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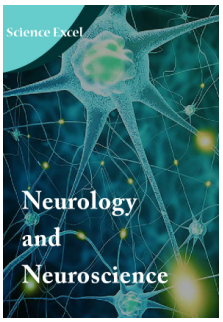
Short Communication



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_1) 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_1 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_1 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_1 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_1 deficiency.

Explanation

There are six different IGF_1-bonding proteins (BP1-6) in the human metabolism, usually holding/storing 99% of the available but inactive IGF_1 in the circulation under physiologic conditions. Bonding protein #3 (BP3) carries the largest amount of IGF_1 during catabolism, but the combination is biochemically inactive. The potential release of IGF_1 attached to the bonding protein (BP3) by competition with cGP (cyclic glycyl-proline), the N-terminal dimeric remnant from IGF_1, may explain the mechanism resulting in a general deficiency of IGF_1. In the presence of added cGP, IGF1 is released from its inactive bound state [6-8]:

IGFBP3-IGF1 + cGP ⟶ IGFBP3-cGP + IGF1

Inactive Active

The IGF1 circulating freely, typically has a half-life of 1-2 minutes; whereas if the IGF_1 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_1 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_1 blocks the genesis of autism [12]. Alternatively, reduced levels of IGF_1 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_1 in the latter case than the former [14,15]. This is important because the IGF_1 promotes axonal myelination in the neonate's synthesis of a functional neural system.

The reaction shown above binds 99% of the ambient IGF_1 in the cellular environment to $IGFBP_3$, making it largely unreactive and unavailable for active IGF_1 supply in vivo unless supplied externally.

Application

Free IGF_1 (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 IGFBP3-IGF1 with cGP, an inexpensive dipeptide, thereby providing IGF1 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_1. 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_1 as a medication is not without some potential risk. In particular, it is known that humans and test animals with elevated IGF_1 tend to have shorter lifespans and possibly enhanced cancer potential [14]. However, elder healthy people with increased cGP/IGF_1 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 D3 [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 D3 increases the circulating level of the IGF_1 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_1 and D3, both of which are found in human milk [36].

As reviewed in this study, serum IGF_1 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_1 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_1 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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