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Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review

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Abstract

Autism is a complex developmental disorder without an established single etiology but with significant contributions from genetic studies, functional research, and neuropsychiatric and neuroradiologic investigations. The purpose of this paper is to review the findings in five studies involving individuals manifesting the characteristic findings of autism spectrum disorder associated with malformations and dysfunctions known to result from early embryogenic defects. These investigations include two associated with teratogens (thalidomide embryopathy, Möbius sequence with misoprostol) and three (most Möbius sequence cases, CHARGE association, Goldenhar syndrome) with no known etiology.

These studies suggest that early embryonic development errors often involving cranial nerve palsies, internal and external ear malformations, ophthalmologic anomalies, and a variety of systemic malformations may be associated with autism spectrum disorders statistically more frequently than expected in a normal population. Although the exact time of developmental insult for each condition cannot be identified, the evidence is that it may occur as early as week 4 to 6+ of embryogenesis.

Keywords: Autism; Autism spectrum disorders (ASD); Thalidomide embryopathy; Möbius sequence; Misoprostol

1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in social interaction and communication, and associated with repetitive behaviors and interests. There are several clinical ASD phenotypes, including autistic disorder/childhood autism, Asperger syndrome, and atypical autism (also referred to as autistic-like condition and pervasive developmental disorders not otherwise specified, or PDD NOS). The pathophysiology of ASD remains elusive, with clues from genetic studies, neurochemistry, autopsy reports, functional research, radiological imaging, research on environmental influences, and many other approaches. The purpose of this paper is to summarize studies in which ASD was present in individuals with conditions and malformations involving brainstem and systemic structures known to result from early embryonic

Abbreviations: ASD, autism spectrum disorder; CARS, childhood autism rating scale; CHARGE, colobomas, heart defects, choanal atresia, retarded growth or development, genital anomalies, and ear abnormalities and/or hearing loss; DSM, diagnostic and statistical manual of mental disorders.

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damage. It is hoped that this information might add another piece to the puzzle of autism by describing associated developmental errors in some individuals with characteristics of ASD.

The tragic thalidomide epidemic of the 1960s resulted in an estimated 10,000-affected fetuses and about 6000 reported live births (Lenz and Knapp, 1962; Lenz, 1986). The drug was distributed worldwide and, because of many informative cases in which the time of drug intake was known, it was determined that the teratogenic sensitive period extended from day 20 to day 36 after fertilization (34–60 days post last menstrual period) (Lenz and Knapp, 1962; Lenz, 1986). Since the drug is rapidly hydrolyzed the teratogen effect is short unless there is continual intake. From the data in the literature, it was known that early exposure with the drug (days 20–25) resulted in involvement of the cranial nerves (especially 6 and 7), external ear, abnormal ocular movement, aberrant lacrimation, and thumb anomalies (Fig. 1). Later exposure caused upper limb and eye malformations, systemic anomalies, and finally lower limb malformations and triphalangeal thumbs (Papst, 1964; Papst and Esslen, 1964; Nowack, 1965; Kida, 1987; Arimoto, 1987).

Some systemic malformations were responsible for spontaneous abortions and early neonatal death, but the critical period for development of systemic anomalies was more difficult to determine, although many appeared to be in the middle of the sensitive period.

During a court trial in the 1960s approximately 100 Swedish children were identified as showing malformations associated with exposure to thalidomide at an early time in their mothers' pregnancies (Strömland and Miller, 1993). Multiple studies ensued in Sweden involving different medical subspecialties (d'Avignon and Barr, 1964; Winberg, 1964; Zetterström, 1966). Between 1989 and 1991, Strömland and Miller (1993), pediatric ophthalmologists, conducted an evaluation of 86 individuals of this original cohort with thalidomide embryopathy, all of whom were then 27–29 years of age. The aim of the study was to describe the ocular motility dysfunctions (strabismus) and other eye anomalies or visual disturbances. From their observations and the known timetable in the literature, the authors concluded that the ophthalmologic and cranial nerve dysfunction involving ocular structures occurred from thalidomide intake in the early sensitive period (Miller, 1991; Miller and Strömland, 1991; Strömland and Miller, 1993). Four individuals were noted to have autism associated with ocular motility and facial nerve involvement typical of the early sensitive period (Strömland et al., 1994).

Intrigued by the association of autism with an uncommon type of strabismus and facial nerve palsy, the literature was reviewed for other conditions with similar findings, and a few articles were identified that described a connection between Möbius syndrome and autism (Ornitz et al., 1977; Gillberg and Winnergärd, 1984; Gillberg and Steffenburg, 1989). To further study this association, a multidisciplinary team initiated a prospective study from 1995 to 1998 of 25 Swedish individuals with Möbius sequence.

Möbius "syndrome" has more recently been designated "Möbius sequence," since the term "sequence" defines a cascade of secondary events that occur after a single embryonic insult from heterogeneous causes. Möbius sequence may be seen with a variety of systemic and functional anomalies, but the most accepted clinical criterion for Möbius sequence is evidence of congenital sixth and seventh cranial nerve involvement. Commonly associated anomalies include other cranial nerve involvement, limb defects, usually the amputation or hypoplastic type; craniofacial anomalies involving the tongue and lip, and pectoralis muscle defect (Poland anomaly). Several possible etiologies have been suggested for some cases of Möbius sequence, but most appear to be sporadic (Ziter et al., 1977). The systemic and ocular findings of the 25 Swedish study patients were fairly consistent with those in the literature, and the presence

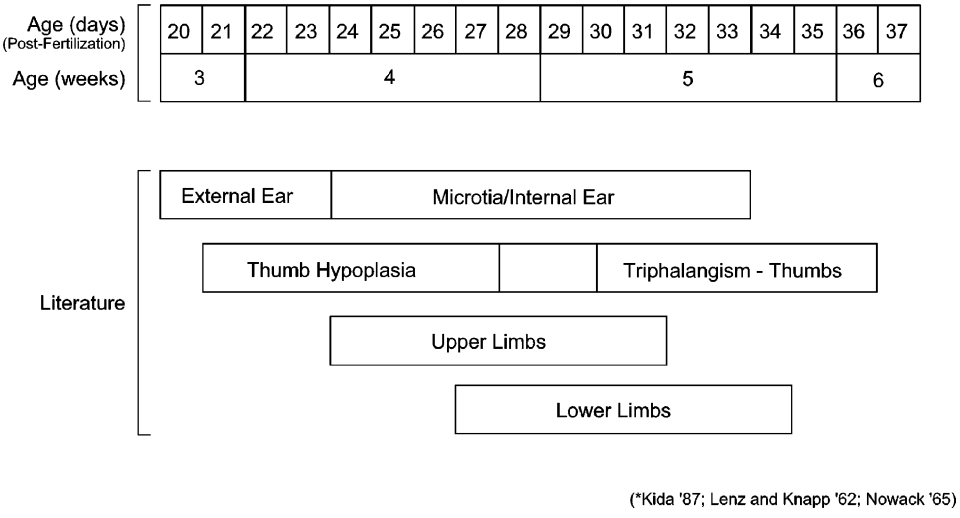

Fig. 1. Thalidomide embryopathy: the historical timetable (literature).

of characteristics of ASD in a significant percentage of patients reaffirmed the previously reported association (Johansson et al., 2001; Strömland et al., 2002).

After the Swedish Möbius study, the multidisciplinary team decided to pursue more clinical research on conditions that had a reported association of ASD with craniofacial or other systemic anomalies. They selected Goldenhar syndrome (oculo-auriculo-vertebral dysplasia syndrome, OAV, hemifacial microsomia, HFM) and the CHARGE association because of case reports of autism in these conditions by Landgren et al. (1992) and Fernell et al. (1999). The study was initiated in 1995.

An ''association'' is defined as a non-random occurrence of congenital malformations that are collectively seen together more often than would be statistically expected. The CHARGE association is one example, and the acronym, suggested by Pagon et al. (1981), signified the frequent presence of colobomas, heart defects, choanal atresia, retarded growth or development, genital anomalies, and ear abnormalities and/or hearing loss. More studies have expanded the observed malformations and possible diagnostic criteria (Davenport et al., 1986; Oley et al., 1988; Blake et al., 1998; Tellier et al., 1998). A number of cases have been found to have chromosomal anomalies, which confuses the basic definition of what is an association and what is a chromosomal or other single etiology syndrome (Källén et al., 1999). Graham (2001) suggests there may be a true syndrome within the CHARGE association.

Hemifacial microsomia (HFM) is a descriptive term used by Gorlin et al. (1952, 2000) to characterize a group of patients who manifest a spectrum of malformations involving the ear, mandible, mouth, eye, and often, cervical spine. It occurs unilaterally in most, but not all, patients. It is usually sporadic but family occurrences, especially with only a few anomalies, are reported (Rollnick and Kaye, 1983). Goldenhar syndrome has been felt by many to represent a subset of HFM (Gorlin et al., 2000). Goldenhar (1952) had described a number of patients with a combination of epibulbar dermoids, lipodermoids, and preauricular skin tags and fistula. Later, upper lid coloboma, facial, and vertebral anomalies became appreciated as part of the syndrome. Duane syndrome has been reported in a number of patients with Goldenhar syndrome, but is not a common characteristic (Miller, 1985). Poswillo (1973) has suggested from animal experiments that a hematoma at the time and site of fetal artery development may be one etiologic factor for HFM. A report of autistic behavior in two girls with Goldenhar syndrome, plus the fact that the clinical characteristics of Goldenhar had some similarity to those in Möbius sequence and thalidomide embryopathy, prompted the inclusion of this syndrome in the new study (Landgren et al., 1992).

In the early 1990s there appeared in the Brazilian literature case reports of infants born with malformations involving limbs, cranial nerves, and other anomalies following self-induced but failed abortions (Fonseca et al., 1991, 1993; Costa and Vessey, 1993; Genest et al., 1999; Coêlho et al., 1991, 1993, 1994, 2000). The abortifacient drug utilized was misoprostol (Cytotec®), a prostaglandin type E analogue. In some of these reports the children exhibited the typical findings of Möbius syndrome with and without limb anomalies (Gonzalez et al., 1993, 1998; Blanchard et al., 1998; Marques-Dias, 1999). The lessons learned from the previous Swedish study on Möbius and the Brazilian reports prompted the design of a prospective multidiscipline study in Brazil by Ventura (2001).

The purpose of the Brazilian Möbius sequence study was to be both descriptive of malformations and functional disorders in these patients, and to address the hypothesis that there was a different gestalt and prevalence of malformations in patients with no known etiology compared to those patients with a history of misoprostol intake during the mother's pregnancy. There was also a particular interest in whether ASD occurred in any patients, and if so, whether it was present in both groups.

2. Methods

2.1. Swedish thalidomide study (1987–1989)

From 1987 to 1989 a study was conducted to document the ocular findings of 86 thalidomide affected Swedish individuals who were then 27–29 years of age. The study targeted the ophthalmologic findings, but the history and medical records summarizing the systemic findings were also included in the data collection. There were about 100 patients originally affected, but a few had left the country, died of other causes, or refused examination. However, the medical records of the 14 unexamined patients were available and there did not seem to be any evidence that they represented a group with significantly different characteristics. Information from previous studies on this group of patients done by other disciplines was reviewed. The ophthalmologic exam consisted of the usual comprehensive clinical evaluation that involved visual acuity, ocular motility, refraction, and examination of the anterior and posterior segments of the eye. The mothers were not available, so there was little direct information on when and how much thalidomide was taken. There was particular interest in the finding of aberrant lacrimation, which included either tearing when eating and/or lack of emotional tearing. This unusual finding was particularly prevalent in this group of patients. All of the systemic and ocular exams were done on a database determined before the onset of the study.

At the end of the study three mentally retarded and deaf patients who showed the classic symptoms of autism were examined. Since the ophthalmologists were not trained to do a formal psychiatric evaluation, a team of psychiatrists subsequently evaluated these three individuals, and two more with reported similar behavior. They confirmed that

four of these these individuals met the criteria for autism (Strömland et al., 1994).

2.2. Swedish Möbius study (1995–1998)

The Swedish Möbius study was designed as a prospective multidiscipline study. The team included ophthalmologists, neuropsychiatrists, neurologists, pediatricians, dentists, otolaryngologists, speech and language therapists, and in some patients, orthopedists.

The team identified 25 patients who met the study criteria of Möbius sequence manifesting (1) congenital facial nerve paresis (7th cranial nerve), either unilateral or bilateral, and (2) congenital limitation of abduction (6th cranial nerve), unilateral or bilateral. Tongue and limb anomalies, pectoralis muscle defects, cleft palate, and other problems were common, but were not included in the entry criteria. All of the medical records of these children were available, so other health problems were known.

A detailed history seeking information of adverse pregnancy occurrences was taken and the medical records were reviewed by an obstetrician for additional information. The patients were only available for one day by the whole team, but some of the psychiatric and other evaluations were done at different times. A common protocol was used for the history and clinical evaluation, and photographic and videotape documentation was done when possible. Radiological evaluations such as MRI and CT were available only on ten patients.

Psychiatric examinations were performed on children old enough to be formally evaluated. It included a structured and semi-structured interview utilizing the diagnostic and statistical manual of mental disorders, third edition, revised (DSM-III-R) (American Psychiatric Association, 1987), childhood autism rating scale (CARS) (Schopler et al., 1980, 1988), Autistic Behavior Checklist (ABC) (Krug et al., 1980), and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1993). The criteria for childhood autism listed in the World Health Organization's (1992) International Classification of Disease and disorder (ICD-10) were checked as operationalized in the ADI-R. Assessment of mental development was based on clinical observation of patients and test results (including appropriate developmental/intelligence tests).

2.3. Swedish charge study (1998–2002)

A multidiscipline study in Sweden evaluated patients referred by the medical profession with a diagnosis of CHARGE association or with a registered diagnosis of CHARGE. Although the literature is not consistent as to what clinical characteristics are necessary to make the diagnosis, the original description of CHARGE association (coloboma, heart, choanal atresia, retarded growth and/or development, genital hypoplasia, and ear anomalies and/or deafness) was used to establish the key characteristics. Most patients had four characteristics, but patients with three, and other commonly associated systemic anomalies were also included. Thirty-one of 33 referred/registered patients were considered to meet the minimal requirements for CHARGE association. The examinations were done on one day by the multidisciplinary team, except for the psychiatric examination, which required further contact with the family and was completed at a later time. The same methodology as in the Swedish Möbius study was utilized, plus completion of the DMV-IV criteria (American Psychiatric Association, 1994). The ophthalmic and systemic evaluations were performed with predetermined protocols similar to the Swedish Möbius study, and by essentially the same team.

2.4. Swedish hemifacial microsomia/' (oculo-auriculo-vertebral, OAV, HFM) syndrome study (1998–2002)

The Goldenhar study was done concurrently with the CHARGE study, and by the same multidisciplinary team. While the database to be collected was essentially the same, there were certain modifications because of the differences in clinical characteristics of these two entities. Vertebral anomalies, ocular dermoids, and mandible hypoplasia are characteristic of the Goldenhar syndrome, but not as frequent in the CHARGE association. In contrast, ocular coloboma, genitourinary, and cardiovascular malformations are frequently noted in the CHARGE syndrome. However, a comprehensive exam was done on all patients; the summary tables represent the frequently-associated anomalies. In the neuropsychiatric evaluation, the same methodology as in the CHARGE study was utilized.

In the neuropsychiatric evaluations of all individuals reported in this paper, care was taken to remove items and criteria in diagnostic instruments when scoring that might be affected by cranial nerve palsy and severe visual and hearing impairment (e.g., items and criteria concerned with facial mimicry, eye-contact, and intonation of speech).

All Swedish studies were approved by relevant ethics committees.

2.5. Brazilian Möbius study 2000–2001

A prospective multidiscipline study was performed in Pernambuco, Brazil and northeastern area of Brazil. Detailed pregnancy and social history was done, with particular attention to the timing, dosage, and method of taking misoprostol or other abortifacient drugs. The inclusion criterion of Möbius sequence was evidence of involvement of the 6th and 7th cranial nerves.

The study was initiated in August 2000, and most of the patients were recruited in the first 6 months. Of the 31 patients presented with a possible diagnosis of Möbius, 28 met the criteria of the study. The patients were divided into two groups. Group 1 was composed of children *without* known exposure to misoprostol, and group 2 were children *with* a history of misoprostol exposure by their mothers in

early pregnancy. Detailed social, demographic, and psychological data were obtained on 26 patients and ophthalmologic data on 28 patients. Initially, the mother was interviewed and a database was gathered about the pregnancy, including medical history, genetic background, and drug exposure. The importance of truth and confidentiality, and the purpose and methods of the study were explained to the mother and an informed consent was signed. The investigators had some concern that there might be reluctance on the part of the mother to admit to taking the drugs. However, the observation of the team was that most mothers were very desirous of discussing their problems with a non-judgmental medical staff. On separate days the children were examined by a multidiscipline team representing pediatric, ophthalmology, neurology, cardiology, otolaryngology, dentistry, genetics, psychiatry, speech and language, and radiology specialties. All examinations were performed using a preset, constant database similar to that of the Swedish Möbius study.

Psychiatric and intellectual evaluations were performed on children old enough to be formally evaluated. It included an interview utilizing the Diagnostic and Statistical Manual (DSM-IV) (American Psychiatric Association, 1994) and childhood autism rating scale (CARS) (Schopler et al., 1988).

The study met the requirements established by the Brazilian National Health Council for Research in Humans.

3. Results

3.1. Thalidomide

Table 1 summarizes the most common systemic anomalies observed in the Swedish thalidomide study. Table 2 shows the ocular findings and aberrant innervation. The most frequently observed ocular motility abnormality was Duane syndrome, a type of ocular motility disturbance that is felt to be caused by paradoxical innervation of the lateral rectus muscle by a branch of the third nerve, and usually combined with a sixth nerve palsy of nuclear origin that would affect abduction of the eye (Duane, 1905; Hoyt and Nachtigaller, 1965; Huber, 1974; Hotchkiss et al., 1980; Miller et al., 1982). The typical clinical findings are limitation of abduction associated with narrowing of the palpebral fissure on adduction caused by co-contraction of the medial and lateral rectus muscles from the aberrant innervation. There are often associated varying degrees of decrease in adduction of the eye. The striking finding in the thalidomide study was that 44% of the patients showed this incomitant type of strabismus typical of Duane syndrome or an accepted variant. Facial nerve palsy, external ear anomalies, and aberrant lacrimation were frequent associated findings in these patients with Duane syndrome. Limb malformations were the most prevalent finding in the study, with the most common being hypoplastic deformities of the thumb, followed by upper, than lower limb anomalies and an unusual finding of triphalangeal thumbs.

Table 1
Swedish thalidomide study "cranial nerve, systemic malformations and functional problems" (n = 86)

Cranial nerve involvement	No. (%) affected
Abducens (6th)	37 (44%)
Facial (7th)	17 (20%)
Hypoglossal (12th)	16 (19%)
Systemic malformations	
Thumbs	70 (89%)
Upper limb (excluding thumb)	59 (69%)
Lower limb	21 (24%)
Ears/hearing	33 (38%)
Kidney[a]	12 (14%)
Cardiovascular[a]	7 (8%)
Chest/lung[a]	4 (5%)
Genitalia[a]	3 (3%)
Anal atresia[a]	4 (5%)
Choanal atresia[a]	2 (2%)
Dental anomalies[a]	4 (5%)
Functional problems	
Mental retardation (moderate to severe)	5 (6%)
Autism	4 (5%)

[a] By history or medical record.

Table 2
Swedish thalidomide study ocular anomalies in Swedish thalidomide study

Anomaly	No. (%) affected
Strabismus (n = 84)	
Incomitant strabismus—Duane syndrome and variants	37 (44%)
Horizontal comitant strabismus (all esotropia)	6 (7%)
Aberrant lacrimation	17 (20%)
Coloboma (uveal or optic disc)	4
Microphthalmos	3
Myelinated nerve fiber or ptosis	2
Glaucoma, lipodermoid or hypertelorism	1

Table 3 summarizes the findings in the four patients who had autistic disorder. The same constellation of early thalidomide effects, i.e. external ear, incomitant strabismus, facial nerve palsy, and aberrant lacrimation were present in most of these patients. An upper limb anomaly (unilateral) was noted in only one patient (Fig. 3).

Using the thalidomide timetable from the literature (Fig. 1), each patient with Duane syndrome was matched with the malformations on the timetable, and the observation was that they all fell in the category of early thalidomide effect. The same was done for facial nerve palsy, lacrimation, and autistic disorder, and they also represented early thalidomide effects. A summary of the timetable of these anomalies and functional disorders is shown in Fig. 2.

3.2. Swedish Möbius study

The age of the 25 patients (18 male, 7 female) ranged from 1 month to 55 years. Table 4 summarizes the prominent findings. Sixteen patients showed involvement of the 12th

Table 3
Patients with autism spectrum disorders: Swedish thalidomide study

Age (year)/sex	Strabismus horizontal pattern	Facial nerve palsy	Abnormal tearing	External ear anomalies	Hearing	Autism type	Mental retardation (iq)	Comments
31/M	Duane syndrome	+	+ (No emotional tears; + tearing while eating)	++	Deaf	AS, CA	++ (<20)	Unilateral upper limb anomaly, mute, self-mutilating, good motor skills
31/M	Duane syndrome	+	+ (No emotional tears; + tearing while eating)	++	Deaf	AS, CA	++ (20–34)	Good visual memory, mute, compulsive behavior
31/F	0	+	0	++	Deaf	AS, CA	++ (35–49)	Mute, self-mutilating, ritualistic
30/F	Duane syndrome	0	0	++	Deaf	AS, CA	+ (50–69)	Absorbed in routine compulsive activity, epilepsy, can do routine self-care

M: male; F: female; +: present; external ear anomalies: (++) present both ears; 0: not present; AS: autism syndrome [diagnostic and statistical manual of mental disorders, third revised edition [DSM-III-R]; CA: childhood autism rating scale (CARS); IQ: intellectual quotient; mental retardation: (++) severe, (+) moderate.

cranial nerve (hypoglossal). The more frequent oral-facial anomalies were tongue malformations, mandibular hypoplasia, cleft lip or palate, and microglossia, but other malformations were noted. Limb anomalies were present in 10 patients, the most common being clubfeet, which was an isolated finding in some but associated with hand malformations in a few (syndactyly or hypoplasia). Two infants had Poland syndrome with absence of the pectoralis muscle in combination with ipsilateral syndactyly or hypoplasia of the hand. Functional complications were frequently severe, and included speech problems, poor sucking in infancy, difficulty swallowing, and hearing deficit. Tearing irregularity existed by history in seven patients, ranging from lack of isolated emotional tearing, no emotional tearing plus aberrant tearing, and late onset and mild abnormalities. Two cases had unilateral 5th cranial nerve palsy (trigeminal), but did not have aberrant lacrimation. Twenty-two of the 25 patients were more than 2 years of age and had a comprehensive neuropsychiatric examination (Table 5). Six of these (five males and one female) fulfilled both the DSM-III-R criteria for autistic disorder and the ICD-10 criteria for childhood autism (Fig. 4). One woman had an autistic-like condition. Two patients were too young for evaluation of mental level. Mental retardation was evident in eight patients, five with IQ < 50 and three with IQ in the 50–70 range. More details of this study have been reported elsewhere (Miller and Strömland, 1999a; Sjögreen et al., 2001; Strömland et al., 2002; Johansson et al., 2001).

Since there was special interest in any adverse occurrences in the pregnancy that might give etiologic insights, a detailed pregnancy history and examination of the obstetrical record was performed. Eight women reported bleeding in pregnancy, but only four in early pregnancy; one had chorionic villi samples done at embryonic week 7; seven had previous spontaneous abortion, six of these having multiple ones.

Ocular motility evaluation in those able to be examined showed not only the inclusion criteria of significant limitation of abduction, but many also had limitations of adduction.

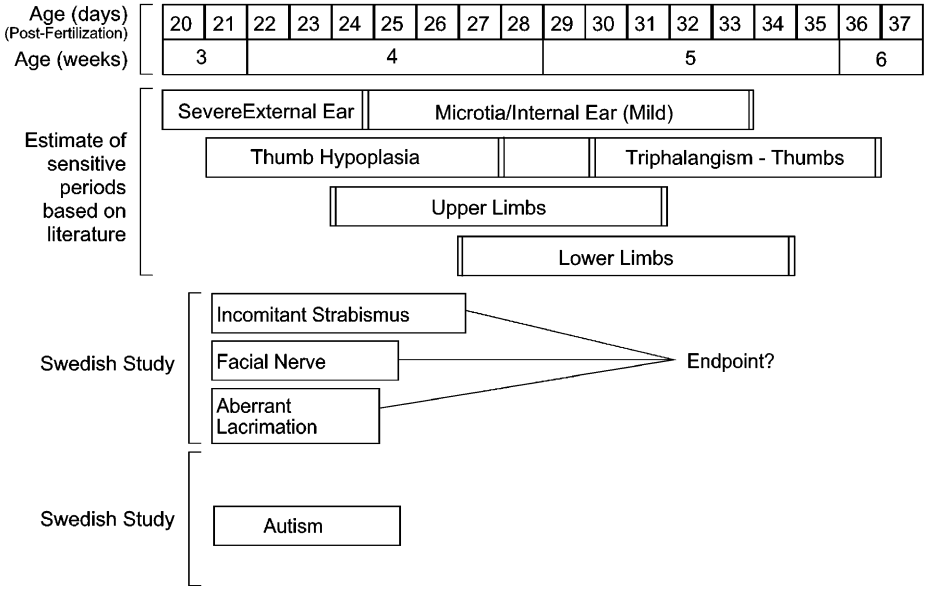

Fig. 2. Swedish thalidomide study: observed malformations compared to literature timetable.

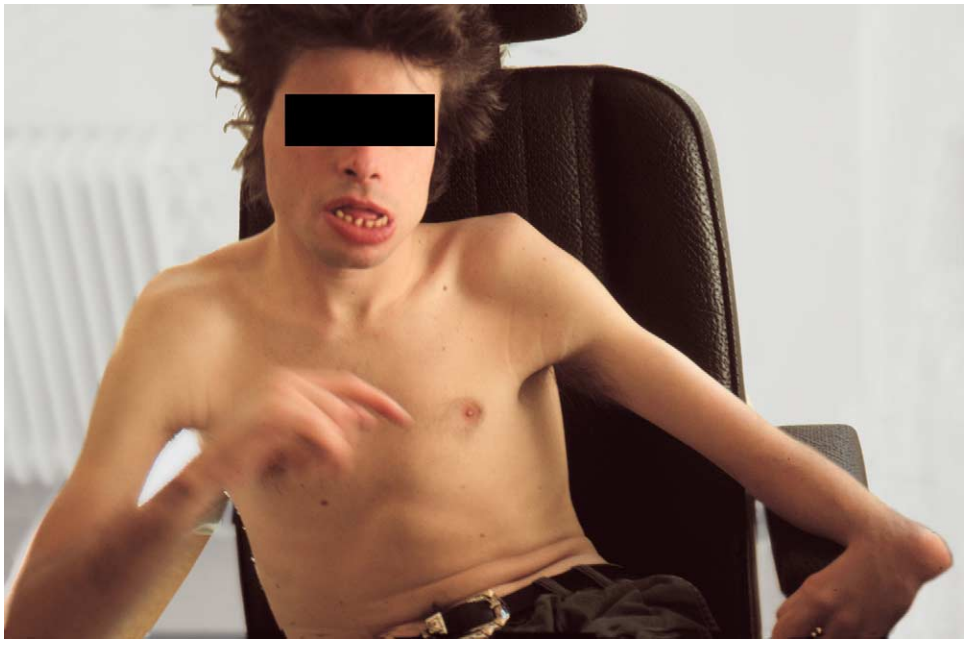

Fig. 3. Thalidomide embryopathy: patient has autism, asymmetric facial palsy, Duane syndrome, and upper limb anomalies.

3.3. Swedish charge study

Of the 31 patients that met the minimum characteristics for the CHARGE association, 15 were males and 16 females, 2 were siblings, but the remaining cases were sporadic. The age range was from 1 month to 31 year, with the median about 7 years. Twenty-eight had ocular colobomas, of which 12 also had microphthalmus both unilateral and bilateral, and one case had only microphthalmus. Severe visual impairment was common. Sixteen patients had cardiovascular anomalies, persistent ductal arteriosus being the most frequent anomaly. Vestibular symptoms were surprisingly frequent. The ear anomalies and hearing loss included a ''characteristic CHARGE ear,'' other external ear malformation, and involvement of the inner ear structures. Twenty-five had chromosomal analysis and were found to be normal. Table 6 is a summary of the systemic and functional findings associated to ASD.

Of the 26 patients able to be evaluated for their psychiatric condition, five met the criteria for autistic disorder (DSM-III-R and DSM-IV) and the ADI-R algorithm criteria for childhood autism. Five patients had an autistic-like

Table 4
Swedish Möbius sequence study ''cranial nerve, systemic malformations and functional problems'' (n = 25)

Cranial nerve involvement	
Abducens (6th)	25/25
Facial (7th)	25/25
Hypoglossus (12th)	16/25
Tearing abnormalities (5th)	7/25
Systemic malformations	
Cleft lip/palate/uvula	7/25
Mandibular hypoplasia	8/25
Microglossia	7/25
Limb malformations (7 club feet)	10/25
Tongue (7 microglossia)	18/25
Poland syndrome	2/25
Functional problems[a]	
Mental retardation (MR)	7/22
Speech	17/22
Dysphagia	14/24
Sucking in infancy	11/24
Autism spectrum disorder (AD, ALC)	7/22
Hearing	5/19

AD: autistic disorder, ALC: autistic-like condition.
[a] Some functional problems were unable to be tested because of age or cooperation.

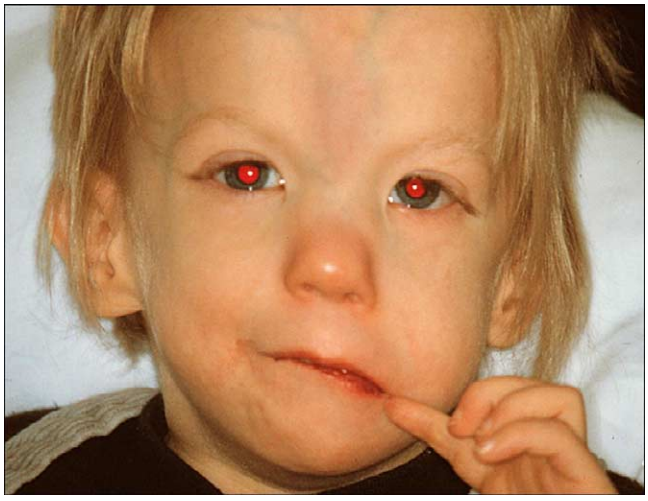

Fig. 4. Swedish Möbius study: patient with autism, asymmetric facial palsy, straight eyes in primary position, but marked limitation of both abduction and adduction.

Table 5
Patients with autism spectrum disorders Swedish Möbius study

Case	Age (year)/sex	Strabismus			Facial nerve palsy	Other cranial nerves	Abnormal tearing	Tongue anomaly	Autism type	Mental retardation	Comments
		Primary	Adduct defect	Abduct defect							
1	4/F	Esotropia	0	++	++	10	0	+	AD, CA	++	Club feet, seizures, sucking problems
2	8/M	Esotropia	0	R > L	++	5 (R)	0	0	AD, CA	++	Corneal scar, poor balance
3	14/M	Straight	++	++	L > R	12	+	+	AD, CA	++	Mute, ear anomaly, epilepsy, decreased hearing, normal MRI, dental anomalies
4	15/M	Small Esotropia	++	++	++	12	+ (No emotional; + when eating)	+	AD, CA	+	Mute, uses sign language, micrognathia, hypoplasia of the pectoralis muscle
5	17/M	Small esotropia	++	++	++	12	+ (No emotional)	+	AD, CA	++	Mute, mild decreased hearing, sucking problems in infancy, mild ptosis, cerebral palsy, micrognathia
6	22/M	Small esotropia	++	+	++	0	+ (No emotional)	0	AD, CA	+	
7	1.7/M	Esotropia	+	++	++	12	0	+	AD, CA	++	Club feet, sucking problems in infancy, eating difficulties
8	55/F	Large angel esotropia	0	++	++	0	0	+	ALC	+	Decreased hearing

M: male; F: female, strabismus: (++) marked decrease abduction or adduction, (+) minimal defect; tongue anomaly: (+) present; 0 = not present; autism type: AD: autism disorder, CA: childhood autism, ALC: autism-like condition; mental retardation: (++) severe, (+) moderate.

condition. All but one of the patients with ASD had mental retardation. A comprehensive report of the clinical and autism data will be described elsewhere (Strömland et al., 2004).

3.4. Goldenhar (oculo-auriculo-vertebral, OAV) syndrome study

In the 18 patients in this study, ear anomalies and functional deficits were frequent but varied (microtia, tags and fistula, abnormal shape, hearing defect). These anomalies plus a number of cases with microstomia, facial asymmetry, and vertebral anomalies made the presumptive diagnosis of hemifacial microsomia. The presence of epibulbar and ocular dermoids put most into the Goldenhar subgroup of hemifacial microsomia. Facial nerve palsy, cardiovascular anomalies, gastrointestinal and genitourinary problems showed the wide spectrum of less common associated conditions.

Two children met the criteria for autistic disorder (DSM-III-R, DSM-IV) and the ADI-R algorithm criteria for childhood autism. Both these children were mentally retarded, one very severely. One further child was diagnosed as manifesting characteristics of an autistic-like condition with average IQ. Table 7 summarizes the associated findings in these cases. A comprehensive report will be described in the future.

3.5. Brazilian Möbius/misoprostol study

Table 8 shows a summary of the pregnancy findings in the 28 patients in the Brazilian Möbius study group. The most used drug to induce abortion was misoprostol reported by 17 patients (group II). In 10 cases they used misoprostol only and in 4 cases they used it plus tea, which was a culturally popular drug felt to induce abortion (Pinto et al., 2003). Three patients took misoprostol plus injection of an unidentified medication. One patient on the unexposed group had also taken tea. Misoprostol was taken both orally and vaginally in 14 patients (82%); vaginally alone in 2 patients (12%); and orally alone in 1 patient (6%). The average number of pills taken was 4.8 (each pill was 200 mg). In the misoprostol exposure group, 15 cases had a history of bleeding early in pregnancy, compared to four in the non-exposed group. The average duration of bleeding was approximately 9–10 days in both groups. Not surprisingly, bleeding was more frequent in the attempted abortion (group 2) than the etiology-unknown group. Cramping occurred in eight of the misoprostol exposed and none in the non-exposed. Table 9 summarizes the frequent systemic and functional problems noted.

Common associated anomalies were micrognathia and posterior rotated ear, with no difference in prevalence between the two groups. Limb anomalies were present in 22 of the 28 patients in the study, with clubfoot and

Table 6
Swedish CHARGE study autism spectrum disorder

Case	Age (year)/sex	Autism	Ocular findings		Heart	Choanal atresia	Development delay (mr)	Genital	Ear		Other anomalies/ functional problems
			Coloboma	Microphalmus					Ext	Hearing	
1	5/M	AD	++	+		−	++	+ Cryptorchism micropenis	+	+	Short stature, spine, hand, dysphagia
2	6/F	AD	++	+	+ PDA, Fallot	+	++	+ Labia hypoplasia	+	+	Short stature, spine, dysphagia
3	7/F	AD	++	+	+ ASD, VSD, PDA	0	++	0	+	0	Cleft palate, anal atresia, renal, spine, dental, dysphagia
4	13/M	AD	++	0	+ PDA	+	++	Micropenis, cryptochisam, delayed puberty	+	+	Cleft palate, trachea esophageal fistula, dental, short stature, dysphagia
5	16/F	AD	++	+	+ PDA, ASD	0	+	0	+	0	Cleft lip/palate, short stature, dental, facial nerve, dysphagia
6	4/M	ALC	+	0	0	0	+	0	+	+	Short stature, dysphagia
7	5/F	ALC	++	0	+ PDA, VSD, PS	+	++	0	+	+	Facial nerve, TE fistula, anal atresia, limb, dysphagia
8	14/M	ALC	0	0	0	0	0	+ Cryptochrism, micropenis	+	+	Facial nerve palsy, delayed puberty, balance, short stature, spine
9	17/F	ALC	++	+	0	0	++	0	+	+	Craniosynostosis, balance
10	18/F	ALC	++	0	0	+	++	+ Delayed puberty	+	+	Delayed puberty, dysphagia

M: male; F: female, autism: AD: Autistic disorder, ALC: autistic-like conditions; coloboma: (++) bilateral, (+) unilateral; +: present, 0: not present; heart: ASD: atrial septal defect, PDA: patient ductus artenosis, PS: pulmonary stenosis, VSD: ventricular septal defect; development delay: MR: mental retardation: (++) severe, (+) mild, (0) not present; ear: (+) malformation or functional deficit present, (0) no malformation or functional deficit present.

clinodactyly the most frequent. Abnormal tearing was present in both groups. Many patients had oral or dental malformations including cleft palate, abnormal tongue anatomy, altered tongue tone, and poor sucking. The only statistical difference between the two groups was the low birth weight, and heart-shaped mouth, which seemed to be more characteristic of the misoprostol group than the non-misoprostol group. A detailed analysis of this study is reported elsewhere by Ventura (2001).

Radiologic imaging was done on 25 of the 28 patients. The main findings were brain stem calcification present in six, Dandy–Walker or variant in two, arachnoid cysts in two, hydrocephalus in three, cerebral atrophy in four, and a variety of other single anomalies. There did not seem to be a significant difference between the misoprostol exposed and the non-exposed groups.

Of the 28 patients, 26 had an evaluation for ASD (Table 10). A few patients were too young or did not attend examination. In these 26 patients, 5 met the diagnostic criteria for autism and 2 had an autistic-like condition (Fig. 5). There was a positive history of misoprostol in three of the five with autism, and one of the two with autistic-like

Table 7
Swedish Goldenhar study patients with autism spectrum disorder

Case	Age (year)/sex	Ear	Decreased hearing	Dermoid	IQ	Autism type	Comments
1	4/M	0	+	+ Epibulbar lipodermoid	Severe MR	AD	Cardiovascular and gastrointestinal anomaly, mandibular hypoplasia, microphthalmos
2	16/F	+	+	+ Epibulbar lipodermoid	Mild MR	AD	Limb anomaly, gastrointestinal and genitourinary problems, vertebral anomaly
3	6/M	+ (Microtia, ear tags, fistula, dimple)	+	+ Epibulbar lipodermoid	Average	ALC	Vertebral anomaly, facial palsy, gastrointestinal problem

M: male; F: female; +: anomaly or functional deficit present; 0: not present; AD: autistic disorder; ALC: autism like condition; IQ: intellectual quotient; MR: mental retardation.

Fig. 5. Brazilian Möbius study: child with autism disorder, bilateral facial nerve palsy, and abduction deficits (6th nerve).

Table 8
Brazil Möbius study pregnancy history (n = 28)

Group I	Group II (not exposed to misoprostol) (n = 11)	(Exposed to misoprostol) (n = 17)
Use of drugs in pregnancy		
Misoprostol	0	10
Misoprostol and tea		4
Misoprostol + other non-identified (1 also had tea)	0	3
Tea alone	1	

Table 9
Brazil Möbius sequence study[a] ''cranial nerve, systemic malformations and functional problems'' (n = 28)

Cranial nerve involvement	
Abducen (6th)	28/28[b]
Facial (7th)	28/28[b]
Trigeminal (5th)	5/28
Hypoglossal (12th)	6/28
Systemic malformations	
Posterior rotated ear	16/28
Heart shaped mouth	18/28
Cleft lip/palate/uvula	15/28 (5 CP)
Micrognathia	18/28
Limb	22/28
Tongue (microglossia/asymmetry/function)	14/25
Poland Anomaly (1 with Poland syndrome)	2/28
Mitral prolapse	8/28
Lagophtalmus	4/28
Functional problems	
Mental retardation	14/23
Seizures	12/27
Speech	11/25
Hearing	8/28
Dysphagia/sucking	19/28
Autism spectrum disorder (AD, ALC)	7/26 (4 in Group II)

AD: autism disorder; ALC: autism-like condition, CP: cleft palate.
[a] Some patients did failed appointments for some examinations and some were too young or difficult to examine.
[b] Inclusion criteria.

condition. In the ''etiology unknown'' group, two had autistic disorder, and one had autistic-like condition. Six cases surpassed the CARS cut-off score for severe autism of over 30, and one for mild autism (28). These were the same cases that met the DSM-IV criteria for autism spectrum disorder. Since the misoprostol cohort had more cases than the diagnosis unknown group (17 to 11), the breakdown of ASD seems to be comparable in the two groups. Bandim et al. (2003) have reported the psychiatric evaluation.

Although the number of patients with autism spectrum disorder in groups with and without exposure to misoprostol is not sufficient for accurate statistical comparison of subgroups. Also, clinodactyly, equinovarus, mitral prolapse, involvement of cranial nerves 9 and 10 occurred in each group. This provides support for a final common pathophysiology that produces the manifestations of the condition designated as Möbius sequence (Fig. 6).

Other malformations and functional disorders also showed a fairly similar percentages in both the misoprostol and the etiology unknown group. Psychosocial data, economic information, and more detailed clinical reports are found in other publications (Costa et al., 2001; Stillitano et al., 2001; Ventura, 2001; Lorenzo et al., 2003; Sena et al., 2003; Boudoux et al., 2000).

4. Discussion

The rate of autistic disorder in the general population is estimated to be about 1–2 in 1000 (Gillberg and Wing, 1999; Fombonne, 2001, 2002; Wing and Potter, 2002; Yeargin-Allsopp et al., 2003). If one expands the diagnosis to include all variants of ASD, the estimate increases to about 0.5–1% of the general population (Gillberg and Wing, 1999). Even if we consider only the patients with the full autism syndrome, the rates of autism in thalidomide, Möbius sequence, CHARGE association, and Goldenhar syndrome are unquestionably significant. The challenge is to try to identify a common thread, if one exists, that somehow links the

Table 10
Patients with autism spectrum disorders: Brazil Möbius study

Case	Age (year)/gender	Misoprostol exposure	Strabismus primary	Facial nerve palsy	Other cranial nerves	Autism type	Cars score	Mental retardation	Comments
1	4/F	+	Straight	+	9, 10	AD	39	+	Cleft palate, micrognathia, clinodactyly, calcification of brain stem
2	2/F	0	ET	+	9, 10	ALC	38	+	Arthrogyposis, micrognathia, club foot, clinodactyly, arachnoid cyst, hydrocephaly, polymiogyria, cerebral atrophy, cleft uvula
3	11/M	+	ET	+	9, 10, 11, 12	AD	45	+	Cleft palate, club foot, arthrogryposis, micrognathia, normal MRI
4	9/F	0	XT	+	9, 10	AD	46.5	+	Mitral valve prolapse, clinodactyly, club foot, Dandy Walker anomaly
5	3/M	0	ET	+	9, 10	AD	47.5	+	Cerebral atrophy, calcification of brain stem, cleft uvula
6	2/M	+	ET		9, 10	ALC	29	+	Cleft uvula, micrognathia, club foot, normal MRI
7	2/F	+	Straight		9, 10	AD	38	+	Clinodactyly, stenosis of aqueduct of Sylvia, hydrocephalus

M: male; F: female; +: anomaly present; 0: absent, ET: esotropia, XT: exotropia; AD: autism disorder (DSM-IV criteria), ALC: autism like condition; CARS: childhood autism rating score (median for Möbius cases without autism 18.4); mental retardation: (+) yes (WISC).

findings in these conditions with autism. Two conditions are associated with teratogens (thalidomide, misoprostol), but three usually are sporadic in occurrence (Möbius, CHARGE, Goldenhar). They all manifest some similarity in clinical findings, but also have significant differences. The seminal, and perhaps most informative, was the Swedish thalidomide study.

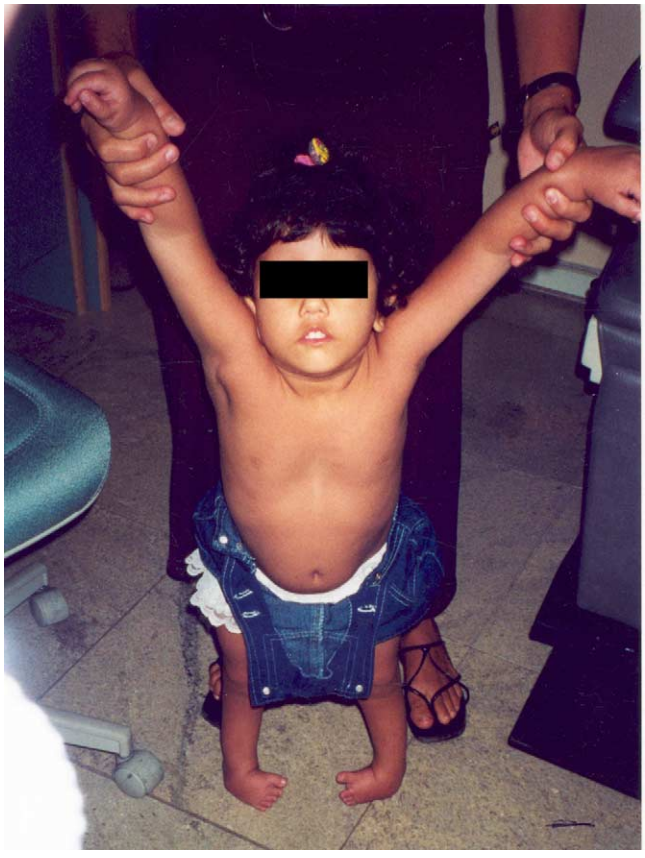

Fig. 6. Brazilian Möbius study: child with severe lower limb anomalies.

The thalidomide epidemic was a wakeup call to the potential of serious malformations caused by drugs and other environmental agents. Thalidomide was synthesized in the 1950s, and on the market in the late 1950s and early 1960s in 46 countries worldwide covering all continents. It was advertised as being safe and harmless for pregnant women, and was claimed to help in treating anxiety, insomnia, and gastritis. In many areas it was sold without prescription. Routine screening tests found it to be non-toxic to rodents, and therefore its potent teratogenicity in humans and higher animals was not anticipated (Lenz, 1966, 1986). In the fall of 1961, Lenz (1962) noted increased congenital malformations in the German population and suggested the correlation with thalidomide taken early in pregnancy. It was also observed in other countries (Smithells, 1962; McBride, 1961). It was taken off the market in most countries in 1961, but not before an estimate of greater than 6000 living children had been affected by the use of this drug by their mothers during pregnancy. The most noticeable malformations initially noted were the limb anomalies, but after more cases were reported it became obvious that thalidomide produced a spectrum of malformations and function problems involving craniofacial structures, extremities, internal organs, and in smaller numbers, a large variety of other structures (Smithells, 1962; Nowack, 1965; Kajii, 1965; Kajii and Shinohare, 1983; Newman, 1985; Kida, 1987; Smithells and Newman, 1992). Thalidomide was never released by the Federal Drug Administration (FDA), so very few cases were known to physicians in the United States. The narrow period of sensitivity (20–36 days post fertilization), potent teratogenicity, popularity, and the fairly accurate histories in many women (due to the fact that it was not a drug of abuse), allowed the construction of a timetable of sensitivity for its effect on different developing organs (Fig. 1).

The Swedish thalidomide study was undertaken to formally evaluate in an adult population the ophthalmologic

findings, especially those related to ocular motility disturbances (strabismus). Sweden also offered an ideal place for this study because of the excellent medical records, a stable population, and the availability of an accurate list of affected individuals. The finding of three individuals with autism at the very end of the study was completely unexpected, but was felt to be an important observation; therefore, psychiatrists were asked to evaluate these patients and two others who had been seen previously. They confirmed the diagnosis of ASD in four cases (Strömland et al., 1994). There was no attempt to look at the rest of the population in a prospective manner at this time, so the prevalence in this of ASD could easily be underestimated.

There were two findings that caught the pediatric ophthalmologists' attention early. They were the presence of an unusual form of ocular motor imbalance (strabismus) and a rare finding of aberrant tearing. Incomitant strabismus is a type of ocular motility disturbance in which the amount of deviation changes as the individual looks in different fields of gaze. Compared to comitant deviation, in which there is no limitation of movement but just the misalignment, congenital incomitant deviation makes up less than 10% of the total types of strabismus seen in children and Duane syndrome is a frequent cause of this congenital type of strabismus. Duane syndrome is estimated to occur in 1% of all strabismus cases, which gives a prevalence of Duane syndrome of about 2–3/10,000, since strabismus occurs in 2–4% of the population (Kirkham, 1970).

Although usually an isolated finding, there is a wide spectrum of associated anomalies reported in the literature with Duane syndrome, but the most frequent are those seen in Goldenhar syndrome (upper lid colobomas, conjunctival limbal dermoids, neurosensory deafness, and spinal cord anomalies) (Pfaffenbach et al., 1972; Alexander, 1973; Aleksic et al., 1976). The thalidomide study showed an extremely high association of individuals with incomitant strabismus (44%), usually of the Duane type. The usual observed associated anomalies were malformations of the thumb and external ear, facial nerve palsy, and hearing loss. It was uncommon to see Duane syndrome with other limb anomalies, unless there was evidence that thalidomide had been taken through a somewhat longer period of pregnancy. It was clearly an early teratogenic effect of thalidomide in days 20–24 or 25. This observation had also been made previously in a large Japanese study (Arimoto, 1987). These findings gave considerable insight into Duane syndrome.

Congenital paradoxical lacrimation, a very rare anomaly, was present in 20% of the thalidomide patients. It was also noted in the Japanese thalidomide series (Arimoto, 1987). The clinical symptoms range from isolated lack of emotional tearing to inappropriate tearing when eating, or both. This condition also goes under the names of paradoxical lacrimation and crocodile tears. The literature reports an almost universal combination of this anomaly with Duane syndrome, itself a condition caused by misdirection of nerves involving ocular muscles (Biedner et al., 1979; Brik and Athayde, 1973; Lutman, 1947; Ramsay and Taylor, 1980; Tachibana et al., 1984; Zhang, 2002). Some suggest that paradoxical lacrimation represents an example of aberrant innervation of the lacrimal system from a branch of the salivary nucleus (Jampel and Titone, 1962), secondary to failure of differentiation of the salivary and lacrimal nucleus. It is interesting that early in embryogenesis the sixth and seventh cranial and lacrimal nuclei are in close proximity. Destruction or failure of development of these structures might result in aberrant repair processes with inappropriate innervation. In the thalidomide study, most were associated with early effects such as horizontal incomitant strabismus (100%), hearing deficit or ear malformation (94%), and facial nerve palsy (71%).

Aberrant innervation does not occur frequently, and yet examples of this appear throughout these studies. The most striking is in thalidomide embryopathy, with both aberrant tearing (20%) and a high prevalence of Duane syndrome (44%). Although none of our Goldenhar study patients demonstrated this finding, the literature reports Duane syndrome frequently in association with this syndrome, or malformation common to this syndrome. There is also a literature report of another type of paradoxical innervation, Marcus–Gunn jaw winking, with CHARGE association. Local vulnerability and critical time may be the necessary factors for these neurologic mismatches to occur.

The similarity of early thalidomide effects to the classic Möbius sequence patients, i.e. limitation of abduction and facial nerve palsy, suggests detailed attention to tearing abnormalities in the Swedish and Brazilian Möbius studies might prove fruitful. Amaya et al. (1990) noted excessive lacrimation in 11 of 18 in a series of Möbius cases, with 3 also manifesting tearing when eating. Careful questioning did reveal abnormal tearing in about a third of the patients in the Swedish study, ranging from tearing when eating, lack of emotional tearing, to late onset of tearing. Of interest is that four of the six Möbius patients with a diagnosis of autism had no emotional tearing, and two of the four in thalidomide embryopathy with autism also lacked emotional tearing. Aberrant lacrimation was a prominent finding in our thalidomide embryopathy series (20%). Abnormal tearing symptoms were also present in many in the Brazilian study, in both the misoprostol-related and etiology-unknown groups.

Möbius (1888, 1892), a German neurologist in the late 1800s, described a number of cases with congenital involvement of the sixth and seventh nerve, and his name is associated with this condition. Most cases have severe limitation of abduction, and often adduction, but near-normal vertical movements (Amaya et al., 1990). Many syndromologists believe that Möbius sequence is not a distinct entity but belongs to a group of conditions characterized by involvement of craniofacial and oral/dental anomalies (especially affecting the tongue), Poland syndrome, and hypoplastic limb anomalies. Möbius sequence is usually a sporadic event, but there is literature of some cases with familial occurrence and also chromosomal anomalies

(Becker-Christensen and Lund, 1974; Baraitser, 1977; Ziter et al., 1977; McDermot et al., 1991; Slee et al., 1991; Donahue et al., 1993; Kremer et al., 1996; Nishikawa et al., 1997; Wilmore et al., 2000; Borck et al., 2001).

The ophthalmologic findings in both of these reported Möbius studies were similar to those in the literature, with either esotropia (inward turning of deviated eye) or no misalignment in the straight-ahead position, with only occasionally an exotropia (outward turning). The systemic and functional problems in both studies were again as expected, with difficulty sucking from the seventh nerve palsy, an important issue in infancy because of feeding problems. The frequency of findings might show some variations because of the recognition of subtle findings noted by the team of specialists. Abnormalities of the tongue, limb, and oral structures were often present. The patients in both the Swedish thalidomide and Möbius cohorts were evaluated comprehensively by psychiatrists, and the results reported in the literature (Strömland et al., 1994; Johansson et al., 2001). Early effects in thalidomide embryopathy and Möbius sequence imply brainstem dysfunction because of the involvement of a number of cranial nerves.

Although the group of ocular and systemic malformations seen with CHARGE association had been previously described by other authors (Hall, 1979; Hittner et al., 1979; Warburg, 1983), the acronym CHARGE was proposed by Pagon et al. (1981). The criteria used in this paper for the diagnosis were the presence of four of the six characteristics (coloboma, heart malformation, choanal atresia, developmental retardation, genital and ear anomalies), or three characteristics and other anomalies. Other reports in the literature have described other malformations, and suggested modifications of the diagnostic criteria (Källén et al., 1999; Brock et al., 2003). Byerly and Pauli (1993) propose that involvement of multiple cranial nerves occurs frequently. Since the findings cover multiple disciplines of medicine, there is often a bias of ascertainment in any series reflecting population evaluated, the interest of investigators and the sophistication of the examination of any given organ or structure (Russell-Eggitt et al., 1990). The estimated prevalence of CHARGE association is about 1:10,000 (Blake et al., 1998).

While the association of ASD with these reported conditions is quite convincing, what connects these conditions to each other that might give insight into common pathways? The initial thalidomide literature had many suggested actions of thalidomide responsible for thalidomide embryopathy. Comprehensive reviews by Zwingenberger and Wendt (1996), Tseng et al. (1996), Argiles et al. (1998), Miller and Strömland (1999b), Stephens (1988), Stephens et al. (2000), and others have summarized more recent theories. Stephens (2000) noted that although there were 2000 papers published in the last 40 years concerning thalidomide teratogenicity, the mechanism of action still remains elusive. He reviewed the present hypotheses, and summarized their strengths and weaknesses.

However, no matter what the mechanism of teratogenic action it is clear from the large clinical data in the literature that thalidomide has a selective action on developing fetal structures in very specific time frames, and the four patients with autism seem to occur in the period days 20–25 after fertilization and associated with cranial nerve involvement, incomitant strabismus, and ear and thumb malformations.

Möbius sequence with no established single etiology, as in the Swedish study and group 1 of the Brazilian series, has received considerable attention and some agreement in the literature as to probable pathophysiology. A popular explanation is that it belongs in a group of disruption syndromes, but there is a disagreement as to the causes of the embryonic disruption. Bamforth (1993) describes a process termed ''organizational disruption'' (blastogenic disruption) as an explanation for some of the observed malformations suggesting that it is a better explanation for some phenotypes. He proposes that there are a group of organizational molecules, highly conserved and determined by chromosomes in a sequential manner, that are important in the early stage of organization. This organization is imposed on embryonic cells by these molecules in a sequence of activation determined by homebox genes. These molecules or morphogenes, as they are sometimes called, at different concentrations can activate different genes. If something interferes with setting up the organization of these morphogenes, higher or lower concentrations may result, activating genes at inappropriate times. The changes would not be visible until differentiation commences and could result in malformation of organs or histological development. This theory is perhaps compatible with the observations that some of the Hox gene defects in the animal models result in brain stem malformations that are sometimes associated with autism in humans (Rodier et al., 1996, 1997; Rodier, 2000).

A more commonly suggested mechanism is that of a vascular disruption in the early embryonic period. Some investigators refer to it as the ''subclavion disruption syndrome'' (Bavinck and Weaver, 1986; Issaivanan et al., 2002). In addition to the primary vascular disruption causing hypoxia from ischemia, edema and hemorrhage, many secondary events can occur affecting other organs (Shepard, 1991; St. Charles et al., 1993; Matsui et al., 1997). Animal models have been developed to show how different malformations can occur (Lipson et al., 1989). The timing extent of this hypoxic event will determine the ultimate malformations based on the sensitive tissues at the time of the hypoxia (Leong and Ashwell, 1997).

There are many clinical examples that will support this vascular disruption concept, but they represent individual case reports. For instance, malformations suggestive of Möbius sequence occasionally occur in fetuses exposed to cocaine, which causes vasoconstriction of the uterine vessels (Hoyme et al., 1990; Kankirawatana et al., 1993). Also, chorionic villi sampling has been suggested as an infrequent cause of limb anomalies and occasionally Möbius sequence, although there are reports both supporting and refuting the

association (Firth et al., 1991; Quintero et al., 1992; Burton et al., 1993; Froster and Jackson, 1996; Hall, 1996; Holmes, 2002). Möbius cases have been associated with hypovolemia in a splenic bleed during pregnancy (Lipson et al., 1996), and to inadvertent exposure to ergotamine, a uterine constrictor (Hughes and Goldstein, 1988; Verlos et al., 1990). Another example was a child with Möbius sequence following a history of polyhydramnios in pregnancy (St. Charles et al., 1993). In the Swedish Möbius study there was an apparent increase of bleeding in early pregnancy reported without known precipitating causes, and also one case with a history of chorionic villi sampling procedure. Courtens et al. (1992) report a case associated with a history of exposure to benzodiazepines. The common characteristic of all these cases in the literature is an early pregnancy event producing a possible short period of hypoxia brought upon by disturbance in the blood supply from uterine constriction. This line of reasoning received support with the association of misoprostol taken early in pregnancy resulting in patients with characteristic Möbius sequence.

Goldenhar syndrome also has some similarity in clinical manifestations to Möbius sequence and thalidomide embryopathy and vascular disruption has been suggested as a mechanism (Gorlin et al., 2000; Poswillo, 1973). Though the time of embryonic insult is not as clear in Möbius sequence or Goldenhar syndrome as it is in thalidomide embryopathy, it is early in pregnancy, probably around 4 to 6+ weeks of development. Lam (2000) proposed a theory that ectodermal non-disjunction involving the otic placode could produce the same malformations. If correct, this would explain the multisystem findings and also place the time early in the 4th week. Another suggestion is that it can be a result of ''reproductive wastage'' in high risk conceptions, based on one case of possible monozygotic twins conceived by vitro fertilization and embryo transfer (Jongbloet, 1987). There were a few invitro fertilization cases in our series.

The pathophysiology of CHARGE association has not been identified. While most cases are sporadic without a known etiology, there are some familial cases and a number with known but different chromosomal anomalies (Mitchell et al., 1985; Clementi et al., 1991; Slee et al., 1991; Wieczorek et al., 1997; Sanlaville et al., 2002; Devriendt et al., 1998). The observation that many of the features suggest defects in neural crest cell development or migration might suggest it should be considered in the group of neurocristopathies (Siebert et al., 1985). Why autism exists in a significant number of cases is still a mystery. However, the time of initial embryonic insult is necessarily early, especially because ocular colobomas are such a significant finding. Ocular colobomas are caused by failure of closure of the embryonic fetal fissure sometime before the 6-week-old embryo, but from the thalidomide study, an earlier insult (25 to 27+ days) can result in an ocular coloboma. The few ocular colobomas noted in thalidomide cases seem to result from exposure close to, but a few days later than, the early-effect malformations of cranial nerves and aberrant tearing. Although not part of the diagnostic acronym, facial nerve palsy is a common characteristic of CHARGE (Lacombe, 1994; Byerly and Pauli, 1993). Blake et al. (1998) propose that cranial nerve dysfunction (anosmia, facial nerve palsy, sensorineural deafness and vestibular problems, swallowing difficulties) be considered a major criterion. This involvement of cranial nerves may be a thread that exists with CHARGE association, thalidomide embryopathy, and Möbius sequence. A common pathway for CHARGE and OAV spectrum has been suggested (Van Meter and Weaver, 1996).

Misoprostol as a drug for self-induced abortions has gained much popularity in South America, especially Brazil, where abortions are not legal except in a few situations. Misoprostol was cheap and readily available because of its accepted use in medical conditions such as gastric ulcers and arthritis (Grazioli et al., 1993; Raskin et al., 1996; Morgan, 1999). Medically-induced abortions have advantages over clandestine abortion from unlicensed ''professionals.'' They avoid risk of anesthesia and surgical complications in unclean environments, and perhaps most important, can be done in privacy. For a number of years it was estimated to be used in more than 50% of attempted abortions (Coêlho et al., 1993, 1994). It has also been utilized for planned abortions, conducted by medical professionals in many countries, but almost always combined with another drug such as mifrostone (Norman et al., 1991; Spitz et al., 1998; Wing, 1999). However, misoprostol alone is a poor abortifacient drug, and many pregnancies continue to term. Considering its frequent usage, misoprostol does not appear to cause many malformations, but because of the tremendous popularity as an abortifacient drug for self-induced abortions, even low incidence complications such as Möbius sequence occurred in sizable numbers (Schüler et al., 1997).

The presence of ASD in both the misoprostol-exposed and non-exposed cases of Möbius sequence in the Brazilian study gives further evidence of the association of autism with early embryonic insults, and also the non-specificity of etiology of Möbius sequence.

While autism is usually associated with cortical dysfunction, brain stem abnormalities have been suggested as a possible mechanism in some patients (Rosenhall et al., 2003). The frontal and temporal lobes, the limbic system and cerebellum are believed to be crucially dysfunctional in autism (Gillberg and Coleman, 2000). Theoretically, such dysfunctions could be related to disrupted brain stem connections projecting to limbic, cortical, and cerebellar structures.

In the group of studies in this paper, early injuries to the embryo are associated with disturbances in the brain stem. Rodier, in a number of papers, summarized the associations of autism with other early embryologic events (Rodier et al., 1997, Rodier, 2000, 2004), The brain stem anomalies do not rule out dysfunction in the forebrain. It is more likely that abnormal input from the brain stem contributes to forebrain

dysfunction in addition to the more direct effects on cranial nerve function.

Valproic acid (VPA) is teratogenic to rodents and causes malformations similar to thalidomide. Exposure to VPA during pregnancy has been reported to be associated with autism in children (Moore et al., 2000). Rodier et al. (1996) and Rodier (2004) used the rat fetus as an animal model and noted that when the pregnant rat was exposed to VPA at the time of neural tube closure, there was as an affect on the cranial nerve motor nuclei.

Rodier et al. (1996) noted almost complete absence of facial nuclei and shortening of brainstem in a patient with autism. Radiologic abnormalities, albeit not consistent or conclusive, have also been reported in Möbius syndrome. They include abnormalities of the brainstem (Thakkar et al., 1977; Nardelli et al., 1983; Harbord et al., 1989; Kuhn et al., 1990; Lengyel et al., 2000; Pedraza et al., 2000; Yoon et al., 1997). There are a number of literature reports of central hypoventilation, brainstem changes, and in some, Möbius sequence (Cohen and Thompson, 1987; Govaert et al., 1989; Konkol et al., 1991; Cortez and Kinney, 1996; Igarashi et al., 1997). In the Swedish Möbius study 2 of the 10 evaluated radiologically revealed brain abnormalities (agenesis of corpus callosum, hydrocephalus). In the Brazilian Möbius study there were a considerable number of MRI abnormalities with the most common being brain stem calcification.

Magnetic resonance imaging (MRI) study by Hashimoto et al. (1995) and Cody et al. (2002) summarize the MRI findings in individuals with autism. Some have suggested a smaller brainstem and cerebellum in patients with autism, compared to control participants.

The most common thread of the observed anomalies associated with autism is that they result from an early adverse embryonic event. The literature can be confusing, and must be read carefully when it relates to embryonic timing issues. ‘‘Gestational age,’’ used by obstetricians and many others, is calculated from the last menstrual period. A gestational age of 1 month of an embryo is actually 2 weeks post conception/fertilization. These 2 weeks are certainly not trivial when looking at early embryonic events. Therefore, if a woman attempts abortion at 4–6 weeks gestational age the embryo is actually at only 2–4 weeks of development. The studies reported here relate most events to the actual age of development of the fetus. The most reliable timing is from the thalidomide data, in which the 4 individuals with autism condition were 20–25 days post fertilization. The next evidence of embryonic timing is from the misoprostol group. Although less precise, it appears to be 4–6 weeks (6–8 weeks from the last menstrual cycle). In Möbius from etiology unknown there is no definite information except that it seems consistent with the misoprostol group as early, e.g. 4–6 weeks. The least established timing is in the CHARGE group, although we know the ocular embryonic fissure is closed in 5–6 weeks of embryogenesis, so the insult must be some time before. From the thalidomide timetable it could be as early as the late 4th week. The Goldenhar group seems to be at 4–6 weeks of embryogenesis, based on associated anomalies.

How do we get from early-onset insult that seems to affect multiple brainstem structures to autism disorders that involve higher centers not yet formed? Are there a group of unidentified cells that are even at this time programmed for higher brain centers, which are damaged, or is there an interruption in a series of connections ultimately crucial for higher centers to develop correctly? These are key questions, but we may only be able to speculate about answers at this time on some evidence from other studies.

Although autism may result from a variety of mechanisms and causes, the combined evidence from the thalidomide, Möbius, CHARGE, and Goldenhar studies seems to establish quite firmly that early insults in embryogenesis, often involving brainstem structures, are sometimes associated with ASD.

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