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THE ASSOCIATION BETWEEN AUTISM AND ERRORS IN EARLY EMBRYOGENESIS: WHAT IS THE CAUSAL MECHANISM?

Abstract

The association between embryonic errors and the development of autism has been recognized in the literature, but the mechanism underlying this association remains unknown. We propose that pleiotropic effects during a very early and specific stage of embryonic development – early organogenesis – can explain this association. In humans early organogenesis is an embryonic stage, spanning day 20 to day 40 after fertilization, which is characterized by intense interactivity among body parts of the embryo. This implies that a single mutation or environmental disturbance can have several phenotypic effects (i.e., pleiotropic effects). Disturbances during early organogenesis can lead to many different anomalies, including limb deformities, craniofacial malformations, brain pathology, and anomalies in other organs. We reviewed the literature and found ample evidence for the hypothesis that autism is associated with errors during early embryogenesis, brain pathologies, major and minor structural anomalies, and various other medical conditions. The proposed mechanism integrates findings from a variety of studies, including neurobiological studies, studies on major and minor anomalies, and studies on prenatal influences on neurodevelopmental outcomes. The implication is that the origin of autism is much earlier in embryological development than has been frequently reported.

Autism is a psychiatric disorder that is characterized by qualitative impairment of social interactions and communication, by restricted patterns of behaviors or interests, and an onset prior to 3 years of age (Volkmar & Pauls, 2003). Its prevalence is considered to be around 7 cases per 10,000 (Williams et al.,

2006), although estimates vary greatly (Newschaffer et al., 2007). Autism spectrum disorders include autism, Asperger's syndrome, childhood disintegrative disorder, Rett syndrome, and PDD-NOS (pervasive developmental disorder – not otherwise specified), and have a prevalence of 20 cases per 10,000 (Williams et al., 2006). It is well-established that autism has a strong polygenic basis (Freitag, 2007; Gupta & State, 2007). Thus, as a polygenic disorder, autism is attributable to the effects of an unknown number of mutations and their possible interaction⁶. However, to understand the genetic etiology of autism, it is useful to take a developmental perspective on how the genetic influences may lead to autism.

Studies have identified a particular stage during embryological development that is very susceptible to both genetic and environmental disturbances (Sander, 1983; Raff, 1994; Galis & Metz, 2001). This stage is called early organogenesis, and occurs in humans from around day 20 to day 40 after fertilization. In this chapter, we present support for the hypothesis that the vulnerability that characterizes this stage, is implicated in the causation of autism. It has been established that autism correlates with conditions due to errors in early embryogenesis (Arndt et al., 2005; Miller et al., 2005), but the underlying mechanism that causes autism remains unknown. We argue that insights from studies in developmental biology reveal a potential underlying mechanism, which allows the meaningful integration of disparate research findings. First, we discuss the results of studies in developmental biology concerning the vulnerability associated with early organogenesis. Second, we review the literature that supports the hypothesis that autism is the result of disturbances during early organogenesis.

The vulnerability of early organogenesis

Early organogenesis is a remarkable embryological stage, because all vertebrates, including humans, look similar during this stage, i.e., the stage displays striking evolutionary conservation. It has been hypothesized that high interactivity among body parts during this stage explains the evolutionary conservation of the stage (Sander, 1983; Raff 1994). Specifically, because of this high interactivity, a change in one part of the body affects other body parts.

⁶ This is not to deny the possible role of environmental influences and possible gene-environment interaction.

Such side-effects are called *pleiotropic effects*. For example, changes in number of digits, which start to develop during early organogenesis, are often accompanied by other anomalies (Biesecker, 2002), and the same holds for an extra vertebra (Galis et al., 2006). This implies that a mutation, which affects early organogenesis, is unlikely to be maintained in evolution: any local beneficial effect is likely to be off-set by pervasive pleiotropic effects, which are likely to be negative. It is assumed that because of the strong selection against new variants during the stage of early organogenesis, all vertebrates look very similar during this stage.

The interactivity of the stage of early organogenesis also leads to a high vulnerability for environmental disturbances, which can induce the same effects as genetic mutations (West-Eberhard, 2003). A review of the literature showed that in several species the incidence of anomalies and mortality as a result from teratological treatments (e.g., the administration of methanol) is greatest if the treatment is administered during early organogenesis (Galis & Metz, 2001). Importantly it is the timing of the disturbance, not necessarily its nature that determines the incidence of mortality and anomalies (DeSesso & Harris, 1996; Wilson, 1965).

Many body parts undergo their first development during early organogenesis, as shown in Table 5.1. The very low threshold of pleiotropic effects during early organogenesis makes the early development of these body parts susceptible to disturbances. As the brain starts to develop during early organogenesis, it is likely that a disturbance in brain development, which is either genetic or environmental in origin, will also affect other body parts, and vice versa. For example a mutation that results in the development of an extra digit, may also induce a neurodevelopmental disorder. We propose that the presence of such pleiotropic effects during early organogenesis provides a plausible explanatory mechanism for the development of autism due to errors during early embryogenesis. Support for this hypothesis comes from studies that show the co-occurrence of autism and physical abnormalities that originate in early organogenesis. We review the evidence for five categories of abnormalities: prenatal complications, neuropathology, major structural anomalies, minor physical anomalies, and other medical comorbidities. For our present purposes, it is of minor importance whether the studies considered specific autism or the broader category of autism spectrum disorders, because we propose that early disturbance of development plays a role in all these disorders.

Table 5.1 Body parts that first appear during the stage of early organogenesis from day 20 to 40 after fertilization

Body part		First appearance of body part in days after fertilization	References
Brain	Brain stem (including the cranial nerves)	29	Larsen, 2001; ten Donkelaar et al., 2006
	Cerebellum	32	Müller & O'Rahilly, 1988a; O'Rahilly & Müller, 2006
	Limbic structures	33	Müller & O'Rahilly, 2006; O'Rahilly & Müller, 2006
	Cerebral hemispheres	33	Müller & O'Rahilly, 1988b; O'Rahilly & Müller, 2006
Limbs		31	O'Rahilly & Gardner, 1975
Heart		23	O'Rahilly, 1971
Kidney		33	O'Rahilly & Muecke, 1972; Larsen, 2001
Lung		31	O'Rahilly & Boyden, 1973
Gastrointestinal tract		23	O'Rahilly, 1978
Skin		23	Larsen, 2001; Holbrook et al., 1975
Eye		29	O'Rahilly, 1983a
Ear		29	O'Rahilly, 1983a
Head		25	Larsen, 2001; ten Donkelaar & Vermeij-Keers, 2006
External genitalia		37	O'Rahilly, 1983b

Comment: The embryonic period is subdivided into 23 stages, termed Carnegie stages, based on morphological criteria. Neurulation starts at stage 8, which is generally listed as 18 days after fertilization, but has recently been corrected to 23 days after fertilization (O'Rahilly & Müller, 2006). All postfertilization days in this Table are adapted to the new classification of O'Rahilly & Müller (2006).

Autism and prenatal complications

The association between early prenatal complications and autism has been recognized in the literature (Arndt et al., 2005; Miller et al., 2005). Here we review the main findings and explain why these findings provide support for our hypothesis.

Thalidomide. Thalidomide was prescribed in the treatment of anxiety, insomnia, tension, gastritis, and pregnancy sickness (Miller & Strömland, 1999). In the 1960s, many pregnant women took thalidomide. Sadly, it turned out that thalidomide use during pregnancy produced a variety of congenital malformations in the newborns. These included limb and craniofacial anomalies, and kidney, cardiovascular, genital, and lung malformations. Because most women knew the date they took the drug, time tables could be reconstructed that showed that thalidomide was teratogenic between 20 and 36 days after fertilization (Lenz & Knapp, 1962), i.e., during early organogenesis. Four percent Swedish individuals, whose mothers took thalidomide in this period, developed autism (Miller et al., 2005; Strömland et al., 1994). This is significantly greater than the 0,1 percent in the general population. The studies of thalidomide defects confirm that early organogenesis is a vulnerable stage of embryological development, leading to many different anomalies. The large variety in effects (i.e., the apparent pleiotropy) is caused by the high interactivity among different body parts that characterize the stage. One of the hypothesized negative effects of this interactivity is a disturbance of normal brain development, eventually leading to the development of autism.

Rubella. A rubella infection suffered during early pregnancy leads to serious malformations in the newborn. The 1964 rubella epidemic in the United States, resulted in 20,000 to 30,000 neonates born with congenital malformations (Desmond et al., 1967). These included heart defects, deafness, eye defects (e.g., cataracts, retinopathy), and neurological impairment. Another study showed that 90 percent of infants infected with the rubella virus during the first ten weeks of pregnancy developed a defect, mostly heart defects and deafness. In contrast, the percentage is much lower in children infected after week 10 of pregnancy: 33% (week 11 to 12), 11% (week 13 to 14), 24% (week 15 to 16), and, finally, zero % (any time after week 16) (Miller et al., 1982). Thus, prenatal exposure to the rubella virus during early organogenesis results in more different defects than later in pregnancy (Ueda et al., 1979). In a study on

243 children with prenatal exposure to rubella, it was found that 10 of them (4.1%) met the criteria of autism (Chess, 1971). In a follow-up with the same sample, four more individuals met the criteria of autism (Chess, 1977). Thus, about 6% percent of the rubella infected children developed autism. These two studies did not provide data on the exact timing of the rubella exposure, but the association with physical anomalies suggest that negative pleiotropic effects during early organogenesis played a role in the development of autism.

Anticonvulsants. Anticonvulsants are prescribed, inter alia, to prevent seizures in epileptics. Women with epilepsy who take anticonvulsants during first trimester of pregnancy have an increased risk of delivering a child with major congenital malformations compared to women with epilepsy who do not take anticonvulsants (3.4 percent versus 1 percent) (Jick & Terris, 1997). Another study showed that among 57 children with fetal anticonvulsant syndromes (characterized by facial dysmorphic features and cardiac malformations), four were diagnosed with autism and another two with Asperger syndrome. Eighty-one percent showed autistic type behaviors, such as poor social interaction and communication skills (Moore et al., 2000). The co-occurrence of autism and congenital malformations is consistent with the hypothesis that pleiotropic effects during early organogenesis resulted in the development of autism.

Misoprostol. Misoprostol is prescribed in the treatment of gastric ulcers, but it is in some countries also used to induce abortions (Norman et al., 1991). Children born after use of misoprostol in the first trimester of pregnancy have several congenital malformations. In a review of 69 case reports of congenital defects associated with misoprostol use during pregnancy, it was found that 83% of the children had lower limb defects, 55% had central nervous system defects involved in the cranial nerves, and 46% had upper limb anomalies (Population Council, 2003). The majority of pregnant women took misoprostol between the third and sixth week after fertilization. Another remarkable consequence of misoprostol use during early pregnancy is the presence of Möbius sequence in children (Bandim et al., 2003). Möbius sequence is a congenital syndrome characterized by facial paralyses, i.e., the disability to smile or frown, being the result of the absence of or underdeveloped sixth and seventh cranial nerves. Other characteristics are malformations of orofacial structures, limb anomalies, and defects of the chestwall (Sudarshan et al., 1985). A study found that 50 percent of 23 children with Möbius sequence had been prenatally exposed to misoprostol. Five of the 23 children met the criteria for autism, and two other children showed autistic-like behavior. Of those

seven children, four had been prenatally exposed to misoprostol (Bandim et al., 2003), suggesting that disturbances during early organogenesis influenced the development of autism.

Prematurity and low birth weight. A study showed that 26 percent of 91 ex-preterm infants with a birth weight lower than 1500 g showed autistic traits at the age of 21 months (Limperopoulos et al., 2008). A review of the literature revealed a substantial association between low birth weight and autism (Kolevzon et al., 2007), and a large population-based study revealed a significant association between prematurity and autism (Larsson et al., 2005). There is substantial evidence for the hypothesis that prematurity and low birth weight are often caused by disturbances during early organogenesis (e.g., Barker, 2007). For example, there is a positive correlation between low birth weight and later cardiovascular (Barker, 1995) and kidney (Schreuder & de Waal, 2006) disease. The structures involved in these diseases are established during early organogenesis (see Table 5.1).

Neuropathologies associated with autism

A recent review on the neuropathology of autism (Schmitz & Rezaie, 2008) summarized the evidence that people diagnosed with autism often have subtle abnormalities in the development of several brain structures, including the cerebellum, limbic structures, brainstem, and cerebral cortex. The prenatal brain starts to develop with neurulation, which marks the start of early organogenesis. Neurulation starts when the neural plate is formed. Around day 23 after fertilization, the neural plate starts to fold, resulting in the neural groove (O'Rahilly & Müller, 2006). Around day 26 after fertilization, the three major divisions (prosencephalon, mesencephalon, and rhombencephalon) of the brain are visible on the folds of the open neural groove. The neural crest, a temporary embryological structure that gives rise to a variety of body structures, starts to develop on the same day.

Around day 29 after fertilization, the neural folds start to fuse, resulting in the neural tube. The brain stem first appears, with distinguishable cranial nerve motor nuclei (Larsen, 2001). Failure of neural tube closure results in an incomplete spinal cord, which leads to defects such as spina bifida and anencephaly (Botto et al., 1999). Around day 32 after fertilization, the cerebellum first appears, and one day later the future cerebral hemispheres and the future amygdaloid region become visible (O'Rahilly & Müller, 2006;

Müller & O'Rahilly, 2006). Thus, the brain structures that are commonly disturbed in people diagnosed with autism, have their origin in early organogenesis. The co-occurrence of deviant brain structures and other physical anomalies suggests that pleiotropic effects play a major role in the development of autism. In addition, studies have shown that pregnant mice infected during early organogenesis have offspring with similar brain deviations as people with autism (Fatemi et al., 2005).

Major structural anomalies

Congenital anomalies were found in 11 percent of 45 children diagnosed with an autism spectrum disorder, compared to 6 percent of 128 children without this diagnosis (Wier et al., 2006). This difference remained statistically significant after correcting for gestational age, plurality, birth order, maternal age, maternal ethnicity, and maternal education. The congenital anomalies included anomalies of the central nervous system, the eye, ear, face, and neck, the heart, the respiratory system, the gastrointestinal system, the genitourinary system, the musculoskeletal system, and the integumentary system. Especially anomalies of the gastrointestinal system were more frequent in children diagnosed with an autism spectrum disorder.

A recent review (Zafeiriou et al., 2007) showed that autism or autistic features are often observed in children with genetic syndromes, such as tuberous sclerosis complex (Wiznitzer, 2004), fragile X syndrome (Clifford et al., 2007), Down syndrome (Lowenthal et al., 2007), and neurofibromatosis type 1 (Williams & Hersh, 1998). Tuberous sclerosis complex is a disorder characterized by anomalies of the integumentary system, brain, retina, heart, kidney, and/or lungs (Crino et al., 2006). Autism spectrum disorders are present in 25 to 50 percent of people with this syndrome, and the prevalence of the syndrome in people diagnosed with autism spectrum disorder is 1 to 4 percent (Wiznitzer, 2004).

Fragile X is a syndrome that is characterized by mental retardation, and several physical features, including macrocephaly, prominent forehead, loose joints, soft skin, prominent ears, high arched palate, and, in males, large testicles (Visootsak et al., 2005). In a group with 33 males and 31 females with full mutation fragile X, 67 percent of the males and 23 percent of the females met the criteria for autism spectrum disorder (Clifford et al., 2007). In a group of

316 people with autism spectrum disorder, 2.2% had fragile X mutations (Reddy, 2005).

The phenotypic features of Down syndrome are mental retardation, brachycephaly, hand and foot anomalies, duodenal atresia, epicanthal folds, flat nasal bridge, and hypotonia (Roizen & Patterson, 2003). In addition, about fifty percent of the children born with Down syndrome have congenital heart disease, hearing loss, and ophthalmological disorders. Autism spectrum disorders are present in 16 percent of children with Down syndrome (Lowenthal et al., 2007).

Neurofibromatosis type 1 is characterized by six or more café-au-lait spots on the skin, and two or more neurofibromas, a type of nerve sheath tumor, usually in the gastrointestinal tract (Reynolds et al., 2003). Four percent of individuals with neurofibromatosis type 1 was diagnosed with autism (Williams & Hersh, 1998). As can be seen in Table 5.1, all body structures involved in these syndromes are established during early organogenesis. The co-occurrence of several anomalies implies that pleiotropic effects, including the development of autism, played a role in the development of the syndromes.

Minor physical anomalies

Minor physical anomalies are morphological abnormalities that can be detected quite easily, but have no serious medical or cosmetic consequences for the individual. Although minor physical anomalies are not life-threatening themselves, it is well-established that they are associated with major anomalies (Marden et al., 1964; Leppig et al., 1987; Mehes, 1985). The relation between autism and minor physical anomalies has been observed frequently (Miles & Hillman, 2000; Walker, 1977; Rodier et al., 1997; Hardan et al., 2006). Most studies used the Waldrop Physical Anomaly Scale, which assesses 18 anomalies in six body regions: head, eyes, ears, mouth, hands, and feet (Waldrop & Halverson, 1971).

Of the three studies concerning the incidence of individual anomalies, the first reported an average of 5.76 physical anomalies in children diagnosed with autism, compared to 3.53 anomalies in matched controls (Walker, 1977). The anomaly with the highest frequency in autism was low-set ears (14.3% of the children with autism, compared to 4.5% of the healthy controls). In addition, children with autism more often had hypertelorism (i.e., a large

interpupillary distance) and syndactylia of toes (i.e., partially fused toes) compared to healthy controls. The second study showed that children diagnosed with autism had a significant posterior rotation of the ears, compared to healthy controls (Rodier et al., 1997). In the same study it was found that children with autism had hypotelorism (i.e., a short interpupillary distance), smaller feet, and an increased total hand length compared to healthy controls. In a recent study in which MRI was used to scan minor physical anomalies, no significant differences were found between non-mentally retarded people diagnosed with autism and healthy controls (Hardan et al., 2006). When only lower functioning individuals (IQ < 103) were analyzed, significant differences in hypotelorism were found; people diagnosed with autism had smaller interorbit distances and a lower interorbit/orbit skull ratio.

Another physical feature that is frequently observed in children with autism is macrocephaly (i.e., a head circumference that is two or more standard deviations above the mean), with an average reported rate of 20 percent (Lainhart et al., 2006). All minor physical anomalies observed in people diagnosed with autism are established during early organogenesis (see Table 5.1).

Medical comorbidities

In a case-control study, 12 percent of people diagnosed with autism were given one or more diagnoses of medical disorders, including congenital malformations of the cardiovascular system, the urinary system, the skeletal system, and the eyes (Lauritsen et al., 2002). Another study found that children diagnosed with autism had significantly more ear infections, more use of antibiotics, and more gastrointestinal problems before the age of 2 years, compared to healthy controls (Niehus & Lord, 2006). Specific medical problems that are found significantly more often in people diagnosed with autism compared to controls are epilepsy (Canitano, 2007), visual impairment, including blindness (Mukaddes et al., 2007), abnormal metabolism (Manzi et al., 2008), vascular changes (Yao et al., 2006), and gastrointestinal problems (Galli-Carminati et al., 2006), which are possibly related to general failure of the immune system (Cohly & Panja, 2005). All these comorbidities involve body structures that are established during early organogenesis.

In addition, the comorbidity of autism with other psychiatric disorders is high: more than 70 percent of the children with autism also meet the criteria of one

or more other psychiatric disorders (Leyfer et al., 2006). Forty-four percent meet the diagnostic criteria of specific phobia, 37 percent those of obsessive compulsive disorders, 31 percent those of ADHD and 10 percent those of major depression. This shows that the psychological/behavioral phenotype of people diagnosed with autism, like their physical phenotype, displays considerable variation. This suggests that pleiotropic effects during early organogenesis result in a diverse array of physical anomalies, including subtle brain anomalies that lead to a diverse pattern of psychological/behavioral problems.

Discussion

Our present review of the literature has shown that autism is associated with

1. errors during early embryogenesis;
2. neuropathologies;
3. major structural anomalies;
4. minor physical anomalies; and
5. several other medical conditions.

So far most studies on the association between autism and physical anomalies were focused on only one of these topics, although a few researchers have recognized the combination of autism, errors during embryogenesis, neuropathologies, and physical malformations (Miller et al., 2005; Rodier, 2002). However, so far no hypothesis has been advanced to explain and integrate all these different research findings. We argued that developmental biology provides this hypothesis. We hypothesized that autism, and the associated physical anomalies, are the result of disturbances during early organogenesis, the embryonic stage from day 20 to day 40 after fertilization. During this stage, high interactivity among body parts renders the organism highly susceptible to pervasive effects of developmental disturbances. Consequently, a single mutation or environmental disturbance can have many different, often deleterious, pleiotropic effects. We proposed that the abundance of pleiotropic effects during early organogenesis is the mechanism that explains why disturbances during embryogenesis can have severe effects such as the development of autism.

A remaining question is whether the cause of autism is limited to disturbances during early organogenesis, or whether disturbances later in development can also cause autism. Studies on the age of onset of autism may provide insight into this issue. On average, parents begin to recognize the first signs of autism

at around 19 months, with 30 percent noticing first abnormalities (e.g., lack of eye contact and smiling) prior to the first birthday (De Giacomo & Fombonne, 1998). However, there is a group of children diagnosed with autism, which first appeared to develop normally, but show regression (e.g., speech loss) between 12 and 42 months. Prevalence rates of regression among children with autism vary from 20% to 49%, and the developmental outcomes of regressed autistic children appear to be worse than those of non-regressed autistic children (Bernabei et al., 2007).

It has been hypothesized that there is an association between regression and vaccinations, but studies could not confirm this association (Fombonne & Chakrabarti, 2001; Taylor et al., 2002). In the literature cases are described of late-onset autism after a herpes infection (Ghaziuddin et al., 2002), so it is possible to develop autism after an environmental insult later in life, but these few cases cannot fully explain the origin of late-onset autism. A recent study revealed that regressed autistic children have a higher incidence of circadian rhythm disorders, and a higher incidence of epilepsy and epileptiform EEG abnormalities, compared to nonregressed autistic children (Giannotti et al., in press). However, epilepsy is not considered a causal factor in autism, but rather as part of brain dysfunction that is implicated in both the development of autism and epilepsy (Gurrieri et al., 1999). The origin of the brain dysfunction still has to be explained.

Late-onset autism does not necessarily imply a later cause of autism (i.e., originating in a stage of development later than early organogenesis). An early developmental disturbance may result in a cascade of effects, which may only be detected relatively later in life (Rice & Barbon, 2000; Meyer et al., 2007). It is possible that there are other vulnerable prenatal periods after the stage of early organogenesis (Kinney et al., 2008), but it cannot be excluded that the later vulnerability was associated with disturbances during early organogenesis.

This may imply that our hypothesis is hardly falsifiable. However, there are two ways to deal with the falsifiability problem. The first way is to perform animal studies in which our hypothesis can be tested experimentally. There are already several animal studies indicating that the stage of early organogenesis is extremely vulnerable for disturbances (Galis & Metz, 2001), and that first trimester rather than second trimester disturbances result in negative neurodevelopmental outcomes (Meyer et al., 2007). In the future, animal studies can be performed in which pregnant animals are subjected to

disturbances at various periods during pregnancy (including early organogenesis). Neurodevelopmental and other physical outcomes then can be related to the specific timing of the disturbance. Studies by Fatemi and colleagues already showed that brain anomalies of newborn mice after prenatal exposure to the influenza virus during early organogenesis, are similar to those in people with autism (Fatemi et al., 2005). A second way to test our hypothesis is to examine a large sample of people diagnosed with autism with respect to a variety of physical deviations. It follows from our hypothesis that disturbances during early organogenesis result in several anomalies, so all possible anomalies associated with body parts that start to develop during this embryonic stage (see Table 5.1) should be examined. It is our expectation that a majority of people diagnosed with autism will show a diverse pattern of anomalies, due to pleiotropic effects that only occur during early organogenesis.