The proposed role of insulin-like growth factor-1 in autism: a review

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Abstract
Introduction
Several lines of research support the hypothesised connection between the level of insulin-like growth factor-1 in the foetus and neonate and the potential of autistic characteristics appearing in the first 2 or 3 years of life. This model could account for the dominance of male over female occurrence, the relationship to maternal antepartum infection and the potential benefit of breast-feeding in preventing or reducing the psycho-neurologic manifestations of autism.

Conclusion
The level of insulin-like growth factor, especially in cases of insulin-like growth factor gene polymorphism, could determine the likelihood in new-borns that they may subsequently exhibit the characteristics of infantile autism. Such suppression of IGF could also serve as a biomarker to aid in the diagnosis of autism.

Introduction
Autism is the result of defective neural development in the foetus, neonate and young child. This disorder is usually not apparent until early childhood through failure to reach appropriate developmental milestones. If one child has been diagnosed with autism, the odds of his or her parents later conceiving a second affected sibling increase about 20 times, suggesting an autosomal recessive trait. Furthermore, some sets of monozygotic twins have one affected and one normal member. It can be concluded from this that autism involves both an environmental trigger and a genetic predisposition.

Autism is a disease diagnosed through neurologic or psychological testing such as the M-CHAT, ADOS-2 and CARS. These examinations entail subjective impressions on the part of the testing professionals; hence divergence of conclusions between examiners may result. It is important to develop a quantitative, objective approach to the diagnostic process. To date, many hypotheses have been advanced, but none have produced sufficient supportive data to substantiate any of them. The aim of this review was to discuss the proposed role of insulin-like growth factor-1 (IGF) in autism.

Discussion
The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Review of some prior hypotheses
- One of the first theories of the aetiology of autism was labelled the ‘refrigerator mom’. It was proposed that cold, unloving mothers would induce the withdrawn characteristics associated with autism. This was later refuted.
- Perhaps the most detrimental hypothesis related vaccination to the subsequent appearance of autism in young children. Although later discredited and withdrawn from publication, this claim continues to provoke parents to avoid needed MMR inoculations in their children, leading to the unfortunate development of measles in particular.
- Lead from environmental sources has been suggested as a promoter of autistic behaviour, but no significant evidence has been documented to confirm this.
- Certain pharmaceutical agents supplied to gravidas in early pregnancy, such as thalidomide and valproic acid, increase the risk of autism, but such exposures are few and cannot account for the majority of cases with this disease.
- Numerous significant genetic mutations have been found in autistic children, but none occur often enough to explain the overall incidence of this condition. To determine the odds that a particular neonate will ultimately exhibit autistic behaviour, attempts have been made to calculate the combined probability of groups of such mutations in affected patients and relate it to the chance of a particular child developing the overt disorder. It is believed that such genetic errors lead to synaptic malfunction, although their infrequency does not explain the majority of cases of autism.

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The risk of developing autism in the first years of extrauterine life has been correlated with maternal exposure to traffic pollution from auto exhausts during pregnancy\textsuperscript{12}. This possibility needs further study to isolate confounding factors.

Older parents have a higher reported risk of conceiving autistic children\textsuperscript{13}. This appears to be related to the aging of germ cells and gamete-producing precursor cells up to the time of fertilisation, resulting in more frequent genetic anomalies. However, this can explain the cause of autism in only 2\% of the cases.

The developing brain is especially sensitive to an inadequate antioxidant defence mechanism (i.e. oxidative stress)\textsuperscript{14}. Biomarkers of such an oxidation-reduction imbalance are often found in autistic children. It is uncertain if these indicators are related to the cause or are the result of such a fault in affected children.

Without a general mechanism to define the genesis of autism in the majority of affected children, the search for one must continue in order to make treatment and/or prevention possible. A more specific analysis, let alone a treatment and prevention, might be possible if the aetiology of autism was known.

**Reduced IGF as an aetiological agent**

IGF is a single-chain polypeptide containing 70 amino acids\textsuperscript{15}. The primary antepartum source of IGF is the placenta, and, postpartum, the liver.

IGF influences numerous functions in the body, most of which are anabolic\textsuperscript{16}. For example, it was previously reported that the rate of multiple ovulations resulting in twinning is largely influenced by the level of IGF\textsuperscript{17}. Some of the more pertinent observations concerning the putative role of this growth factor in autism include the following:\textsuperscript{18}

- A series of lumbar punctures performed on autistic children (for other medical indications) display lower levels of IGF in the cerebrospinal fluid up to the age of 4 years than in neurologically normal children\textsuperscript{19}.
- At 28 weeks of pregnancy, a higher level of placental growth hormone (GH) has been found in the sera of women carrying female foetuses than males\textsuperscript{20}. GH is the primary controlling factor in determining the level of IGF in the neonate\textsuperscript{13}. On average, four times as many males display autistic behaviour as females in later years\textsuperscript{1}. This would support the contention that defective neurogenesis in autism actually starts prior to delivery.
- Small-for-gestational age (SGA) newborns have lower levels of IGF in their umbilical cord blood than normal-sized babies\textsuperscript{21}. Such SGA children also have a higher incidence of autism.
- IGF stimulates gene expression in the oligodendrocytes in the foetus and neonate to myelinate the central neural pathways being developed (Figure 1)\textsuperscript{22, 23}. This process begins in the late second trimester of pregnancy and reaches its peak growth by 1-year post-delivery. Biopsies of the brains of autistic children reveal hypomyelinated neurons\textsuperscript{24}. Furthermore, IGF promotes dendritic branching and formation of neocortical connections\textsuperscript{25}.
- Maternal infection-related fever in the first trimester of pregnancy (e.g. with influenza) increases the chance of autism appearing in the offspring\textsuperscript{26}. This has been related to the ability of interleukin-6, released in such situations, to reduce the production of IGF by the placenta\textsuperscript{27}.
- Children conceived by IVF have an autism rate three times of those conceived naturally and have significantly lower IGF levels at 3 months of age\textsuperscript{18}.
- The longer the children are breast-fed, the lower the likelihood of their developing autism\textsuperscript{28–30}. Breast milk contains a higher level of IGF than bovine milk or formula\textsuperscript{31}. This might also point to an appropriate preventative to reduce or eliminate the subsequent manifestations of autism.

These and other findings would suggest that depressed serum IGF levels at birth could portend deficient CNS myelination and, ultimately, the appearance of pervasive developmental disorders from defective neural development (i.e. autism).

**IGF as a biomarker**

Assuming that reduced IGF concentration is a fundamental aspect of the development of autism, it would appear practicable to utilise this concept to develop a quantitative method for the diagnosis of this disease than with psychoneurologic evaluation alone. IGF gene polymorphism, especially involving the promoter region of the gene, can be the cause of reduced hepatic growth factor release\textsuperscript{32} but a possible interac-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Myelination during CNS neurogenesis as controlled by the IGF gene.}
\end{figure}
ative coexistence of this genetic variation, and autism remains to be demonstrated.

Antepartum chorioamnionitis, a known antecedent to infan
tile autism, is often associated with reduced IGF in the newborn. Our ongoing study is examining the level of IGF in umbilical cord blood samples following PPROM and the subsequent appearance of autism. If such a correlation is substantiated, routine testing of all neonates for this parameter, with and without known prenatal inflammation exposure, would allow early detection of autistic tendencies and the potential benefit of IGF supplement in such children.

Two additional serum parameters involved in neurogenesis often increased in cases of autism are serotonin and anti-myelin basic protein (MBP). One reported cause of decreased IGF is gene polymorphism. For example, such nuclear variation of the IGF-I gene influences the age-related decline in circulating total IGF-I levels. Combining these two values with the level of IGF in the umbilical cord makes possible the calculation of the Autism Index (AI). Such a value could quantitate the likelihood of a newborn later developing overt manifestations of autism.

\[
AI = \left[ p_1 p_1 + p_2 p_2 + p_3 p_3 \right]
\]

\( p = \) weighted probability of depressed or elevated in the general population
\( n = \) absolute percent (decimal) depression or elevation of biomarker below or above

Thus, the AI in a hypothetical example of an (impending) autistic newborn would be >0.00 and in a perfectly normal newborn would be ~0.00. The magnitude of AI may also correlate with the CARS result (i.e. the severity of the condition in an individual child on the Autism spectrum), but this remains to be investigated.

**Conclusion**

As of this date, no proposed aetiology of autism has been clearly and convincingly supported with laboratory and clinical data. Essentially all the hypotheses that have been advanced have either been disproven with subsequent observations or remain to be investigated thoroughly.

The hypothesis presented here is that the level of insulin-like growth factor could determine the likelihood that a particular newborn may subsequently exhibit the characteristics of infantile autism. More than being just a biomarker, this parameter may also point to the advisability of supplementing the IGF in the child (e.g. with prolonged breastfeeding) to enhance neuronal myelination in the central nervous system. In this way, the ‘miswiring’ of neural pathways characteristic of autism would be reduced.

Polymorphic IGF genomes are typically found in children born SGA. If such genetic alterations appear in both children with autism and their parents, it is plausible that preconception genotyping could identify couples with an increased probability of producing autistic children.

**Abbreviation list**

ADOS-2: autism diagnostic observation schedule; AI: autism index; CARS: childhood autism rating scale; CNS: central nervous system; GH: growth hormone; IGF: insulin-like growth factor-1; IVF: in vitro fertilisation; MBP: myelin basic protein; M-CHAT: modified checklist for autism in toddlers; MMR: mumps, measles, rubella; PPREM: preterm premature rupture of membranes; SGA: small for gestational age

**References**