

## Etiology of Autism

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### Abstract

The causative factor for autism now appears to be a deficient supply of insulin-like growth factor-1 (IGF<sub>1</sub>) and vitamin D3 in many newborn and infants, thereby leading to persistently insufficient myelin in developing cranial nerves. Various malformed neurologic networks last into adulthood. Of particular concern is a pregnancy exposed to febrile viral conditions, where interleukins suppress IGF<sub>1</sub> production. Breastfeeding of the newborn may be preventative in many such cases.

### Introduction

Cases of autism were formally recognized and reported first in 1943 [1]. Following this, the etiologic emphasis was on a search for dominant genetic errors [2]. When fewer than 10% of autistic cases examined were found to have such anomalies, attention was turned to plausible biochemical/metabolic causes.

Diligent research has expanded the insight into the etiology of autism and the biochemical basis of its development. In this way, effective modes of prevention could be researched. Understanding the central roles of (insulin-like growth factor-1) IGF<sub>1</sub> and Vitamin D3 in this malady in particular now make possible the development of approaches to preventing or ameliorating the disease in susceptible children beginning at birth. In particular, breast-feeding and vitamin D3 supply are now emphasized (see below).

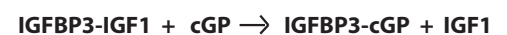
Beyond several similarities to true autism (TA), distinguishing effects found in patients with Rett Syndrome (RS), an autism-like condition, for example, involves cholinergic neurons. In contradistinction, predominantly serotonergic neurons in TA are affected. Furthermore, in RS, almost all affected patients are female, whereas in TA, 4 times as many males harbor this condition as females. In the case of true autism, the deficiency of IGF1 reduces the velocity of essential cranial nerve impulses in particular [3,4].

Distinguishing characteristics based on gender have not been explained fully as yet. It is interesting to note the biochemical findings in a seemingly normal group of 54 boys and 45

girls at ages of 11-12 months. The mean blood IGF<sub>1</sub> level for the girls was approximately 120 ng/ml and for the boys 70 ng/ml [5]. This is relevant to the aforementioned overall greater incidence of autism in males than females. A common problem found in autistic children is a persistence of insufficiently myelinated neo-neurons, apparently a direct result of IGF<sub>1</sub> deficiency.

### Explanation

There are six different IGF<sub>1</sub>-bonding proteins (BP1-6) in the human metabolism, usually holding/storing 99% of the available but inactive IGF<sub>1</sub> in the circulation under physiologic conditions. Bonding protein #3 (BP3) carries the largest amount of IGF<sub>1</sub> during catabolism, but the combination is biochemically inactive. The potential release of IGF<sub>1</sub> attached to the bonding protein (BP3) by competition with cGP (cyclic glycyL-proline), the N-terminal dimeric remnant from IGF<sub>1</sub>, may explain the mechanism resulting in a general deficiency of IGF<sub>1</sub>. In the presence of added cGP, IGF1 is released from its inactive bound state [6-8]:



Inactive

Active

The IGF1 circulating freely, typically has a half-life of 1-2 minutes; whereas if the IGF<sub>1</sub> is attached to one of the six bonding proteins, it may endure for up to 12 hours. Although these reactions can occur spontaneously, the release of IGF<sub>1</sub> from a BP-based complex can be accelerated by proteases [9-11].

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Because of its known function in nerve myelination, it has been proposed that sufficient IGF<sub>1</sub> blocks the genesis of autism [12]. Alternatively, reduced levels of IGF<sub>1</sub> signal increase the probability of the later development of autism [13]. An example of this is the comparison of babies who have been bottle-fed versus breast-fed. This difference in food source appears related to the greater concentration of IGF<sub>1</sub> in the latter case than the former [14,15]. This is important because the IGF<sub>1</sub> promotes axonal myelination in the neonate's synthesis of a functional neural system.

The reaction shown above binds 99% of the ambient IGF<sub>1</sub> in the cellular environment to IGFBP<sub>3</sub>, making it largely unreactive and unavailable for active IGF<sub>1</sub> supply in vivo unless supplied externally.

### Application

Free IGF<sub>1</sub> (a 70-member linear polypeptide) can be produced in vitro by the union of individual amino acids for commercial applications. However, this makes it today a very costly potential pharmacological or research agent. It is possible to react IGFBP<sub>3</sub>-IGF<sub>1</sub> with cGP, an inexpensive dipeptide, thereby providing IGF<sub>1</sub> itself under more affordable conditions (see reaction above).

Several potential mammalian sources containing this carrier-reactant combination exist, especially in addition to vitamin D [15,16]. On the other hand, febrile gravidas infected with viruses run the risk of elevated IL-6 (interleukin-6) and depressed IGF<sub>1</sub>. This enhances the chance of giving birth to a baby destined to become overtly autistic in 1-4 years [16-18].

The use of IGF<sub>1</sub> as a medication is not without some potential risk. In particular, it is known that humans and test animals with elevated IGF<sub>1</sub> tend to have shorter lifespans and possibly enhanced cancer potential [14]. However, elder healthy people with increased cGP/IGF<sub>1</sub> molar ratios display better cognition [19-22].

Autism is now considered to be due in many cases to a deficiency of vitamin D in the gravida and her baby [23]. With such a diminished supply of the vitamin, there are increased inflammatory/cytokine levels [24]. A number of years ago, the American Medical Association warned gravidas to avoid prolonged sun exposure, resulting in an increased occurrence of autism. For partial compensation and protection, many women consumed large levels of fish which are rich in vitamin D<sub>3</sub> [25]. In a number of these cases, the outcome for the baby was improved [26,27]. Another preventative is regulated sun exposure, especially with darker-skinned people, thereby adjusting the level of calcitriol [24]. Also, inflammatory cytokines are reduced as a result [28,29].

Lower-than-normal levels (<40 ng/ml) of serum vitamin 25(OH)D are found in many children destined to develop autism, typically in infancy and early childhood [30-32]. After birth, about 90% of human vitamin D comes from sun exposure of the individual's skin. Postpartum development of autism can be promoted by a lack of sufficient vitamin D. In a study of rats, vitamin D deficiency resulted in depressed neural development [33-36].

In addition, it has been reported that vitamin D<sub>3</sub> increases the circulating level of the IGF<sub>1</sub> factor. With prolonged breast feeding of the infant, the incidence of autism can be reduced still further. This is apparently due to the cooperative action of IGF<sub>1</sub> and D<sub>3</sub>, both of which are found in human milk [36].

As reviewed in this study, serum IGF<sub>1</sub> is depressed in maternal or fetal antepartum/prenatal/neonatal febrile states in particular. In many such cases, the risk of autism in the baby is especially enhanced. If breast-feeding is displaced by bovine nutrition at the infant stage, the potential for autism to appear in human babies is elevated, since the acquired IGF<sub>1</sub> level is lower. Just the opposite, breastfeeding should be encouraged more aggressively to raise the ingestion of such nutrients. Breastfeeding increases the intake of IGF<sub>1</sub> by the baby, especially for the first six postpartum months. In a review of 13 prior studies of breastfeeding in total, this practice helped lower the risk of autism by 76% [37].

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