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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.
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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

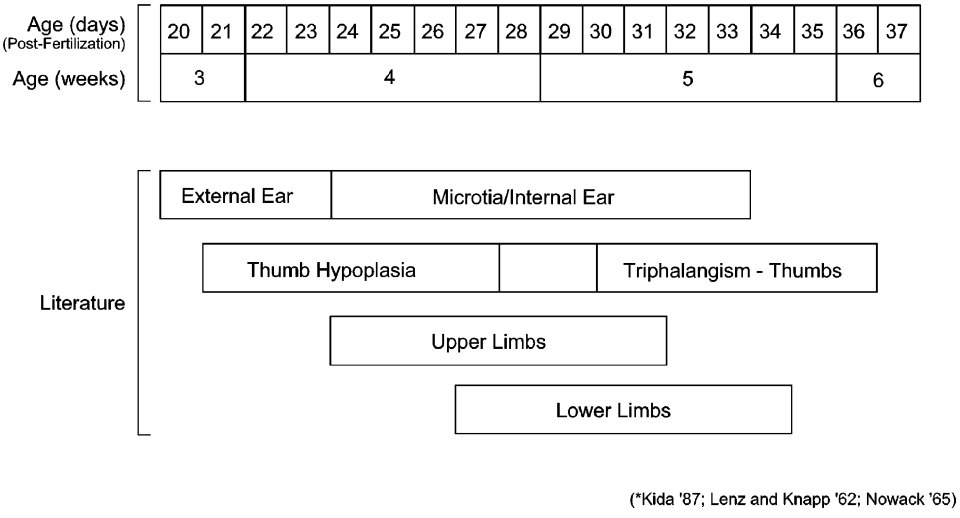

Fig. 1. Thalidomide embryopathy: the historical timetable (literature).

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