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Research Article

Research Insights into the Etiology of Autism

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Abstract

A variety of environmental factors affecting the internal biochemical milieu have been found to coexist with autism. Efforts to convincingly demonstrate a cause-and-effect relationship with any of them are explored here. Several have been discarded after extensive research has failed to corroborate a cause-and-effect relationship. Currently, the most plausible appears to be the attenuated role of insulin-like growth factor in promoting myelination of neurons in neonates.

INTRODUCTION

Autism is characterized by abnormal neurodevelopment involving deranged connectivity between specific regions of the brain as well as aberrant neural linkage between the central nervous system and particular peripheral motor activities [1]. As a result, individuals affected by this condition exhibit varying degrees of an inability to maintain normal social contact, hyper-reactivity to sensory input, and a strong preoccupation with atypical objects [2].

While the fundamental cause of autism has yet to be discerned conclusively, it is generally agreed among researchers in this field that the etiology of this malady is in part due to a genetic proclivity and to an environmental trigger. As will be discussed, a specific recurring genetic abnormality that explains the origin of the disorder in nearly all of the diagnosed cases has yet to be defined. On the other hand, a number of biochemical alterations in response to environmental factors are often coexistent with the appearance of autism [3]. Whether or not such correlations represent cause-and-effect events or are merely contemporary phenomena remains uncertain.

The following illustrates the proposed overall cooperative relationship between genetics and environmental factors in promoting the appearance of autism:

GENETIC PROPENSITY + ENVIRONMENTAL TRIGGER →AUTISM

GENETICS = genomic proclivity to be translated into neuropathologic characteristics mediated by appropriate promoters (triggers) TRIGGERS = heavy metals, oxidative stress, viruses, hypoxia, pesticides, inflammation, hyperglycemia

IN OTHER WORDS

To develop autism, a fetus/infant would typically:

- Possess a specific genetic modification, and
- Be exposed to one or more environmental triggers.

Discussion – Environmental triggers

Mercury, lead

Certain children are more sensitive to heavy metal accumulation because of an apparent genetic predisposition. The defect relates to dysfunction of methylene tetrahydrofolate reductase, which is responsible for efficient metal export. Metallothione in modification in such poisonings can affect binding and mobilization of heavy metals [4]. However, the specific role of the alterations in autism remains to be ascertained.

That heavy metals can induce neurotoxicity has been known for some time. For example, following mercury pollution of water in the Minamata industrial disaster, many children developed neurologic malfunctions [5]. Subsequently, methyl mercury was found to be elevated in fish in waters surrounding Japan, but a specific relationship with autism in particular was not substantiated. At high ingested levels of mercury, myelination and neuron growth are attenuated, which decreases long-distance connectivity normally coupled with the growth of axons in the young [6].

Lead

Alters the balance of calcium, protein kinase C, and glutamate to interfere with neurotransmitter release and nerve conduction in the developing brain [7]. Some autistic children have serum lead in markedly elevated amounts, but this abnormal result is absent in most neurologically affected youngsters [8]. Heavy metal chelation has been applied in some cases of autism for putative therapeutic purposes, but no consistent symptom improvement can be demonstrated [9].

Oxidative stress

Although oxygen is needed to transform chemical bond energy into ATP, reactive oxygen species and free radicals formed

in metabolism in excess can pose a threat to proper cell function and integrity. Normally, glutathione removes factors promoting oxidative stress [10]. Abnormal glutathione synthesis in some autistic patients can cause decreased S-adenosyl methionine (SAM) and glutathione. This can attenuate epigenetic methylation, phosphatidylcholine function, conversion of norepinephrine to epinephrine, and free radical suppression, as well as creatine, cytosine, tetrahydrofolate, and methionine synthesis [11]. Diminished glutathione availability can reduce the activity of the detoxification enzyme, glutathione-S-transferase (GST), as well. A group of pregnant mothers were evaluated for the presence of GSTP1 haplotype [12]. Deficits in this cellular pathway were found to make a neonate apparently more susceptible to autism. In addition, levels of glutathione-cysteine ligase were 14% lower in affected individuals [13]. In more than two-thirds of autistic patients examined, reduced levels of the two anti-oxidants, transferrin and ceruloplasmin, are found [14]. Increased oxidative stress might be concurrent with these changes. Similarly, decreased omega-3 fatty acids are often present in affected individuals. Such lipids are important for proper signal transduction, regulation of inflammation, and neuron repair and survival [15]. In some autistic patients, lactic acid, a possible indicator of mitochondrial dysfunction, is elevated [16]. Down's syndrome, which is sometimes accompanied by autistic-like behavior, is associated in many cases with increase in hydrogen peroxide, which exhausts the glutathione supply [17]. The activity of aconitase, used to measure mitochondrial dysfunction and oxidative damage, is 45% lower in the brains of autistic children when compared to normal controls [18]. Superoxide dismutase, glutathione peroxidase, and malondialdehyde are similarly lower in autistic patients. These findings, when taken together, imply a deficiency in the detoxification system associated with autism [19].

Pesticides and Air Pollution

Several studies have suggested that pesticides and air pollutants are significant environmental triggers in the appearance of autism. Pesticides often contain organophosphates (OP). Large doses of OP inhibit the esterase breaking down acetylcholine (Ach). Especially in autistic patients, the neurotransmitter is frequently elevated. Ach normally plays an important role in synaptic transmission and neurological signaling. The damage to normal neuronal signaling and the depletion of working synapses in the brain are now believed to be key events in the susceptible aspects of autism as well [20]. Alternatively, pesticides containing organo chlorides affect GABA (the neurotransmitter, gamma-aminobutyric acid) development [21].

Traffic air pollutants induce both inflammation and oxidative stress. Especially in pregnant women, they appear to have a direct effect on placental production of insulin-like growth factor (see discussion below) [22]. One such group of pollutants, polycyclic aromatic hydrocarbons, interact with MET (mesenchymal-epithelial transition factor) gene. MET is a potent modulator of synaptogenesis in late-stage fetuses and in newborns. Interruption of neurodevelopment at this time can lead to behaviorial problems [23]. The odds of taffic-related pollutants affecting the genesis of autism in prenatal fetuses have been correlated with the distance the gravid as lived from freeways, especially during late pregnancy [24].

Insulin-Like Growth Factor

Insulin-like growth factor (IGF), under the control of insulin in early pregnancy and growth hormone in advanced pregnancy and in postnatal life, has as one of its main functions during gestation the stimulation of oligodendrocytes in the central nervous system. They support the synthesis and placement of myelin sheathing on the axons of developing neurons. Myelination begins in the late second trimester of pregnancy and reaches its peak growth by one year post-delivery. This allows impulses to travel 100 times faster than prior to myelination by strengthening, lengthening, and finalizing the most functional course of the nerves to allow saltatory action potential conduction between the nodes of Ranvier [25]. Lumbar punctures in children being tested for other medical reasons revealed lower levels of IGF in the cerebrospinal fluid of autistic children than normal ones up to the age of 4 years [26]. Very-small-for-gestational age (VSGA) neonates display lower levels of IGF in their umbilical cord bloods than normal-sized babies, as well as a higher incidence of autism [27]. Hypo-myelinated neurons are more commonly found in postmortem brain biopsies of autistic than normal children [28]. Transgenic mice which lack the ability to produce IGF have reduced axonal diameters and decreased nerve conduction velocities [29]. Magnetic resonance imaging has identified decreased myelination in autistic young children [30]. Reduced levels of IGF are found in neonates where the mother experienced an inflammatory process during pregnancy (especially viral). This is thought to result from the persistence of interleukin-6, which causes the placenta to produce less of the growth factor. The relationship of this to the occurrence of neuro developmental ailments in such children may be expected to reduce oligodendrocytes activity, causing suppression of myelin synthesis [31]. In addition, IGF inhibits oxidative stress-induced apoptosis in stem cells [32]. One way to possibly alleviate this growth factor deficiency in the newborn is through breastfeeding. The natural source with the highest readily available concentration of IGF is human breast milk. Children who have been breastfed exclusively for a full year have a lower incidence of autism [33].

Folic Acid

Tetrahydrofolate and the amino acid, methionine, form a pathway that is essential for cellular redox balance, deoxynucleotide synthesis, and DNA methylation. This vitamin is also utilized to reduce the level of potentially neurotoxic homocysteine [34]. Some polymorphic genes involved in folic acid metabolism cause reduction in the availability of folate. It has been observed that gravidas who consume folic acid around the time of conception to reduce the risk of neural tube defects also produce fewer autistic children [35].

Gluten

Some youngsters with autism have increased intestinal wall permeability. It has been proposed that such leakage could increase the circulatory level of gluten and casein metabolites (casomorphin and gluteomorphin) which may interfere with normal behavior in children [36]. However, diets restricting the

ingestion of these foods have done little to change the incidence or intensity of autism.

Genetic proclivity

The primary discovery that revealed an apparent genetic connection to the etiology of autism was made with monozygotic (MZ) twins. It is popularly assumed that monozygotic twins are totally identical. Such binary sets presumably possess at birth indistinguishable genotypes since they arise from the same fertilized egg ("natural clones"). This similarity may be modified somewhat by epigenesis as postpartum time passes, especially if each member of the twin set is raised in a separate environment. The rate of spontaneous mutation is more similar within sets of MZ twins than between sets. This suggests that the contribution of concordant genetics in the determination of mutation frequency is substantial and delimiting [37]. However, small variations of environmental factors even in utero may lead to identifiable intraset diversity after birth. For example, a study of monozygotic quadruplets reported identifiable differences in their fingerprints, where the initial pattern is genetically determined but may be modified with varying degrees of direct pressure between fetuses [38].

If the somatic translation of the genetic sequence were exact within a set and if autism occurrence were controlled by the genome exclusively, one would expect the appearance of this disorder in one member to be duplicated in the second in the same manner. Whereas concordance of autism in twin sets was found in one study to be 31% for dizygotic pairs, it was 88% (but not 100%) for monozygotic twins. The latter result would suggest that occurrence of autism is in part determined by genetic factors and that additional causes (e.g., the presence or absence of environmental triggers) influence the appearance of this neurologic condition [39]. Siblings of autistic children have a 7.5 times greater chance of also having the disorder than the general population at random [40].

Autism is considered to be one of the most heritable neuropsychiatric illnesses. Recent studies conclude that the degree of heritability is closer to 55%, so that the combination of genetic tendency and environmental triggers needs to be considered in elucidating the etiology of this ailment [41]. The recent development of whole genome analysis has made possible the expedited search for gene variations/mutations in autistic patients. As a result, the hunt for genotypic sequences that may be involved has widened. As of January, 2014, almost ten SNPs (single nucleotide polymorphisms) have shown a statistically significant correlation with autism [42]. De novo mutations associated with autism have been found in hundreds of different genes across the genome. The majority of them appear in only some affected cases, but the search continues for the key promoters of this disease. For example, a few instances of mutations have been identified in the gene, NTNG1, which plays a role in the organization of nerve cells, and in the FOXP1 gene, which is associated with language development [43]. However, no discrete mutations have been found consistently in the majority (let alone in 100%) of autism subjects tested. This suggests that autism may be a genetically heterogeneous condition, whereby similar phenotypes may arise from variants of multiple genes.

An additional possibility is gene polymorphism. The potential role of IGF deficiency in autism was discussed above. Essentially all of the polymorphic forms of this gene result in the production of lower levels of the growth factor [44]. If the proposed consequence of reduced IGF promoting one of the apparent hallmarks of autism, hypo-myelinated axons, a central determinant of this mechanism could be polymorphism of the IGF gene, although this remains to be demonstrated in the laboratory. It was recently reported that persistent intrauterine hyperglycemia in pregnant diabetic females induces epigenetic modification of the IGF gene in particular. Autism risk is significantly increased in the children of mothers with diabetes during pregnancy [45].

DISCUSSION

Both factors in the external environment (e.g., pesticides, oxidants, and heavy metals) and those originating within the body of the fetus and/or neonate (e.g., IGF gene polymorphism) may have detrimental effects on the developing neurologic system. It remains to be determined if any of them dominate the initiation of autism in particular.

Recent research has been emphasizing the role of insulin-like growth factor (IGF) in neonatal neurogenesis. In the absence of adequate myelination, brain dysconnectivity appears to dominate [46]. IGF supplementation has improved the neurologic status of children with autism-like Phelan-McDermid Syndrome [47].

CONCLUSION

Much scrupulous, convincing research remains to be completed to corroborate hypotheses suggesting the fundamental etiopathology of autism. Whereas a great deal of effort and funding has been dedicated to this effort so far, little appears to be conclusive at this stage. In the process, much has been learned about neurochemistry and neurophysiology. The modes utilized by the body to transmit neurologic signals within the central nervous system and to the peripheral areas of function are better understood today than when autism was first identified as a unique condition in 1943. At this point of time, it would appear that the primary etiology of autism is related to an impeded ability to myelinate new neurons in infants, whether due to environmental factors or inborn errors of metabolism or genetics. If correct, the key reducing the incidence of this neuropathology may be testing newborn for reduced levels of IGF and then supplementing them for the first year or so of life, when myelination of the young nervous system reaches its peak.

REFERENCES

1. Steinman D, Mankuta R, Zuckerman F, Gray E. "The Cause of Autism Concepts and Misconceptions". Baffin Books Publishing. New York. 2014.
2. Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol. 2007; 17: 103-111.
3. Martin JJ, Schlote W. Central nervous system lesions in disorders of amino-acid metabolism. A neuropathological study. J Neurol Sci. 1972; 15: 49-76.
4. Lithe R. Autism, brain, and environment. Jessica Kingsley Publishers. 2006.

5. Eto K, Marumoto M, Takeya M. The pathology of methylmercury poisoning (Minamata disease): The 50th Anniversary of Japanese Society of Neuropathology. Neuropathology. 2010; 30: 471-479.

6. Onuma TA, Ding Y, Abraham E, Zohar Y, Ando H, Duan C. Regulation of temporal and spatial organization of newborn GnRH neurons by IGF signaling in zebrafish. J Neurosci. 2011 Aug 17; 31:11814-24.

7. Goldstein GW. Lead poisoning and brain cell function. Environ Health Perspect. 1990; 89: 91-4.

8. Cohen DJ, Paul R, Anderson GM, Harcherik DF. Blood lead in autistic children. Lancet. 1982; 2: 94-5.

9. Davisa TN, Reilly MO, Kang S, Lang R, Rispolid M, Sigafoos J, et al. Chelation treatment for autism spectrum disorders: A systematic review. Res Aut Spec Dis. 2013;7: 49-55.

10. Meguid NA, Dardir AA, Abdel-Raouf ER, Hashish A. Evaluation of oxidative stress in autism: Defective antioxidant enzymes and increased lipid peroxidation. Biol Tr Elem Res. 2011; 143: 58-65.

11. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr. 2004; 80: 1611-7.

12. Makkonen I, Kokki H. Kuikka J, Turpeinen U, Riikonen R. et al. Effects of fluoxetine treatment on striatal dopamine transporter binding and cerebrospinal fluid insulin-like factor-1 in children with autism. Neuroped 2011; 42: 207-209.

13. Gu F, Chauhan V, Chauhan A. Impaired synthesis and antioxidant defense of glutathione in the cerebellum of autistic subjects: Alterations in the activities and protein expression of glutathione-related enzymes. Free Rad Biol Med. 2013; 65: 488-496.

14. Chauhan A1, Chauhan V. Oxidative stress in autism. Pathophysiology. 2006; 13: 171-81.

15. Ghezzo A, Visconti P, Mazzanti I. Oxidative stress and erythrocyte membrane alterations in children with autism: Correlation with clinical features. PLoS One. 2013; 8: 66418.

16. Harvey RA, Ferrier DR. "Biochemistry"- 5th edition. Wilkins, Philadelphia, 2011.

17. Zimmerman AW, "Autism: Current theories and evidence". Humana Press, Baltimore, 2008.

18. Rose S, Melnyk S, Pavliv O, Bai S, Nick TG, Frye RE, et al. Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. Transl Psychiatry. 2012 Jul 10; 2: 134.

19. Ghanizadeh A. Malondialdehyde, Bcl-2, superoxide dismutase and glutathione peroxidase may mediate the association of sonic hedgehog protein and oxidative stress in autism. Neurochem Res. 2012; 37: 899-901.

20. Tsai GE. Editorial: Regulating the CNS grand regulator; N-methyl-D-aspartate receptor-mediated neurotransmission. Curr Pharm Des. 2014; 20: 5115-5117.

21. Belmonte MK, Bourgeron T. Fragile X syndrome and autism at the intersection of genetic and neural networks. Nat Neurosci. 2006; 9: 1221-1225.

22. Patterson PH. Maternal infection and immune involvement in autism. Trends Mol Med. 2011; 17: 389-394.

23. Sheng L, Ding X, Ferguson M, McCallister M, Rhoades R, Maguire M, et al. Prenatal polycyclic aromatic hydrocarbon exposure leads to behavioral deficits and downregulation of receptor tyrosine kinase, MET. Tox Sci. 2010; 118: 625-634.

24. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect. 2011; 119: 873-877.

25. D Purves, G.J.Augustine, D.Fitzpatrick, et al., eds. Neuroscience 5th edition, Sinauer Assoc. Sunderland, MA. 2012; 51-55.

26. Riikonen R, Makkonen I, Vanhala R, Turpeinen U, Kuikka J, Kokki H, et al. Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism. Dev Med Child Neurol. 2006; 48: 751-755.

27. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH, et al. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. Pediatrics. 2011; 128: 883-891.

28. Zikopoulos B, Barbas H. Changes in prefrontal axons may disrupt the network in autism. J Neurosci. 2010 3; 30: 14595-609.

29. Ye P, Li L, Richards RG, DiAugustine RP, D'Ercole AJ. Myelination is altered in insulin-like growth factor-I null mutant mice. J Neurosci. 2002; 22: 6041-6051.

30. Acosta MT, Pearl PL. Imaging data in autism: from structure to malfunction. Semin Pediatr Neurol. 2004; 11: 205-13.

31. Garay PA, Hsiao EY, Patterson PH, McAllister AK. Maternal immune activation causes age- and region-specific changes in brain cytokines in offspring throughout development. Brain Behav Immun. 2013; 31: 54-68.

32. Li Y, Shelat H, Geng YJ. IGF-1 prevents oxidative stress induced-apoptosis in induced pluripotent stem cells which is mediated by microRNA-1. Biochem Biophys REs Commun 2012; 426: 615-619.

33. Steinman G1, Mankuta D. Breastfeeding as a possible deterrent to autism--a clinical perspective. Med Hypotheses. 2013; 81: 999-1001.

34. Kałużna-Czaplińska , Żurawicz E, Michalska M, Rynkowski J. A focus on homocysteine in autism. Acta Biochim Pol. 2013; 60: 137-142.

35. Surén P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA. 2013; 309: 570-577.

36. Elder JH, Shankar M, Shuster J, Theriaque D, Burns S, Sherrill L, et al. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006; 36: 413-420.

37. Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs. J Child Psychol Psychiatry. 1977; 18: 297-321.

38. Steinman G. Mechanisms of twinning. I. Effect of environmental diversity on genetic expression in monozygotic multifetal pregnancies. J Reprod Med. 2001; 46: 467-472.

39. Rosenberg RE, Law JK, Yenokyan G, McGready J, Kaufmann WE, Law PA, et al. Characteristics and concordance of autism spectrum disorders among 277 twin pairs. Arch Pediatr Adolesc Med. 2009; 163: 907-914.

40. Grønborg TK, Schendel DE, Parner ET. Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study. JAMA Pediatr. 2013; 167: 947-953.

41. Geschwind DH1. Genetics of autism spectrum disorders. Trends Cogn Sci. 2011; 15: 409-16.

42. Welter D, MacArthur J, Morales J, Burdett T, Hall P, Junkins H, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res. 2014; 42: 1001-1006.

43. Hamdan FF, Daoud H, Rochefort D, Piton A, Gauthier J, Langlois M , et al. De novo mutations in FOXP1 in cases with intellectual disability, autism, and language impairment. Am J Hum Genet. 2010; 87: 671-678.

44. Arends N, Johnston L, Hokken-Koelega A, van Duijn C, de Ridder M, Savage M, et al. Polymorphism in the IGF-I gene: clinical relevance for short children born small for gestational age (SGA). J Clin Endocrinol Metab. 2002; 87: 2720.

45. Zinkhan EK, Fu Q, Wang Y, Yu X, Callaway CW, Segar JL, et al. Maternal Hyperglycemia Disrupts Histone 3 Lysine 36 Trimethylation of the IGF-1 Gene. J Nutr Metab. 2012; 2012: 930364.

46. Steinman G. Plausible etiology of brain dysconnectivity in autism - Review and prospectus. Med Hypotheses. 2015; 85: 405-107.

47. Kolevzon A, Bush L, Wang AT, Halpern D, Frank Y, Grodberg D, et al. A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome. Mol Autism. 2014; 5: 54.

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