

Febrile Corona virus and Autism

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Abstract

Background: A number of reports have pointed to the apparent relationship between reduced IGF1 in pregnancies and the development of autism in the offspring. Fever due to inflammatory processes in the gravida emerges as a potential key factor in this phenomenon.

Methods of inquiry: Investigations have reported an increase in neonatal autism related to an enhanced production of interleukins in some gravidas before delivery. The medical records of the mothers of autistic children were examined retrospectively for pertinent factors. Women who had endured infection-related fevers during their pregnancies were more likely to have delivered children with neurologic deficiencies such as autism and schizophrenia.

Conclusions: Inflammatory occurrences such as with women infected by Covid-19 during pregnancy produce enhanced levels of cytokines, especially interleukin-6, which can disrupt IGF1-mediated neurogenesis and CNS circuitry formation in the neonate.

Keywords

COVID 19; Autism, Corona Virus, Interleukin, IGF1, Cytokine, Myelin

Introduction

Retrospective studies have evaluated the recorded data of autistic youngsters in Denmark, Norway, and the United States born to women who had experienced febrile prenatal episodes, especially in the second trimester, compared to those with totally afebrile antepartum courses. Autism frequency increased about 1.4-fold in the offspring of gravidas who had been affected with antepartum fever related to various viral ailments. The highest rate of neonatal autism occurred when the mother experienced three febrile episodes during the same pregnancy. In one such retrospective study in the United States, the increased risk of autism was reduced when the mothers were treated with antipyretics [1-9].

As per the US Food and Drug Administration, the possibility of side-

effects in treating maternal fever in the second half of pregnancy may be associated with over-use of non-steroidal anti-inflammatory drugs (NSAIDs), other than low-dose aspirin. This would include ibuprofen, naproxen, diclofenac, and celecoxib. Harm to the fetus could include oligohydramnios, kidney problems, and cardiac trouble. The possibility of toxic effects on brain development in the neonate following excessive gravid consumption of acetaminophen has been detected in test animals [10,11].

Insulin-like growth factor-1 (IGF1) has numerous roles in the body's chemistry and homeostasis. Among these functions is the development of the components of the central and peripheral nervous systems, including brain growth, oligodendrocytes, and axonal myelin

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sheaths. Sufficient IGF₁ in the neonate is essential for the proper introduction and integration of newly formed nerves, especially during the first postpartum year. This contributes to the development and persistence of functional brain neuronal patterns, and the avoidance of supratentorial neurologic defects (dysconnectivity) in the child, especially in the psycho-behavioral pathways [12-15].

In some viral-promoted gravid infections, the fetus while still *in utero* appears to be fairly shielded in some cases. Certain maternal blood-borne viruses attacking during pregnancy, such as Zika, cytomegalovirus, herpes simplex, and rubella, are able to cause serious defects in the growing fetus. Recent studies, on the other hand, have not identified any major immediate detrimental effects on the conceptus by vertical transmission whose mother is battling severe Covid-19, mainly a respiratory agent. The rise of interleukin IL-6 in a “cytokine storm” governs the extent of corporal temperature elevation, which reduces the level of IGF₁ in the neonate. Consequently, cerebro-neural dysconnectivity may persist, thereby enhancing the chances of autism developing in the child [11-13,15,16].

However, inflammation in pregnant mothers such as from corona viruses has been linked to mental disorders in their offspring [17]. Postpartum neonatal complications such as autism, ADHD, depression, cerebral palsy, schizophrenia, poor cognition, or mental retardation may still be consequences of antepartum maternal inflammation. Interleukins such as IL6 may conceivably cross-over to the fetus, especially during the middle months of the gestation. Excessive proinflammatory maternal cytokines reaching the fetal brain could be toxic to fetal neurons and oligodendrocytes in such instances [18].

There appears to be an inverse relationship between the level of maternal IL-6 during a pregnancy and the newborn’s functional brain connectivity. Also, the formation of neonatal synapses may be altered by

elevated IL-6 in the mother and the consequential reduction of IGF₁ in the fetus during the gestation. The diminution of IGF₁ is central to subnormal myelination in the infant at basic stages of neural pathway development but may no longer be apparent in the older autistic patient (16). Thus, a correlation exists between the degree of disturbance of the neonate’s brain networks and the level of IL-6 concentrations in the gravida. Similarly, an inverse association has been observed between frontolimbic cognitive development in the first 12 months of life of the neonate (or later) and the maternal IL-6 concentration during the antecedent pregnancy. These are like the cognitive deficits commonly seen more clearly in autism. Persistence of neuroinflammation with IL-6 in the brains of mature autistic patients has been reported [13-18].

In related neurologic studies, behavior deviations found in children 2 years of age paralleled changes in maternal interleukin-6 levels during the prior gestation. In such cases, alterations in the mother’s amygdala, in particular, preceded increased emotional and stress reactivity in their offspring [20-24].

Cytokine storm in the gravida, with fever and serious dyspnea, may follow a mild initial disease course. A surge in immune molecules, such as IL-6, and small blood clot production may result in fatal damage to the patient’s lungs from acute respiratory distress syndrome (ARDS) [12,25]. This may well be the result of enhanced maternal hypoxemia and circulatory insufficiency.

Pathophysiology of IL-6 vs IGF-1

Increased levels of maternal interleukins (especially IL-6) have been measured in some samples of fetal blood and amniotic fluid [5,6]. Elevated IL-6 was detected postmortem in autistic brain tissue from affected individuals with an imbalance of neural circuitry. Maternal inflammation during the pregnancy, as measured by temperature and the IL-6 level, appears to

be associated with the newborn baby's reduced brain connectivity [12,13]. Overall, maternal fever for any infectious reason during gestation, especially within the middle months of the pregnancy, may enhance the potential for neonatal autism. Typically, with an increase in IL-6, the level of IGF-1 falls. Especially in the newborn, IGF1 is the primary stimulant for myelination of new axonal fibers in the Central Nervous System. Patterson examined in detail the effect of glial and maternal-derived cytokine production in pregnancies. In particular, interleukin-6 activated the placental JAK-STAT3 intermediate. As a result, the concentration of IGF-1 in the cerebrospinal fluid of neurologically normal youngsters was found to be higher than in autistic children of the same age [19-23].

Under stable biochemical conditions, the level of IGF-1 often changes in the opposite direction from that of IL-6. For example, it has been reported that for babies born on or about the mean gestational age of 27.8 weeks, the average total serum level of IGF-1 is 46.6 ng/ml, whereas if the child is born at term without experiencing nutritional complications, the mean serum level is 88.7 ng/ml. In contradistinction, the concentration of serum IL6 between these two gestational durations falls from 9.5 to 2.3 pg/ml ($p < 0.001$) [24]. The physiologic states under which IL-6 or IGF-1 change dominates are central in defining the basis of various biomedical phenomena. For example, interleukin-6 increases in children with pathological inflammatory phenomena, cystic fibrosis, growth restriction bowel diseases, premature delivery due to maternal infection, and juvenile idiopathic arthritis. Similarly, chronic inflammatory states can be associated with IGF-1 insufficiency, IGF-1 resistance, or down-regulation of IGF receptors [25-31].

In recent years, infusion with rhIGF1 has been used to sustain and strengthen markedly premature babies born between 23 and 28 weeks of gestation. rhIGFBP-3 (IGF1 binding protein-3) is added to

enhance and lengthen the duration of IGF1 support. This decreased the occurrence of severe bronchopulmonary dysplasia in the infants treated in this manner [32,33].

On the one hand, IGF-1 reduction is observed in mammals which endure cardiovascular stresses [25]. Furthermore, growth-retarded neonates often present with higher concentrations of IL-6 in their placentas [19]. Local brain inflammation upsets the normal secretion of growth hormone from the baby's pituitary gland, resulting in IGF-1 insufficiency. Corona viruses have been reported to invade neurons, causing demyelination [34,35]. Viral dissemination is possibly due to pathological changes in neurons which disturb brain circuits in particular [36].

It has been hypothesized that maternal immune activation (MIA), fever, and cytokine storm during pregnancy, associated with increased levels of IL-6, may be the etiologic disorder promoting neonatal neurologic ailments [13,37-40]. The exact role of IL-6, if exclusive, remains to be elucidated in the laboratory, but its relationship to IGF1 decrease may be the key to this febrile phenomenon.

The possible relevance of severe ARDS was again examined in June of this year. Five reports of IL6 elevation in Covid-19 cases in 2020 were compared with three prior reports (2014-2018) in other hyperinflammatory diseases. In the latter cases, the mean IL6 levels were 9 times or more higher than in the former cases. The analytical procedures were different in the former and latter sets [41]. However, this could intimate that inflammatory cytokines/interleukins in addition to IL6 are operative in Covid-19. For example, the occurrence of cytokine storm in compromised individuals infected with Covid-19 is enhanced by chronic low-grade inflammation due to the combined effects of IL-1 β , IL-6, IL-17A, and TNF- α (tumor necrosis factor) [39,42]. In autistic children, the more severe the autism, the higher are their serum interleukin levels such as IL-17A [43,44]. Also, TNF release by macrophages is toxic to

oligodendrocytes, thereby reducing myelin production and increasing the risk of subsequent infantile brain dysconnectivity [45].

Brain dysconnectivity apparently due to defective myelination is a key finding in autism [42]. In test mice, decreased myelin-basic protein and other myelin-related components have been found following influenza implantation [46,47]. This is especially worrisome in human babies experiencing long-term neurologic sequelae, as happened in Spanish flu.

Prophylaxis

It is concluded that positive action should be taken with all corona-exposed babies to compensate for any IGF1 deficiency, as measured in the umbilical cord blood at birth. Prior investigations have reported that infants who were nourished by breastfeeding exclusively for at least a full year had a lower incidence of autism subsequently. Human milk contains a higher level of IGF1 than milk from other sources. In addition, IGF1 survives gastric digestion in the baby, apparently due to the casein coating of the polypeptide [48-50].

A study is now being initiated in cases of gravidas who survived severe Covid-19 during their pregnancies which examines the data related to the extent of breast feeding the neonate and the degree of formation of autistic characteristics (if any) of the child at ages 1-2 years. This will be compared to mothers who were unaware of any febrile episodes during their pregnancies.

Hence, IGF-1 mediated myelination of developing CNS nerves in the neonate is central to understanding the effect of fever-promoted interleukins on patients affected by Covid-19 [51,52]. Such insight will be helpful if additional coronavirus-like pandemics occur in the future. Without being prepared for dealing with this, neuropsychiatrists will be challenged and short-staffed. In essentially all cases,

febrile gravidas with flu-like symptoms should be treated with antipyretics actively. Finally, the wide distribution of corona immunization, once successfully developed, would apparently result in a drop in autism rates in the offspring of pretreated women.

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