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COVID-19 and autism

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A B S T R A C T

The current pandemic of Covid-19 has created a paradigm for possibly gaining greater insight in two conditions:

1) Inflammatory maladies in pregnancy, and.
2) The biology of IGF-1 in autism.

Studies since the beginning of this century have supported the view that IGF-1 deficiency in the neonate defines the basis of autism. As a result, it appears that interleukin-6 in corona virus-based infections causes reduced defenses because of suppressed IGF-1, especially in older patients. This may also portend an increase of autism in the offspring of gravidas currently affected severely by Covid-19.

Introduction/background

One of the dominant theories about the etiology of autism relates to a postulated newborn deficiency of insulin-like growth factor-1 (IGF-1) [1–6]. This component is central to neo-neuronal myelination via oligodendrocytes in the pre- and postpartum infant [7]. The IGF-1 deficiency may be a consequence of inherited polymorphisms [8]. Such defects cause diminished translation of IGF-1 by the IGFR/IRS1/PI3K/AKT/mTOR intracellular pathway [9]. Another possibility of reduced mTOR activity is decreased IGF-1 in the circulation. From puberty onward, the normal level of IGF-1 gradually falls. Such age-dependent change contributes to the activation of cytokine IL6 and is postulated to correlate with the frailty and increased incidence of some diseases in older people [10].

At the beginning of the present century, Patterson and coworkers applied the concept that the developing fetus, although insulated somewhat by the placenta and membranes, could be affected by coexistent disease processes in the gravida. Maternal immunologic activation produces an increase in pro-inflammatory cytokines. This would elevate the amount of interleukin IL6 within the placental environment in particular, thereby activating JAK/STAT-3. Such change would decrease the placental synthesis of growth hormone and IGF-1. Downstream this would decrease the fetus's ability to myelinate its developing nervous system, leading to brain dysconnectivity [5,11]. If such a myelinogenetic deficiency persists following birth, a neurologic deficit would persist and exacerbate. The goal of dealing with such a problem is early detection and correction, before lasting neurologic miswirings in the brain occur.

At birth, the baby's cord blood IGF-1 concentration is largely independent of the mother's level [12]. Depressed levels of neonatal serum IGF-1 could be a consequence of antepartum exposure to IL6. Reduced postpartum brain growth may be the result of this, especially in SGA (small for gestational age) babies. Consequently, such an occurrence could be a predicter of reduced or delayed CNS development, especially in preterm infants [13]. Thus, deficiency of IGF-1 *in utero* or postpartum can cause autistic brain dysconnectivity in the neonate. Behavioral and psychological problems characteristic of autism usually do not appear before the child is at least 1 year old, whereas dysconnectivity originates much earlier.

Several studies have reported the reduction of autism in children who were breastfed exclusively, especially for the entire first postpartum year. This is apparently due to the enhanced supply of IGF-1 found in breast milk, in contradistinction to the lower level in bovine milk [14,15]. What remains to be determined is the umbilical cord serum IGF-1 limit below which aggressive postpartum growth factor replacement is indicated, as well as the minimum breast milk IGF-1 concentration that can be remedial in this regard.

Other forms of IGF-1 that can be administered orally are bioencapsulated in lettuce cells and rice seeds [16,17]. An additional approach that has been proposed is giving the neonate oral supplementation with cyclic-glycyl-proline, which enhances the unbound (active) form of IGF-1 [18]. However, this new agent has not yet passed final FDA standards of review for general use.

Current relevance

Maternal infection with fever during pregnancy doubles the postpartum risk of autism in the infant [19]. The elevated production of cytokine IL6 in particular has been identified in the symptomatic pathogenesis of the Spanish Flu pandemic of 1918, the SARS-CoV (Severe

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Acute Respiratory Syndrome) outbreak of 2003, the H5N1 avian influenza of 1987, and the MERS-CoV (Middle Eastern Respiratory Syndrome) epidemic of 2012. In severe cases, “cytokine storm”, with elevated IL6 being produced, is essentially pathognomonic. In a study of SARS in murine macrophages, cytokines TNF-α and IL8 were found to be elevated as well [20–24].

In a recent report from China, elevated IL6 was determined to be related to the severity of COVID-19 [25]. Thus, IL6 could be used as an acute-phase biomarker in corona-induced disease monitoring. Its decrease appears to correlate with recovery progress as well. Lung parenchyma in such cases produces the excess IL6 [25,26]. The monoclonal antibodies against IL6, siltuximab and tocilizumab, have been used to reduce cytokine release [27,28].

Proposed investigation

Unfortunately, a number of pregnant women have recently been found to be suffering with COVID-19. Several possible parameters could be investigated in these gravid cases without affecting the primary modes of pulmonary therapy:

1) The relationship of the level of maternal serum IL-6 and the severity of the malady during the period of treatment while still pregnant.
2) The level of IGF-1 in umbilical cord samples at birth.
3) The frequency and extent of breast-feeding of the newborn during the first postpartum year.
4) The psychological diagnosis of possible childhood autism and the determination of what position on the “spectrum” each case falls during the first 2–3 years of postpartum life in Corona-positive cases.

[Any researcher who is appropriately equipped and interested in participating in this important study is invited to do so via email. Assurance of patient disclosure, agreement, and confidentiality must be ascertained and protected.]

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109797.

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