AUTISM IN THALIDOMIDE EMBRYOPATHY: A POPULATION STUDY

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In the late 1950s thalidomide was synthesized and independently introduced in Germany, Great Britain and Japan as a potent sedative drug with few negative side-effects. In 1961 reports came from Germany, Australia and Great Britain (Kosenow and Pfeiffer 1961, McBride 1961, Wiedeman 1961, Lenz 1962, Smithells 1962) that children were being born with serious malformations that might be associated with the mother's intake of thalidomide during pregnancy. The drug was withdrawn from the market in late 1961, but was still prescribed in Japan until September 1962. Approximately 5000 children with thalidomide defects were observed in West Germany; Japan and Great Britain each had around 700 cases, and thalidomide embryopathy was reported from another 26 countries (Kajii 1965). In Sweden approximately 150 children were affected, but about one-third of these died from serious birth defects in early infancy (Winberg 1964*a*, *b*). Approximately 100 Swedes suffering from thalidomide embryopathy are alive today.

The most frequent anomalies that affected the children were upper- and lower-limb defects, but other organ systems (such as the ears, heart, kidneys and genitals) were also shown to be involved.

Based on studies of the exact time of ingestion of thalidomide (Lenz and Knapp 1962, Nowack 1965), the sensitive period for the teratogenicity of the drug was considered to be 20 to 36 days after conception (35 to 51 days from the first day of the last menstrual period). The effects on different organs according to exact time of ingestion of thalidomide have been analysed in some detail (Fig. 1). Anomalies of the ears and cranial nerves, and deformities of the thumbs and upper limbs, were shown to be induced in the early teratogenic period of thalidomide, while defects of the lower limbs and triphalangism of the thumbs originated later in the sensitive period.

Material and method

A study was made by two of the authors (K.S. and M.M.) of ophthalmological findings in the Swedish group of 100 thalidomide embryopathy patients (Miller and Strömland 1991; Strömland and Miller 1992, 1993). 86 of these individuals (49 males, 37 females) were personally examined during a two-year period (1987 to 1989). Detailed medical records were available for the remaining 14 patients. All patients were between 27 and 30 years of age. Ocular abnormalities proved to be the second most common type of defect (54 per cent), surpassed only by limb defects (81 per cent).

The most common ocular findings were motility defects, which were found in 43 patients (50 per cent) and which most

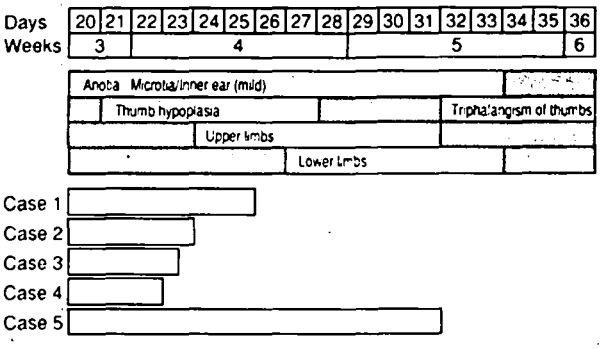

Fig. 1. Postconceptional age at introduction of thalidomide and its resulting effects, in relation to five cases in present study.

often appeared as incomitant (paretic) strabismus (37 patients, 43 per cent). Of these, 26 patients (30 per cent of the total group of 86) had unilateral or bilateral Duane syndrome. Four patients had a limitation of abduction and seven had gaze paresis of congenital origin. Comitant (non-paretic) strabismus occurring as esotropia was found in six patients (7 per cent). In addition, 17 patients had facial palsy and 17 had abnormal lacrimation (so-called 'crocodile tears'). Other infrequent ocular abnormalities were microphthalmia (N = 2), coloboma of the optic disc (N = 3), uveal coloboma (N = 1), congenital glaucoma (N = 1), and conjunctival lipodermoid which was part of a Goldenhar-like syndrome (N = 1).

The medical records of five cases suspected to have severe learning disorder were examined. Four of these had documented IQ levels below 70 according to testing at the age of eight to 24 years. These four were examined by C.G., who used a Swedish DSM-III-R interview (von Knorring, personal communication) and the Childhood Autism Rating Scale (CARS) (Schopler *et al.* 1988). All the criteria for childhood autism listed in the ICD-10 (WHO 1992) were also checked. Parents and other caregivers (who had known the patients for more than two years) were interviewed about early developmental history, previous and current signs and symptoms of autistic disorder. Vineland interview (Sparrow and Cicchetti 1985) was also performed. No neuro-imaging studies were made. Chromosomal cultures undertaken many years previously were normal. Fragile X syndrome was not suspected on clinical grounds in any of the five patients, but a specific search for this anomaly had not been made when the chromosomes were examined.

The fifth case was not examined by C.G. This patient suffered from myelomeningocele and hydrocephalus and attended a special school for children with mild mental retardation. In his records, it was stated that he behaved like somebody of 'low-normal intelligence', but we have been unable to retrieve test results supporting this. He was not suspected of having autism when examined by the ophthalmologists.

Results

All four examined cases met full criteria for autistic disorder and childhood autism (Tables I and II). The four had shown severe abnormalities of social interaction, communication and behaviour before their second birthday. One of the four had profound mental retardation (IQ < 20), two had severe mental retardation (IQ 20 to 49) and one had mild mental retardation (IQ 50 to 70). One man and one woman were unequivocally deaf. Another man was probably completely deaf, but he did react when approached by other people, even if he could not see them. However, this was interpreted by people close to him as a sign of his overdeveloped sense of air movements, rather than a real ability to hear. The mildly mentally retarded woman had a moderate hearing deficit, but could take

TABLE I
Characteristics of four individuals with thalidomide embryopathy and autism plus one patient not neuropsychiatrically examined (case 5)*

Characteristic	*Case*				
	1	*2*	*3*	*4*	*5*
Sex	M	M	F	F	M
Age (yrs)	31	31	31	30	30
Mental retardation	Profound	Severe	Moderate	Mild	Near-average intelligence?
IQ	<20	20-34	35-49	50-69	70-84?
Autistic disorder	+	+	+	+	?
DSM-III-R criteria met	12	12	10	12	?
Childhood autism (ICD-10)	+	+	+	+	?
Epilepsy	–	–	–	+	–
Hearing deficit	+	+	+	+	+
Deafness	+	+	+	–	–
Incomitant strabismus	+ (Duane syndrome)	+ (gaze paresis)	–	+ (Duane syndrome)	+ (Duane syndrome)
Facial nerve palsy	+	+	+	–	+
External ear anomalies	+	+	+	+	+
Abnormal lacrimation	+	+	–	–	–
Upper-limb anomalies	+	–	–	–	+
Lower-limb anomalies	–	–	–	–	+

*– = not present; + = present to a considerable degree.

TABLE II
Behavioural problems in four individuals with autistic disorder*

	Case			
	1	*2*	*3*	*4*
Sex	M	M	F	F
Haptic defensiveness	+ +	+ +	+	+
Self-injurious behaviour	+	+ +	+	+ +
Aloofness	+ +	+ +	+ +	+
Muteness	+	+	+	—
Echolalia	–		–	+
Repetitive questioning	–	–	–	+ +
Islet of ability	+ (motor)	+ (visual recognition)	—	+ (drawing, reading)
Hand-flapping	+	–	–	–
Other stereotypical *movements*	+ +	+ +	+	+
CARS score	41·5	51	35	52

*– = not present; + = present to a considerable degree; + + = present to an extreme degree.

part in a spoken conversation with the help of hearing aids. The four individuals with autistic disorder are briefly described below, with particular focus on the autistic symptomatology.

Case reports

CASE 1

This 31-year-old man with profound mental retardation and severe hearing impairment was examined in a group home for the mentally disabled where he had lived for several years (although he had been brought up in his biological home). He was completely mute and had no sign language. He avoided people's gaze, and showed no social smile or imitation. However, although he avoided other people, he liked to stand some way away and observe them from the corner of his eye. He had relatively good self-help skills (feeding, bathing and dressing), but he would hit and

bite himself, and shy away from any physical approach. He exhibited hand-flapping and extreme motor stereotypies involving the whole body, spinning his body like a ballet dancer for minutes on end, and becoming extremely upset if interrupted in these rituals. He met criteria A1, 2, 3, 4 and 5, B1, 2 and 3, and C1, 2, 3 and 4 for DSM-III-R autistic disorder. His CARS score (41·5) indicated severe autism.

CASE 2

This 31-year-old man with severe mental retardation and deafness was examined in a group home for the mentally disabled, where he had lived for several years. He had been brought up in his biological home and later in an institution for people with autism and autistic-like conditions. He was completely mute, with no sign language. He avoided eye-contact and exhibited no social smile, although there were minimal signs of imitation (such as setting the table in preparation for drinking coffee, his favourite pastime). He always preferred to stand alone, several yards from everyone else, and avoided all physical contact with other people. He had good vision and visual memory, and could remember people and how to get to places he had visited years before. Involuntary movements consisted of rocking his whole body. He reacted to other people approaching, even when he could not see them, probably through smell or vibration, and would immediately distance himself. He met A1, 2, 3, 4 and 5, B1, 2 and 3, and C1, 2 and 3 of the DSM-III-R autistic disorder criteria. His CARS score (51) indicated severe autism.

CASE 3

This 31-year-old woman was deaf, and also had mental retardation (according to performance tests). She was living in a group home and was examined in a hospital outpatient setting. Having been admitted to institutional care in infancy, within 18 months she was reported actively to avoid all kinds of contact. She was passive and friendly except when routines were broken, but she would throw tantrums if challenged. She had good self-help skills. She was mute, with repetitive sign language with limited communicative intent. She did not want to be touched physically by other people, and kept aloof. Behaviours included biting herself and rocking her body, and she was ritualistic. She met criteria A1, 3, 4 and 5, B2, 3 and 6 (for sign language) and C1, 2 and 3 of the DSM-III-R for autistic disorder. Her CARS score of 35 indicated mild autism.

CASE 4

This 30-year-old woman with mild mental retardation and a mild to moderate hearing deficit was examined in a group home for mentally retarded people. Her behaviour fluctuated between passive and friendly, and active but odd. She was uninterested in other people, and there was no change in her docile facial expression during our long verbal interchange. She was completely absorbed by a number of routines. There was perfect order in her room; she collected knick-knacks that were lined up in a particular fashion. She exhibited extremes of delayed and immediate echolalia, and her voice was a flat monotone. She could read well aloud, but had very poor comprehension. She met A2, 3, 4 and 5, B2, 3, 4, 5 and 6, and C1, 3 and 5 of the DSM-III-R criteria for autistic disorder. Her CARS score (52) indicated severe autism.

Discussion

With a minimum prevalence of autistic disorder of 4 to 5 per cent in thalidomide embryopathy, and an autistic disorder prevalence in the general population of about 0·08 per cent (Gillberg *et al.* 1991), it appears that there is at least a 50-fold higher rate of autism in those with thalidomide embryopathy than in the general population.

All four patients with autism in our study also had different degrees of mental retardation, which makes it hazardous to conclude that the association is with autism rather than with mental retardation. However, the fact that all the clearly mentally retarded patients in the study had autism supports a specific association with autism: if the link had been specifically with mental retardation, one would have expected the majority of the four patients to have had mental retardation but not autism, given the epidemiological data showing that only a minority (albeit a considerable one) of mentally retarded patients have autism (*e.g.* Wing 1981, Gillberg *et al.* 1986). Nevertheless, the numbers are small and it is not possible to draw a firm conclusion.

Autism can be caused by brain damage sustained at different times of neural development (Gillberg and Coleman 1992). Most of the available literature supports a second-trimester aetiology for many cases of autism: partly because most children with autism look relatively normal, whereas if damage to the nervous system occurs in the first three months of

fetal life, the child will usually also show major physical stigmata. The cases with autism and thalidomide embryopathy in our study showed abnormal physical features, and it has been well documented that damage to the fetus occurred in the first trimester of pregnancy. In fact it has been convincingly shown that in thalidomide embryopathy with the type of physical stigmata encountered in our group of autism cases—*i.e.* ocular motility defects (mostly Duane syndrome) and other cranial nerve disorders, ear and upper-limb anomalies—the teratogenic effect occurred approximately 20 to 24 days after conception (Lenz and Knapp 1962, Nowack 1965, Strömland and Miller 1993). Nevertheless, this does not necessarily mean that the damage to the brain which possibly caused autism could not have occurred later in pregnancy. Some of the mothers may have continued taking medication during the second and third trimesters. Since our cases did not have triphalangism or lower-limb anomalies (only occurring when medication was taken late in the teratogenic period), it would also seem unlikely that the mothers took thalidomide continuously. However, intermittent medication in pregnancy may have produced the brain pathology at a later time than the damage that led to the physical abnormalities.

All four patients with autism also showed sensory deficits. Two were completely deaf, one was probably deaf and the other had a moderate hearing deficit. All four showed restriction of eye movements, but did not have major reductions of visual acuity. The woman who was least affected by hearing problems (case 4) was the one with the highest level of intellectual functioning. However, she was no less severely affected by autism than the other three patients. Therefore, in our small sample there was no clear correlation between the degree of sensory deficits and the degree of autism. Furthermore, many of the non-autistic probands in the total thalidomide sample also had sensory deficits. This finding suggests that there is no straightforward mechanism linking sensory deficits and autism in thalidomide embryopathy. Nevertheless, the possibility that hearing deficits could be associated with autistic symptomatology merits further exploration.

In summary, it seems that autism can be produced by damage to the fetus around 20 to 24 days after conception. According to a recent survey of the autism literature, this does not appear to be a common timing for the type of injury that leads to abnormal neural development in autism (Gillberg and Coleman 1992). However, the brain structures most likely to be injured in thalidomide embryopathy are those that are formed and developed earliest in the teratogenic period, *i.e.* ear and upper-limb structures and cranial nerve cell nuclei. These are the brain areas most often implicated in the pathogenesis of autism. Thus, even though second-trimester brain insults may be a more common associated background factor in autism, the disorder could also arise on the basis of first-trimester damage. There are also many examples of autism associated with postnatal brain damage. It seems that autism may be associated with brainstem and temporal lobe dysfunction arising at any time during the first years of neuronal development.

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SUMMARY
Of a population of 100 Swedish thalidomide embryopathy cases, at least four met full criteria for DSM-III-R autistic disorder and ICD-10 childhood autism. Thalidomide embryopathy of the kind encountered in these cases affects fetal development early in pregnancy, probably on days 20 to 24

after conception. It is argued that the possible association of thalidomide embryopathy with autism may shed some light on the issue of which neural circuitries may be involved in autism pathogenesis.

RÉSUMÉ

Autisme dans l'embryopathie thalidomide: une étude de population

Dans une population de 100 cas suédois d'embryopathie thalidomide, au moins quatre cas présentaient tous les critères du trouble autistique du DSM-III-R et de l'autisme infantile du ICD-10. L'embryopathie thalidomide du type recontré dans ces cas affecte le développement en début de grossesse, probablement entre le jour 20 et le jour 24 après la conception. Les auteurs pensent que l'association possible de l'embryopathie thalidomide avec l'autisme peut jetter quelques lumières sur la nature des circuits neuronaux impliqués dans la pathogenèse de l'autisme.

ZUSAMMENFASSUNG

Autismus bei Thalidomid Embryopathie: eine Populationsstudie

Von 100 schwedischen Thalidomid Embryopathiefällen erfüllten mindestens vier alle Krtiterien für die DSM-III-R Form des Autismus und für den ICD-10 Autismus des Kindesalters. Die Thalidomid Embryopathie, die bei diesen Kindern vorlag, stört die fetale Entwicklung in der frühen Schwangerschaft, wahrscheinlich an den Tagen 20 bis 24 nach der Konzeption. Die Autoren denken, daß die mögliche Beziehung zwischen Thalidomid Embryopathie und Autismus zur Klärung der Frage beitragen könnte, welche fetalen Verbindungen bei der Pathogenese des Autismus involviert sind.

RESUMEN

Autismo en la embriopatia por talidomina. Estudio de una población

De una población de 100 casos en Suecia de embriopatia talidomínica, por lo menos cuatro cumplían los criterios establecidos por el DSM-III-R para una alteración autística y por el ICD-10 para el autismo infantil. La embriopatia talidomínica del tipo encontrado en estos casos afecta el desarrollo prenatal precozmente en la gestación, probablemente en los dias 20 al 24 después de la concepción. Se argumenta que la posible asociación de la embriopatía talidomínica con el autismo pueda ser de alguna ayuda sobre el tema de cuales son los circuitos neuronales afectados en la patogénesis del autismo.

References

Gillberg, C., Coleman, M. (1992) *The Biology of the Autistic Syndromes, 2nd Edn. Clinics in Developmental Medicine, No. 126.* London: Mac Keith Press.

— Persson, E., Grufman, M., Themnér, U. (1986) 'Psychiatric disorders in mildly and severely mentally retarded urban children and adolescents: epidemiological aspects.' *British Journal of Psychiatry,* **149,** 68–74.

— Schaumann, H., Steffenburg, S. (1991) 'Is autism more common now than 10 years ago?' *British Journal of Psychiatry,* **158,** 403–409.

Kajii, T. (1965) 'Thalidomide experience in Japan.' *Annals of Paediatrics,* **205,** 341–354.

Kosenow, W., Pfeiffer, R. A. (1961) 'Micromelia, haemangioma und duodenal stenosis.' *Monatschrift für Kinderheilkunde,* **109,** 227.

Lenz, W. (1962) 'Thalidomide and congenital abnormalities.' *Lancet,* **2,** 1358.

— Knapp, K. (1962) 'Die Thalidomid-Embryopathie.' *Deutsche Medizinische Wochenschrift,* **87,** 1232–1242.

Miller, M. T., Strömland, K. (1991) 'Ocular motility in thalidomide embryopathy.' *Journal of Pediatric Ophthalmology and Strabismus,* **28,** 47–54.

Nowack, E. (1965) 'Die sensible Phase bei der Thalidomid-Embryopathie.' *Humangenetik,* **1,** 516–536.

Schopler, E., Reichler, R. J., Renner, B. R. (1988) *The Childhood Autism Rating Scale (CARS)—Revised.* Los Angeles: Western Psychological Services.

Smithells, R. W. (1962) 'Thalidomide and malformations in Liverpool.' *Lancet,* **1,** 1270–1273.

Sparrow, S. S., Cicchetti, D. V. (1985) 'Diagnostic uses of the Vineland Adaptive Behavior Scales.' *Journal of Pediatric Psychology,* **10,** 215–225.

Stromland, K., Miller, M. T. (1992) 'Refractive evaluation in thalidomide embryopathy.' *Graefe's Archive for Clinical and Experimental Ophthalmology,* **230,** 140–149.

— — (1993) 'Thalidmode embryopathy: revisited 27 years later.' *Acta Ophthalmologica,* **71,** 238–245.

Wiedeman, H. R. (1961) 'Hinweis auf eine derzeitige Häufung hypo- und aplastischer Fehlbildungen der Gliedmassen.' *Medizinische Welt,* **37,** 1863–1866.

Winberg, J. (1964*a*) 'Investigation concerning the possible connection between birth defects and medical drugs.' *Läkartidningen,* **61,** 718–741. (*Swedish.*)

— (1964*b*) 'Investigation concerning the possible connection between birth defects and medical drugs.' *Läkartidningen,* **61,** 814–831. (*Swedish.*)

Wing, L. (1981) 'Language, social and cognitive impairments in autism and severe mental retardation.' *Journal of Autism and Developmental Disorders,* **11,** 31–44.

World Health Organization (1992) *International Classification of Diseases and Disorders (ICD-10).* Geneva: WHO.