius and aberrant tearing was strengthened in the Swedish Möbius study.[43,44] This prospective, multidisciplinary study was actually designed to explore the possible association of autism spectrum disorder (ASD) with a group of patients with similar findings to the early effect group of the Swedish thalidomide study (eg, sixth and seventh nerve involvement). Maternal pregnancy history in this Möbius study did not indicate exposure to drugs except in one patient. The findings were that autism syndrome was noted in a significant number of patients (6 of 25), and 4 of them had variations in tearing (Table 4, second row). A few patients had some increased tearing that seemed related to mild exposure from their facial nerve palsy, but this was not considered as aberrant lacrimation. The anomalous tearing symptoms in the Möbius study ranged from isolated lack of psychic tearing (n = 2) to no psychic tearing plus crocodile tears (n = 3) and crocodile tears alone (n = 1). A few others had abnormal, late-onset tearing or less severe symptoms.

In the interview of 28 patients with Möbius sequence (or their parents) at the Italian Möbius Support Group Meeting in 2007, further support of this association with abnormal lacrimation was noted. In response to our oral questions, 7 of 28 individuals reported some type of anomalous tearing (Table 6), and also some had a history of late onset of tearing. No Schirmer tests were done that might give more information as to the degree of dry eyes.

Möbius syndrome is thought to be more correctly termed *Möbius sequence,* since the term *sequence* defines a cascade of secondary events that occur after a single embryonic insult from heterogeneous causes. The accepted criterion is evidence of sixth and seventh nerve paralysis, although many other craniofacial and limb anomalies are frequently noted. Most cases are sporadic, and one theory is that Möbius sequence belongs to a group of "disruption syndromes," although various explanations are given for the causes of the disruption.[65-70] The explanation is that there is a vascular disruption at a similar time early in embryogenesis causing hypoxia, ischemia, edema, and hemorrhage followed by a sequence of secondary events. Supporting this concept are cases of Möbius sequence with a history of drugs or events that could cause a hypoxic episode, usually due to uterine contraction early in pregnancy. The drugs misoprostol and cocaine, along with chorionic villi sampling, have been associated with infants with Möbius sequence.[65,68-73]

Misoprostol is an abortifacient agent frequently used in South America for clandestine abortions. Many cases of Möbius sequence have been reported after unsuccessful attempts of abortions with misoprostol, in which the pregnant women describe 1 or 2 days of cramping and some bleeding, but no abortion.[45,74] Ventura and associates[45] have done extensive studies on patients with Möbius sequence, comparing systemic and functional findings in children whose mothers had taken misoprostol with findings in children with no gestational history of misoprostol exposure. Autism was noted in both groups, supporting the concept of Möbius sequence resulting

from different causes (Figure 6).[75] Recently at a Möbius Support Group party, Ventura asked families of children with Möbius sequence to respond to a questionnaire on tearing characteristics (Table 7). Findings from the 20 persons who agreed to participate support the conclusion that aberrant tearing occurs frequently with Möbius sequence, since 9 of 20 gave a history of crocodile tears, and 7 of 20 had lack of emotional tearing. There were also a number of parents who said the children had a decreased amount of tears. There was a history of misoprostol exposure in some but not all children with absent tearing.

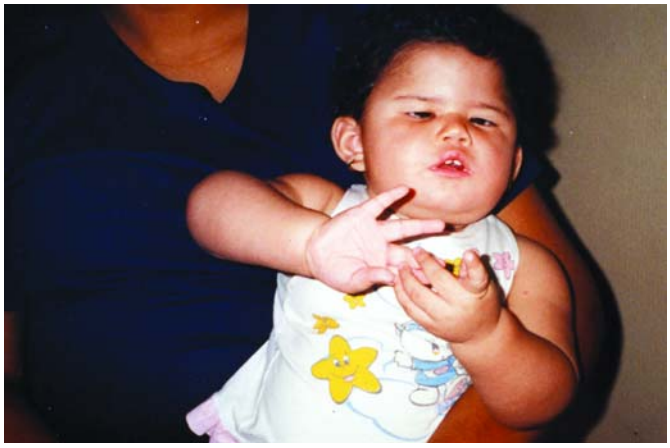

FIGURE 6

Patient from Brazilian Möbius study. Child has autism disorder, bilateral facial nerve palsy, and abduction deficits (sixth nerve). (Reprinted with permission from Miller MT, Strömland K, Ventura L, et al. Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review. *Int J Dev Neurosci* 2005;23:201-219.)

TABLE 7. RESULTS OF 2008 INTERVIEWS WITH THE BRAZILIAN MÖBIUS SUPPORT GROUP (n = 20)*

TYPE OF ANOMALOUS TEARING	NO.
Crocodile tears and absent emotional tearing	3/20
Crocodile tears only	6/20
Lack of emotional tearing only	1/20
Anomalous tearing with misoprostol exposure history	5/9†

*Age range, 2-19 yr; sex, 11 M, 9 F.
†Nine of 16 patients with Möbius sequence had history of misoprostol exposure, with 5 noting abnormal tearing; 4 had unknown history of misoprostol exposure.

Support groups are often not a true random sample of any characteristic or finding, so accurate prevalence data cannot be inferred, but they do offer the opportunity to find out information on large numbers of individuals with rare conditions. In the interviews conducted in Italy, Brazil, and the United States, there was strong evidence that anomalous tearing of both the paradoxical gustatory lacrimal type and lack of psychic tearing are common findings in Möbius sequence and that they may occur together or separately in any one patient with Möbius sequence. Additionally, the presence of autism syndrome is not a rare association.

There have been a number of speculations for the link between these forms of anomalous tearing with involvement of the sixth cranial nerve and, at times, the seventh cranial nerve. The most common explanation suggests a disturbance in normal development of the cells destined to form the sixth and seventh nerve nucleus and the superior lacrimal nucleus in the brain stem, which are thought to be in close proximity in early embryogenesis. Ramsay and Taylor[23] suggested that the most logical explanation of this combination 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 with facial nerve palsy, Duane syndrome, and aberrant tearing strongly support this theory of a nuclear location. There must 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 lack of emotional tearing. It appears that a variety of embryonic insults may affect these structures at the same crucial time in embryogenesis, resulting in the abnormal neurologic connections associated with Duane syndrome and aberrant tearing.

The time of the embryonic insult responsible for sixth nerve involvement and aberrant tearing in the thalidomide studies is quite accepted to be about days 21 to 24 after fertilization but seems to be slightly later in the Möbius-affected patients whose mothers took misoprostol in attempted but failed abortions (estimated time of gestation, 5 weeks). This raises the question of the relationship between Duane syndrome and the lateral rectus dysfunction seen in Möbius syndrome. However, the fact that 2 different teratogens can implicate a fairly definite time of action does not prove that adverse embryonic events at other times could not cause the same effect. There is probably a period in development in which the system is more plastic and a disturbance locally may lead to abnormal neurologic connections. Information on the length of this time period would give important information about developmental issues.

An important question is whether we are missing cases of anomalous tearing because we fail to ask specific questions about tearing of our patients with Duane syndrome, and because the parents or patients do not make the association between the ocular motility disturbance and abnormal tearing. Although the prevalence is probably higher than recognized, anomalous tearing is still not a common characteristic of Duane syndrome. It does, however, give us some insight into the time and location of the embryonic insult and, therefore, can be useful to better understand some developmental issues associated with Duane syndrome.

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PEER DISCUSSION

DR. MICHAEL C. BRODSKY: In this analysis, Dr. Miller accesses her vast database to estimate the prevalence of crocodile tears in children with Möbius sequence, a condition that has recently been classified as one of the congenital cranial dysinnervation syndromes.[1] This study is not a meta-analysis but a combined literature review, patient questionnaire, and ophthalmologic examination. The inherent limitations of this study are that it is mostly retrospective and largely historical. If anything, this methodology would underestimate the prevalence of the association in question. Dr. Miller elicits a history of crocodile tearing in 33 to 50% of patients with Möbius sequence.

So what can we learn from this study? First, it is clear that crocodile tearing is an overlooked ophthalmologic sign of the Möbius sequence. After reading Dr. Miller's study, I examined a child with Möbius sequence and asked the mother if there was crocodile tearing. The mother said, "I don't think so, but I've always wondered why we his nose runs and why we are always wiping it every time he eats." Second, the range of stimuli that elicit this response in children with Möbius sequence still need to be elucidated. Third, we need to determine the range of conditions in which aberrant tearing can occur. The phenomenon of crocodile tears could even explain some cases of "refractory" congenital nasolacrimal duct obstruction.

As with any good study, Dr. Miller's paper raises as many questions as it answers. Can exposure to the known teratogens for Möbius sequence produce crocodile tears as an isolated condition? Do crocodile tears signify aberrant innervation (as in Duane syndrome) or augmentation of a normal physiologic synkinesis? Is the crocodile tearing of Möbius sequence a central or peripheral phenomenon? Jampel and Titone[2] considered the congenital gusto-lacrimal syndrome to result from failure of dispersion and differentiation of cells within the salivatory and lacrimal nuclei, which lie in close juxtaposition within the pons.[3] Is the clinical expression of this synkinesis related to the timing or severity of injury? Is the observed response taste-specific (biochemical), stimulus-specific (eating), or psychic (thinking about food)? Does the finding of crocodile tears correlate with congenital corneal anesthesia, another recognized component of the Möbius sequence?[4] Do these patients have an underproduction of baseline tears? How often is crocodile tearing present in patients with unilateral Duane syndrome?

In conclusion, Dr. Miller has demonstrated that crocodile tearing is an integral component of the Möbius sequence. As ophthalmologists, we need to be more attuned to crocodile tearing, study its pathophysiology, determine its range of clinical expression, and examine its prevalence in other congenital cranial dysinnervation syndromes.

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DR. IRENE H. LUDWIG: Several years ago, I had the opportunity to examine a large series of children with congenital central hypoventilation syndrome, Ondine's Curse. I was struck by the similarity of eye findings in these children to those in Dr. Miller's series of thalidomide patients. This leads me to believe that perhaps there is a teratogenic cause of the congenital central hypoventilation syndrome. Our patients had strikingly high rates of attention deficit disorder, autism, and convergence insufficiency. I was wondering if you saw any of these traits in your group.

DR. BARTLEY R. FRUEH: I have no conflicts of interest, but just a comment about crocodile tearing. We see this in my practice largely in adults who have had VII nerve injuries with aberrant regeneration. We have determined that injecting Botox® into the lacrimal gland can alleviate the symptoms of crocodile tearing. I wondered if this might also be helpful for these congenital cases.

DR. MARILYN B. METS: I am going to make a tangential comment about teratogenesis. I believe that it is important to take every opportunity to make people aware of teratogens and to prevent their complications. I am referring to an organism called lymphocytic choriomeningitis virus, which is harbored in mice and hamsters and can produce dramatic CNS abnormalities, as well as visual abnormalities. I mention this so members will know to tell their patients or relatives who are young and having children that they should not purchase a pet, such as a mouse or a hamster for their four or five year olds, if they are planning on having more children. These rodents can expose the pregnant woman to the organism and have dramatic effects on the unborn child. Thank you.

DR. MARILYN T. MILLER: Thank you, Dr. Brodsky and all of the discussants for your very interesting comments. I think I am going to start with the last comment first, Dr. Brodsky. Interestingly enough, if you have unilateral tearing and unilateral Duane syndrome they always occur on the same side. The literature does have cases of unilateral presentation, but you do not see a unilateral ptosis in one side and a unilateral Duane on the other, so I think that even brings us closer. I reviewed the published findings of congenital corneal anesthesia and they just do not seem referable to this group of patients. Furthermore, the corneas are really normal in our patients with congenital aberrant tearing. We do a very superficial test of corneal sensation, and it is normal. The question of taste specific is also reported in the published literature; however, and I did not have the time to discuss this topic. Some patients lacrimate only when they taste sour food. Some will not tear if they chew, but only if they experience a specific taste sensation. One patient told us that she really cried when eating an apple. We confirmed this by observing her cry profusely while she ate an apple. Regarding the comment on the acquired form of the condition, I also did not have time to discuss this. I believe that the most common cause of aberrant tearing with the crocodile tears is acquired facial nerve injury and occurs about 4 to 6 months after the injury. This paper dealt only with the congenital type because the explanation is different with respect to the neurological implications. I believe the congenital form is central in origin mostly because of the combination with VI and VII and the development at a certain time. We do not completely understand neurological development or why an insult at a certain time results in really two aberrant innervational situations, Duane syndrome and aberrant tearing. I certainly agree that there is a wide range of symptoms. I do not know if this might be related to refractory nasal duct problems.

Dr. Ludwig, we have talked about this often, although I think I previously discussed autism. Autism is present in this condition. Since this was a thalidomide study, we evaluated for Möbius syndrome and were not looking for other findings. There is a 24% prevalence of the autism spectrum disorder in Möbius syndrome. In the Brazil group that included patients with a history of misoprostol and those of unknown etiology, we observed autism spectrum disorder in both subsets of patients. The whole autism spectrum disorder is present in all of these. I mentioned the acquired form, and I agree with Marilyn that we should be attuned to dangers of potential teratogens. They are very difficult to identify because so often they are not very teratogenic. A combination of teratogens, genetic predisposition, and other environmental factors may result in a syndrome, the cause of which is very difficult to determine in a series.