



## IGF – Autism prevention/amelioration

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### ABSTRACT

Autism continues to be a significant cause of psychosocial pathology in affected children and adults. Until recently, the predominant research thrust to uncover the cause of this condition has been the search for a major nuclear mutation. Although a small percentage of cases do demonstrate such a DNA fault, recent effort has come to emphasize problems in the biochemistry of its sufferers. In particular, insulin-like growth factor-1 (IGF) has become the center of concern in many laboratories. A deficiency in this growth factor, leading to insufficient neuron myelination and defective synapse function, appears to result in brain dysconnectivity during the first year of postpartum life, and cause social malfunction in childhood years and beyond. At least three approaches have been reported by which this deficiency can be corrected in neonates before irreversible damage has been caused. The overall purpose of this report is to bring together related observations and to evolve a coherent, plausible explanation of the cause and prevention of autism.

### Introduction

A review of studies made on autism could be divided into two groupings:

- 1) Preventive actions before symptoms appear; and
- 2) Pharmacologic and psychotherapeutic approaches to managing behavioral problems in affected children.

The purpose of early (first postpartum year) diagnostic procedures is to forewarn health professionals of the possibility of manifest autism developing later. The covert pathological processes underlying this disorder occur mainly during the first year of postpartum life, whereas overt symptoms and behavioral changes of varying degrees become apparent between one and four years of age [1,2]. Although most of the procedures and approaches to be discussed here are still in the research/developmental stage, confirming data could ultimately support this combination of techniques to derive a practicable approach to reducing the incidence of autism.

#### First grouping (0–12 months)

Prenatal parameters that may bear on this diagnosis have yet to be refined. For example, IRS1 (insulin receptor substrate-1) is a key mediator of the IGF metabolic pathway in the nervous system. IRS1 receives signals from the cell membrane IGF-1 receptor for information transfer to the intracellular PI3K-AKT-mTOR mechanism to inhibit neuronal apoptosis [3,4]. In a case-control study comparing autism-affected individuals and normal controls, a statistically significant occurrence of the single-nucleotide polymorphism (SNP) of the IRS1

mediator (rs1801123) was found in affected individuals [5]. Discriminating probability results were additive  $p = 0.022$  and dominant  $p = 0.013$ . Heritability in autism has been estimated to be greater than 90% [6]. Such polymorphisms cause a reduced production of IGF. Thus, a differentiating genetic parameter such as IRS1 could conceivably be detected by antepartum amniocentesis as well.

Another example of IRS1 polymorphism involves glucose metabolism [7]. A glycine/arginine change of codon G972R “shortens” the effective portion of the gene. This reduces tyrosine phosphorylation by greater than 60%, thereby increasing the risk of type 2 diabetes.

In diagnosing autism spectrum disorder (ASD) at birth, pertinent biochemical characteristics can be quantified using the Autism Index (AI) [8]. Autism is a spectrum of conditions which might be differentiated by AI values. This index is the sum of three blood tests that are often abnormal in affected neonates: insulin-like growth factor-1 (IGF), serotonin, and anti-myelin basic protein [1,9,10]. Such a calculation could be used to determine at birth the likelihood that each seemingly unaffected neonate would ultimately be somewhere on the autism spectrum or not after one year of age.

Magnetic resonance imaging gives some early postpartum warnings of a child possibly at risk (e.g., born markedly premature or with an already diagnosed older sibling) in the age range 6–12 months. Such studies have showed enlarged brain surfaces and reduced prefrontal white (myelinated) matter of some who later demonstrated autism [11,12].

A condition which may lead to irreversible brain dysconnectivity during neural circuit formation in the first year of life is hypo-myelination of axons and decreased numbers of cerebellar Purkinje cells [1,13]. In a normal child, this process fixes in place the central nerve pathways which are the most functional [14]. IGF activation of

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oligodendrocytes is a primary factor promoting myelination. Brain biopsies of individuals who are autistic display markedly under-myelinated neurons [15]. As a result, synapses cannot develop properly because of reduced nerve impulse velocity. In unaffected children on the other hand, the greatest increase in the number of active synapses occurs during the first 12 postpartum months, the same time myelination is taking place [16]. This is consistent with the observation that IGF-I mRNA in the nervous system reaches its highest level during late fetal stage and the first postpartum year [17].

Other than paracrine secretion, the main sources of IGF are the placenta before birth and the liver after [18,19]. There are at least three loci where the ultimate effect of this factor can be realized (and possibly modified):

- 1) the liver itself;
- 2) the intracellular transfer of information from cell membrane IGF receptor components;
- 3) and incorporation of such information into nuclear biosyntheses.

An example of practicable findings is identifiable polymorphic modifications, such as that of IRS1 noted above. These aberrations may reduce the final effects of endocrine IGF by diminishing its intracellular information transfer to nuclear functions. Such a factor may be one of the underlying causes decreasing myelination in developing neurons.

Exploratory studies in the first-year grouping of children are increasingly pointing to the 67-unit C-terminal truncated polypeptide, (Des)IGF, which might aid in achieving normal myelination in myelin-deficient babies [20]. This peptide was first identified in milk colostrum and human brain. It is believed (Des)IGF promotes IGF production once it reaches the neurogenic site. As a result, the chance of later developing autism would be reduced.

At least three methods have been reported which can elevate the IGF factor if the neonate is found to be deficient:

- 1) IGF can be given by injection. Derivatives of tripeptide IGF<sub>1-3</sub> now under development may be administered by mouth and serve this purpose as well [21,22]. Such medications ameliorate some of the symptoms of children with Rett Syndrome, a condition which is like autism in some aspects.
- 2) Babies nourished exclusively with breastfeeding for the first full year of life exhibit a significantly lower incidence of autism than those with mixed diets [23,24]. Human milk has higher levels of IGF than cow's milk or formula [25].
- 3) Massage therapy has been found to increase the IGF level especially in preemies, which typically have a higher incidence of autism than full-term babies [26]. Children who had undergone treatment soon after birth with this method scored higher in Mental Development Index tests at two years of age than those untreated [27]. Small studies have suggested that massage therapy may benefit individuals with ASD [28].

The issue raised in method #3 above reexamines an idea promoted in the 1950s and 1960s. Based on the proposal formulated by Leo Kanner, John Bowbly, and Bruno Bettelheim, early professionals in the field of autism, the concept of the "Refrigerator Mom" was proposed. It was concluded that mothers who had little physical contact with their newborns were less likely to thwart the development of autism in them. However, after much debate and discussion, the concept was discarded. In contrast, the benefit of massage therapy and regular physical contact could deter the subsequent development of autism in the child [29].

### Second grouping (1–4 years)

In the second grouping, which involves children who overtly exhibit the behavioral traits of autism, the objective is to reduce undesirable social characteristics once hypo-myelination has caused irreversible

brain dysconnectivity [13,21,30]. These pharmacologic agents include risperidone, aripiprazole, fluoxetine, oxytocin, and naltrexone. Derivatives of IGF have been found to mollify the adverse behavior common to autistic patients. Such agents are typically produced from N-terminal tripeptides of IGF. Like truncated (Des)IGF, IGF<sub>1-3</sub> is significantly more potent than IGF itself, is more weakly fixed to and inactivated by IGF-binding proteins (IGFBP<sub>1-6</sub>), possesses less mitogenic potential, and is able to cross the blood–brain barrier (BBB) much more easily than the parent 70-unit polypeptide [21,31]. Inside the BBB, these peptides appear to stimulate the local production of IGF. By a mass-action effect, the reduced activity of polymorphic IRS1 in processing the ambient IGF signal would be compensated.

### Conclusions

By the end of the first postpartum year, the rates of myelination and synapse formation in neo-neurogenesis have peaked and have begun to decrease thereafter [16]. Hence, once clinical analyses such as MRI support a diagnosis of early autism, therapy might be initiated during this window of opportunity before the end of the first postpartum year [8,11]. More clinically significant, prognosticating biomarkers identified at birth such as elevated Autistic Index and IRS1 polymorphism could support replacement therapy to begin in the neonatal stage [5,8]. The timelier reparative treatment is instituted (e.g., myelination), the better is the ultimate chance for improvement in fundamental neural functions.

These insights give an expanded understanding of what constitutes a developing case of autism and what modes of therapy can be applied to reduce or eliminate the progress of the disease. ASD appears to be a complex assortment of signs and symptoms. The present discussion was intended to define essential biochemical and neurologic factors which characterize the etiology of this condition. As a result, more productive means for dealing with the malady may well reduce distress for the patients, their families, and the participating medical and psychosocial personnel endeavoring to control the manifestations of it.

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### Conflict of interest

The author currently has no conflict of interest in this matter.

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### References

- [1] Riikonen R. Insulin-like growth factors. In: Zimmer AW, editor. Autism current theories and evidence. Totowa, NJ: Humana Press; 2008 chapter 10.
- [2] Coleman M, editor. The neurology of autism. New York: Oxford Univ. Press; 2005 chapter 3.
- [3] LeRoith D, Zumkeller W, Baxter RC, editors. Insulin-like growth factors. New York: Kluwer Academic/Plenum Publishers; 2003 chapter 8.
- [4] Chen J, Alberts I, Li X. Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in autism spectrum disorders. *Int J Devl Neurosci* 2014;35:35–41.
- [5] Park HJ, Kim SK, Kang WS, et al. Association between IRS1 gene polymorphism and autism spectrum disorder: a pilot case-control study in Korean males. *Int J Molec Sci* 2016;17:1227–34.
- [6] Burmeister M, McInnis MG, Zollner S. Psychiatric genetics: Progress amid controversy. *Nat Rev Genet* 2008;9:527–40.
- [7] McGettrick AJ, Feener EP, Kahn CR. Human insulin receptor substrate-1 (IRS-1) polymorphism G972R causes IRS-1 to associate with the insulin receptor and inhibit

- receptor autophosphorylation. *J Biol Chem* 2005;280(8):6411–6.
- [8] Steinman G. Predicting autism at birth. *Med Hypoth* 2013;81:21–5.
- [9] Singh VK, et al. Antibodies to myelin basic protein in children with autistic behavior. *Brain Behav Immun* 1993;7(1):97–103.
- [10] Leboyer M, et al. Whole blood serotonin and plasma beta-endorphin in autistic probands and their first-degree relatives. *Giol Psychiatry* 1999;45:158–63.
- [11] Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum. *Nature* 2017;542(7641):348–51.
- [12] Chen R, Hiao Y, Herskovits EH. Structural MRI in autism spectrum disorder. *Pediatr Res* 2011;69(5pt2). 63R–68R.
- [13] Steinman G. Plausible etiology of brain dysconnectivity in autism – review and prospectus. *Med Hypoth* 2015;85:405–7.
- [14] Steinman G, Mankuta D. Insulin-like growth factor and the etiology of autism. *Med Hypoth* 2013;80:475–80.
- [15] Zikopoulos B, Barbas H. Changes in prefrontal axons may disrupt the network in autism. *Neuron* 1996;30(44):14595–608.
- [16] Purves D, Augustine GJ, Fitzpatrick D, editors. *Neuroscience*. 5th ed. Sunderland, MA: Sinauer Associates; 2012 Chapters 2-8,23,24.
- [17] Sullivan KA, Kim B, Russell JW, Feldman EL. IGF-1 in neuronal differentiation and neuroprotection in IGFs in the Nervous System. Berlin: Springer-Verlag; 1998. p. 28–46.
- [18] Goodman HM. *Basic Medical Endocrinology*. 4th ed. New York: Academic Press; 2009 chapter 11.
- [19] Gerber DG, Shoback D. *Greenspan's Basic & Clinical Endocrinology*. New York: McGraw Hill Co.; 2007 Chapter 7.
- [20] Ballard FJ, Wallace JC, Francis GL, et al. Des(1–3)IGF-1: a truncated form of insulin-like growth factor-1. *Int J Biochem Cell Biol* 1996;28(10):1085–7.
- [21] Vahdatpour C, Dyer AD, Tropea D. Insulin-like growth factor 1 and related compounds in the treatment of childhood-onset neurodevelopmental disorders. *Front Neurosci* 2016;10:450.
- [22] Singh-Mallah G, Singh K, McMahon C. Maternally administered cyclic glycine-proline increases insulin-like growth factor-1 bioavailability and novelty recognition in developing offspring. *Endocrinology* 2016;157:3130–9.
- [23] Steinman G, Mankuta D. Breastfeeding as a possible deterrent to autism. *Med Hypoth* 2013;81(6):999–1001.
- [24] Tseng PT, Chen YW, Stubbs G, et al. Maternal breastfeeding and autism spectrum disorder in children: A systematic review and meta-analysis. *Nutr Neurosci* 2017;18:1–9.
- [25] Diaz-Gomez NM, Domenech E, Barroso F. Breastfeeding and growth factors in preterm newborn infants. *J Pediatr Gastroenterol Nutr* 1997;24(3):322–7.
- [26] Field T, Diego M, Hernandez-Reif M, et al. Insulin and insulin-like growth factor 1 (IGF-1) increased in preterm neonates. *J Dev Behav Pediatr* 2008;29(6):463–6.
- [27] Procianoy RS, Mendez EW, Silveira RC. Massage therapy improves neurodevelopment outcome at two years correct for very low birth weight infants. *Early Human Dev* 2010;86:7–11.
- [28] Owen-Smith Ashli A, et al. Prevalence and predictors of complementary and alternative medicine use in a large insured sample of children with autism spectrum disorder. *Res in ASD* 2015;17:40–51.
- [29] Co S, Kaufman M. Refrigerator mothers in The Cause of Autism. New York: Baffin Books Publishing; 2014 chapter 2D.
- [30] Riikonen R. Treatment of autistic spectrum disorder with insulin-like growth factors. *J Europ Paediat Neuro Soc* 2016;20:816–23.
- [31] Guan J, Gluckman P, Yong P, et al. Cyclic glycine-proline regulates IGF-1 homeostasis by altering the binding of IGFBP-3 to IGF-1. *Sci Rep* 2014;4:4388–96.