

Short Communication

Gene Polymorphism in the Genesis of Autism

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Introduction

Several publications have reported extensive efforts to locate a gross genetic mutation which triggers autism spectrum disorder (ASD).

Which triggers autismspectrum disorder (ASD)? No one high-impact mutation discovered so far has been found in more than a few severe autism cases. This suggests that no specific gross nuclear defect is the primary etiology of this disease in the majority of occurrences, if any [1]. Conditions that do bear some of the characteristics of this disease but are not true autism, such as Fragile X and Rett Syndrome, are identified with specific defective genes, unlike ASD [2,3]. That genetics may play some role is assumed since

- 1) both members of a monozygotic set are affected in 90% of such cases; and
- 2) a neonate in a family with one other autistic sibling has a 1-in-5 chance of also bearing this malady, in contrast to 1-in-64 in the general population [3,4].

Background

Insulin-like growth factor-1 (IGF) modulates, among many other activities, the myelination of axons via oligodendrocytes, especially in infants (4). Timely IGF administration can enhance myelination repair of axons subjected to transection or hypoxia. Deficient hepatic production of IGF can be the result of abnormal growth hormone receptor or polymorphism-affected IGF-1 gene [5].

Autism appears to be related to the amount of insulin-like growth factor-1 present in youngsters. One such investigation found depressed levels of IGF in the cerebrospinal fluid (CSF) of autistic children, compared to normal children, in the ages of 1-4 years. That the genesis of autism was confined to biochemical abnormalities in early age was shown by normal levels of IGF-1 found in the CSF of older affected children [6]. Biopsies of the brains of autistic children reveal diminished neuronal myelin layers, compared to non-autistic youngsters [7]. It has been proposed that such a deficiency could explain the dysconnectivity typically found in such patients with this condition [8].

Human breast milk is known to supply enhanced amounts of IGF, compared to bovine milk or baby formula. The polypeptide survives passage through the digestive tract. Children who have been breast-fed exclusively for up to one year of age exhibit markedly fewer cases of autism than those feeding by alternative methods [9,10].

Until now, the majority of postulated genetic causes of autism relate to synaptic function. This could be the result of under-myelinated neurons [3,8]. In contrast to the multiple genetic variants of idiopathic autism, such syndromes as Rett [MECP2], Fragile X [Xq27.3], Tuberous Sclerosis [9q34;16p13.3], and Phelan-McDermid [SHANK3] can be correlated with single gene defects [in brackets] [11-13]. Conditions such as Rett Syndrome bear characteristics which differ significantly from true autism such as microcephaly, cholinergic neuron damage, frontal cortex pathology, and involvement almost exclusively with females [3]. Whereas no single gross genetic mutation has yet been correlated with the appearance of autism, multiple SNP polymorphisms of the IGF gene promoter have been identified in a number of conditions [14-16]. Each leads to a reduced production of IGF. For example, a statistically significant identification of single-nucleotide polymorphisms of two receptor substrate IRS mediators of the IGF pathway were found in

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patients with autism when compared with normal youngsters [17].

Genetic polymorphism, unlike gross, malfunctioning mutations, may involve single base pair changes (SNPs) in a given functional DNA sequence. A synonymous SNP, if within a coding sequence, does not affect the resultant protein sequence but can be translated into reduced ribosomal product synthesis. The findings discussed earlier support the proposal that depressed IGF levels in the newborn, especially those due to genetic polymorphisms, can lead to the development of autism spectrum disorders in early childhood [18]. Identification of this deficiency at birth could promote the administration of IGF during the first year or so of life when central myelination of new neurons and establishment of functional neural pathways occur, especially in the brain [3].

Proposal

Des (1-3)IGF-1 in combination with glatiramer has been recommended for this purpose. Truncated IGF-1, which links more weakly to IGF-binding protein (IGFBP), is about 10 times more potent in cell stimulation than unmodified IGF [19,20]. Also, it is more effective in penetrating the blood-brain barrier and is believed to be less mitogenic than the 70-amino acid unit IGF itself [21]. In a clinical setting, this form of modified IGF seems to be useful in treating the symptoms of certain neuropathology such as Rett Syndrome [22].

As noted earlier, reduced levels of IGF can be associated with several abnormalities in the various stages of life such as acne, esophageal metaplasia, and prostate cancer. To rationalize why all such maladies are not apparent in autistic persons at the same time, epigenetic processes governing the rate of production of IGF need to be considered. For example, very-small-for-gestational-age neonates are known to display autism much more often than normal-sized babies [23]. Also, programmed metabolic disorders of the newborn are often a consequence of maternal malnutrition, whereby essential amino acids would have been in short supply during the prenatal period [24]. If a baby were born with uncorrected low IGF levels, consequences such as autism first identified during early childhood could develop.

A further factor determining the timing of IGF polymorphism translation is which allele is the modified one. For example, in the IRS case noted earlier, the involved genetic SNPs are rs1801123 and rs4773092 [17], whereas definition of teenage height achieved by milk intake is determined by rs680 [25]. Also, rs35767 has a fundamental role related to osteoporosis and mineral density in the postmenopausal population [26]. Hence, each genetic polymorphic variant controlling IGF output at a particular time in life has its own temporal translational characteristics which appear to be independent of others that may or may not be epigenetically suppressed simultaneously in the same individual.

Conclusions

Of particular interest here is the incorporated polymorphism units which reduce output of IGF needed for proper neuron development in the newborn. Such deficient candidates become especially susceptible to developing autistic brain dysconnectivity as a result, unless IGF supplementation is provided. To reduce the occurrence of autism, it has been suggested that all newborn have their cord bloods tested for IGF levels [4]. The present review indicates that such perinatal testing should include determination of the IRS1 polymorphic gene as well [17]. Abnormal results could indicate the need for IGF supplementation via injection or breast-feeding to reduce the chance for autism development. Massage therapy is also able to raise the IGF level in premature neonates [27].

References

1. Iossif I, Levy D, Allen J (2015) Low load for disruptive mutations in autism genes and otherwise biased transmission. *PNAS* 112(41): E5600-E5607. PNAS.org/cgi/doi/10.1073/PNAS.1051676112
2. Moy SS, Nadler JJ, Young NB (2009) Social approach in genetically-engineered mouse line relevant to autism. *Genes Brain Behav* 8(2): 129-142.
3. Steinman G (2014) (editor-in-chief): "The cause of autism", Baffin Books Publishing, New York.
4. Steinman G, Mankuta D (2013) Insulin-like growth factor and the etiology of autism. *Med Hypotheses* 80(4): 475-480.
5. Cianfarani S, Clemmons DR, Savage MO (2005) (eds): IGF-1 and IGF binding proteins, basic research and clinical management. *Endocr Dev Basel Krager* 9: 8,11,38,144.
6. Riikonen R (2006) Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism. *Devel Med & Child Neuro* 48(9): 751-755.
7. Zikopoulos B, Barbas H (2010) Changes in prefrontal axons may disrupt the network in autism. *J Neurosci* 30(44): 14595-14609.
8. Steinman G (2015) Plausible etiology of brain dysconnectivity in autism – review and prospectus. *Med Hypotheses* 8(4): 405-407.
9. Steinman G, Mankuta D (2013) Breastfeeding as a possible deterrent to autism. *Med Hypotheses* 81(6): 999-1001.
10. Tseng PT, Chen YW, Stubbs B (2017) Maternal breastfeeding and autism spectrum disorder in children: A systematic review and meta-analysis. *Nutr Neurosci* Oct 18: 1-9.
11. Riikonen R (2017) Insulin-like growth factors in the pathogenesis of neurological diseases of children. *Int J Mol Sci* 18(10): 2056-2073.

12. Voineagu I, Wang X, Johnston, P (2011) Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 474(7351): 380-384.
13. Jiang Yh, Yuen RKC, Jin X (2013) Detection of clinically relevant genetic variants in autism spectrum disorder by whole-genome sequencing. *Am J Hum Genet* 93(2): 249-263.
14. Rahaman SMA, De D, Handa S (2016) Association of insulin-like growth factor (IGF)-1 gene polymorphisms with plasma levels of IGF-1 and acne severity. *J Am Acad Dermatol* 75(4): 768-773.
15. McElholm AR, McKnight AJ, Patterson CC (2010) A population-based study of IGF axis polymorphisms and the esophageal inflammation, metaplasia, adenocarcinoma. *Gastroenterology* 139(1): 204-212.
16. Qian J, Zhou H, Chen J (2014) Genetic polymorphisms in IGF-1 and IGFBP-3 are associated with prostate cancer in the Chinese population. *PLoS One* 9(2): e85629. doi: 10.1371/journal.pone.0085609
17. Park HJ, Kim SK, Hang WS (2016) Association between IRS1 gene polymorphism and autism spectrum disorder: A pilot case-control study in Korean males. *Int J Mol Sci* 17(8): pii.E1227. doi:10.3390/ijms17081227.
18. Khalil RB (2017) Is insulin growth factor-1 the future for treating autism spectrum disorder an/or schizophrenia?. *Med Hypotheses* 99: 23-25.
19. Steinman G (2017) A new pharmacologic approach for the potential reduction of autism and multiple sclerosis. *Sci Pages Ped Neuro* 1(1): 1-5.
20. Ballard FJ, Wallace JC, Francis GL (1996) Des(1-3)IGF-1: A truncated form of insulin-like growth factor-1. *Int J Biochem Cell Biol* 28(10): 1085-1087.
21. Neuren Pharmaceuticals.
22. Riikonen R (2016) Treatment of autistic spectrum disorder with insulin-like growth factors. *Europ J Paedia Neuro* 20(6): 816-823.
23. Lampi KM, Lehtonen L, Tran PL (2012) Risk of autism disorders in low birth weight and small for gestational age infants. *J Pediatr* 161(5): 830-836.
24. Reynolds CM, Perry NK, Vickers MH (2017) Manipulation of the growth hormone-insulin-like growth factor (GH-IGF) axis: A treatment to reverse the effects of early life developmental programming. *Int J Mol Sci* 18(8):1729-1750.
25. Dedousis GV, Louizou E, Papoutsakis C (2010) Dairy intake associates with the IGF rs680 polymorphism to height variation in periadolescent children. *Europ J Clin Nutr* 64: 253-258.
26. Yun-Kai L, Hui W, Xin-wei Z (2014) The polymorphism of insulin-like growth factor (IGF-1) is related to osteoporosis and bone mineral density in postmenopausal population. *Pak J Med Sci* 30(1): 131-135.
27. Field T, Diego M, Hernandez-Reif M (2008) Insulin and insulin-like growth factor 1 (IGF-1) increased in preterm neonates. *J Dev Behav Pediatr* 29(6): 463-466.