REVIEW

The Association Between Autism and Errors in Early Embryogenesis: What Is the Causal Mechanism?

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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 affecting development at this stage 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 association between autism and different kinds of physical anomalies, which agrees with the hypothesis that pleiotropic effects are involved in the development of autism. The proposed mechanism integrates findings from a variety of studies on autism, including neurobiological studies and studies on physical anomalies and prenatal influences on neurodevelopmental outcomes. The implication is that the origin of autism can be much earlier in embryologic development than has been frequently reported.

Key Words: Autism, critical periods, early organogenesis, medical comorbidities, physical anomalies, prenatal complications

Autism is a neurodevelopmental disorder that is characterized by qualitative impairment of social interactions and communication, restricted patterns of behaviors or interests, and an onset before 3 years of age (1). Autism spectrum disorders include autism, Asperger's syndrome, childhood disintegrative disorder, and pervasive developmental disorder—not otherwise specified. The prevalence of autism is approximately 20/10,000, whereas the prevalence of autism spectrum disorders is approximately 60–70/10,000 (2). It is well-established that autism has a strong polygenic basis (3,4). Thus, as a polygenic disorder, autism is attributable to the effects of an unknown number of mutations and their possible interaction (1). However, knowledge about the genetic background of autism does not reveal the causal mechanism that underlies the relation between a particular genetic composition and the development of autism. To find this causal mechanism it is necessary to take a developmental perspective on how genetic predispositions might lead to autism.

Studies have identified a particular stage during embryologic development that is very susceptible to both genetic and environmental disturbances (5–7). This stage is called early organogenesis and occurs in humans from approximately Day 20 to Day 40 after fertilization. In the present article, we provide support for the hypothesis that the vulnerability that characterizes this stage is often implicated in the causation of autism. It has been established that autism correlates with conditions due to errors in early embryogenesis (8,9), but the underlying mechanism that causes autism remains unknown. We argue that insights from studies on the vulnerability of early organogenesis reveal a potential underlying mechanism. This mechanism can explain several research findings concerning autism, which so far have been treated separately in the literature. To understand why the stage of early organogenesis is so vulnerable, we first discuss this stage more extensively.

The Vulnerability of Early Organogenesis

Early organogenesis is a remarkable embryologic stage, because all vertebrate embryos, including those of humans, look similar during this stage (i.e., the stage displays striking evolutionary conservation). Before this stage, embryos look remarkably different across species, and after this stage, development diverges again. It has been hypothesized that high interactivity among body parts during early organogenesis explains the evolutionary conservation of the stage (5,6). Specifically, because of this high interactivity, a change in one part of the body affects other body parts. 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 (10), and the same holds for an extra vertebra (11). This implies that a mutation, which affects early organogenesis, is usually selected against: any local beneficial effect is likely to be offset 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.

For many genes a phenomenon called "gene-environment equivalence" is known (12). In such cases perturbations of the developmental process can be caused either by a mutation or by an environmental stimulus. Because of the interactivity in the stage of early organogenesis, environmental stimuli can result in similar correlations between various conditions as with pleiotropically induced correlations. A review of the literature showed that in several species the incidence of anomalies and mortality as a result of teratological treatments (e.g., the administration of methanol) is greatest if the treatment is administered during early organogenesis (6). In humans, it is estimated that 90% of the pregnancies of embryos that experienced disturbances during early organogenesis result in a miscarriage (13). Importantly, it is the timing of the disturbance and not necessarily its nature that determines the incidence of mortality and anomalies (14,15).

Why is the stage of early organogenesis much more vulnerable than other stages of embryologic development? At earlier stages there are fewer interactions among body parts, because organ primordia have yet to develop. At later stages, body parts show a relatively high degree of modularity. This implies that the

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Table 1. Body Parts that First Appear During the Stage of Early Organogenesis from Day 20–40 After Fertilization

Body Part	First Appearance of Body Part in Days After Fertilization	References
Brain		
Brain stem (including the cranial nerves)	29	17,18
Cerebellum	32	19,20
Limbic structures	33	20,21
Cerebral hemispheres	33	20,22
Limbs	31	23
Heart	23	24
Kidney	33	17,25
Lung	31	26
Gastrointestinal Tract	23	27
Skin	23	17,28
Eye	29	29
Ear	29	29
Head	25	17,30
External Genitalia	37	31

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 (20). All postfertilization days in this table are adapted to the new classification (20).

effects of mutations or other disturbances will be limited to the module itself and not to other parts of the organism (16).

Many body parts undergo their first development during early organogenesis, as shown in Table 1 (17–31). The 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 could be 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 might 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 provide support from five categories of abnormalities: prenatal complications, neuropathology, major structural anomalies, minor physical anomalies, and other medical comorbidities. So far, this diverse array of abnormalities in autism has not been explained in the literature from a unitary point of view. 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 can play a role in all these disorders.

Autism and Prenatal Complications

The association between early prenatal complications and autism has been reviewed in the literature (8,9). Here we discuss research findings that agree with our hypothesis that the association is the result of pleiotropic effects during early organogenesis. The fact that we discuss environmental influences on the development of autism first does not imply that genetic influences are less important. Genetic disturbances (e.g., mutations) are presumably more important than environmental disturbances, but research on environmental influences gives a clear indication of the importance of the timing of the disturbance.

Thalidomide

Thalidomide was prescribed in the treatment of anxiety, insomnia, tension, gastritis, and pregnancy sickness (32). 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, timetables could be reconstructed that showed that thalidomide was teratogenic between 20 days and 36 days after fertilization (33). Four percent of Swedish individuals whose mothers took thalidomide in this period developed autism (9,34). This is significantly higher than the .2% in the general population (2). The studies of thalidomide defects confirm that early organogenesis, in humans from Day 20–40 after fertilization, is a vulnerable stage of embryologic development, leading to many different anomalies. The large variety in effects is likely caused by the high interactivity among different body parts that characterize the stage. One of the possible 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 often leads to serious malformations in the newborn. The 1964 rubella epidemic in the United States resulted in 20,000–30,000 neonates born with congenital malformations (35). These included heart defects, deafness, eye defects (e.g., cataracts, retinopathy), and neurological impairment. Another study showed that 90% of infants infected with the rubella virus during the first 10 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 11–12), 11% (week 13–14), 24% (week 15–16), and, finally, 0% (any time after week 16) (36). Thus, prenatal exposure to the rubella virus during early organogenesis results in more different defects than later in pregnancy (37). 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 (38). In a follow-up with the same sample, 4 more individuals met the criteria of autism (39). Thus, approximately 6% 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 (37) suggests 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 epileptic persons. Women with epilepsy who take anticonvulsants during the first trimester of pregnancy have an increased risk of delivering a child with major congenital malformations compared with women with epilepsy who do not take anticonvulsants (3.4% vs. 1%) (40). Another study showed that, among 57 children with fetal anticonvulsant syndromes (characterized by facial dysmorphic features and cardiac malformations), 4 were diagnosed with autism and another 2 with Asperger's syndrome. Eighty-one percent showed autistic-type behaviors, such as poor social interaction and communication skills (41). 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 (42). 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 (43). Most 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 (44). Möbius sequence is a congenital syndrome characterized by facial paralyses (i.e., the inability to smile or frown), being the result of absent or underdeveloped sixth and seventh cranial nerves. Other characteristics are malformations of orofacial structures, limb anomalies, and defects of the chestwall (45). A study found that 50% of 23 children with Möbius sequence had been prenatally exposed to misoprostol. Five of those 23 children met the criteria for autism, and 2 other children showed autistic-like behavior. Of those 7 children, 4 had been prenatally exposed to misoprostol (44), suggesting that disturbances during early organogenesis influenced the development of autism.

Neuropathologies Associated with Autism

A recent review on the neuropathology of autism (46) 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. These abnormalities can be the result of genetic disturbances or environmental influences or an interaction between the two.

The prenatal brain starts to develop with neurulation, which marks the start of early organogenesis. Neurulation starts when the neural plate is formed. At approximately Day 23 after fertilization, the neural plate starts to fold, resulting in the neural groove (20). At approximately 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 embryologic structure that gives rise to a variety of body structures, starts to develop on the same day.

At approximately 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 (17). At approximately Day 32 after fertilization, the cerebellum first appears, and one day later the future cerebral hemispheres and the future amygdaloid region become visible (20,21). Thus, the brain structures that are commonly disturbed in people diagnosed with autism have their origin in early organogenesis.

Major Structural Anomalies

Congenital anomalies were found in 11% of 45 children diagnosed with an autism spectrum disorder, compared with 6% of 128 children without this diagnosis (47). The congenital anomalies included anomalies of the central nervous system, eye, ear, face, neck, heart, respiratory system, gastrointestinal system, genito-urinary system, musculoskeletal system, and integumentary system. Especially anomalies of the gastrointestinal system were more frequent in children diagnosed with an autism spectrum disorder.

A recent review (48) showed that autism or autistic features are often observed in children with genetic syndromes, such as tuberous sclerosis complex (49), fragile X syndrome (50), Down syndrome (51), and neurofibromatosis type 1 (52). Tuberous sclerosis complex is a disorder characterized by anomalies of the integumentary system, brain, retina, heart, kidney, and/or lungs (53). Autism spectrum disorders are present in 25%–50% of people with this syndrome, and the prevalence of the syndrome in people diagnosed with autism spectrum disorder is 1%–4% (49).

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 male subjects, large testicles (54). In a group with 33 male and 31 female subjects with full mutation fragile X, 67% of the male subjects and 23% of the female subjects met the criteria for autism spectrum disorder (50). In a group of 316 people with autism spectrum disorder, 2.2% had fragile X mutations (55).

The phenotypic features of Down syndrome are mental retardation, brachycephaly, hand and foot anomalies, duodenal atresia, epicanthal folds, flat nasal bridge, and hypotonia (56). In addition, approximately 50% of the children born with Down syndrome have congenital heart disease, hearing loss, and ophthalmologic disorders. Autism spectrum disorders are present in 16% of children with Down syndrome (51).

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 (57). Four percent of individuals with neurofibromatosis type 1 were diagnosed with autism (52). As can be seen in Table 1, all body structures involved in these syndromes are established during early organogenesis. The co-occurrence of several anomalies, including the development of autism, suggests that pleiotropic effects 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. These anomalies are caused by genetic disturbances or are environmentally induced. Although minor physical anomalies are not life-threatening themselves, it is well-established that they are associated with major anomalies (58–60). A meta-analysis of seven studies on the association between autism and minor physical anomalies revealed that this association is significant (61).

Anomalies reported most frequently in people with autism were low-seated ears (62), hypertelorism (i.e., a large interpupillary distance) (62), syndactylia of toes (i.e., partially fused toes) (62), hypotelorism (i.e., a short interpupillary distance) (63), smaller feet (63), and an increased total hand length (63). Most minor physical anomalies observed in people diagnosed with autism are established during early organogenesis (see Table 1).

Other Medical Comorbidities

In a case-control study, 12% 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 (64). Specific medical problems that are found significantly more often in people

diagnosed with autism compared with control subjects are epilepsy (65), visual impairment, including blindness (66), abnormal metabolism (67), vascular changes (68), and gastrointestinal problems (69), which are possibly related to general failure of the immune system (70). 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% of children with autism also meet the criteria of one or more other psychiatric disorders (71). 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 overview of the literature has shown that autism is often 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 have focused on only one of these topics, although a few researchers have recognized the combination of autism, errors during embryogenesis, neuropathologies, and physical malformations (9,72). However, so far no hypothesis has been advanced to explain and integrate all these different research findings. We hypothesized that autism and the associated physical anomalies are most likely 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.

Is it possible to develop autism after the stage of early organogenesis? It has been suggested that there is an association between autism and vaccinations, but studies could not confirm this (73). In the literature, cases are described of late-onset autism after a herpes infection (74), which suggest it is possible to develop autism after an environmental insult later in life. However, 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 might result in a cascade of effects, which might only be detected relatively later in life (75,76). It is possible that there are other vulnerable prenatal periods after the stage of early organogenesis (77), but it cannot be excluded that the later vulnerability was associated with disturbances during early organogenesis.

Does this imply that our hypothesis is hardly falsifiable? An ideal situation to test our hypothesis would be to create a list of body parts that start to develop during early organogenesis and a separate list of body parts that start to develop later and to study whether autism is associated with anomalies in structures that arose during early organogenesis and whether it is not associated with structures that arose later. Unfortunately, a strict division between anomalies in structures that arise during early organogenesis and structures that arise later is not possible, because the basic structures, such as all the organs and limbs, start to develop during early organogenesis. Anomalies in structures that develop later might be related to or the result of anomalies in some of the basic structures that arose during early organogenesis. 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 (7) and that first trimester rather than second trimester disturbances result in negative neurodevelopmental outcomes (76). 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 *et al.* (78) 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. Also in animal studies, detailed experiments can be performed that show the causal relatedness between different pleiotropic effects (e.g., the interactivity during early patterning of the anterior-posterior axis and brain development) (11).

The best support for our hypothesis in humans would come from a study that examines a large sample of people diagnosed with autism with respect to a variety of physical deviations. So far, research has shown that people diagnosed with autism have significantly more physical anomalies compared with control subjects, but it has not been shown that most people with autism have physical anomalies. However, no study has been published in which all physical anomalies that can be caused by pleiotropic effects during early organogenesis were systematically examined. These anomalies would include major and minor physical anomalies, brain deviations, limb abnormalities, and organ dysfunction. It is our expectation that a majority of people diagnosed with autism will show a diverse pattern of anomalies, due to pleiotropic effects that occur during early organogenesis.

A systematic study can also examine whether the different kinds of expected anomalies are randomly spread over the sample or whether there are specific kinds or subgroups of anomalies that co-occur with autism. In a forthcoming report, we show that there is evidence that schizophrenia also originates from disturbances during early organogenesis, because people diagnosed with schizophrenia also show more physical anomalies established during this stage, compared with control subjects (79). There seems to be an overlap in physical anomalies found in people with autism and schizophrenia, but there are also remarkable differences. For example, the major structural anomalies that frequently co-occur with schizophrenia are Velocardio-facial syndrome (80) and Prader–Willi syndrome (81), which are different from the ones found in people with autism. This implies that the physical anomalies that co-occur with either autism or schizophrenia are not entirely random. Thus, the genetic or environmental disturbance has pleiotropic effects during early organogenesis, resulting in a variety of anomalies, but there seems to be a pattern in these anomalies. For example, exposure to thalidomide during early organogenesis resulted in a variety of anomalies, including autism, but not schizophrenia.

With the research available to us, we can only speculate why this would be the case. One possibility might be the influence of genomic imprinting, which results in the expression of genes from only one of the two parental chromosomes (82). The expression of an imprinted gene can lead to two different developmental pathways, depending on whether the genes are

maternally or paternally expressed. Imprinted genes are involved in neurodevelopment (83) and might play a role in the development of autism and schizophrenia (84). In addition, imprinted genes are highly pleiotropic (85) and are expressed during early embryogenesis (83), so it is likely that they play an important role during early organogenesis. Genomic imprinting might also explain gender differences in autism, with autism being an extreme paternally biased imprinted brain, which is more common in boys than in girls (86). Perturbations during early organogenesis are, because of the abundance of pleiotropic effects during this stage, the start of disturbed developmental pathways that have cascading effects with far-reaching consequences.

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