Mini Review

Antepartum COVID-19 and Postpartum Autism

Steinman G* and Mankuta D

Department of Obstetrics & Gynecology, Hebrew University-Hadassah Hospital, Israel

*Corresponding author: Gary Steinman, Department of Obstetrics & Gynecology, Hebrew University-Hadassah Hospital, Ein Kerem, Jerusalem 12000, Israel; Email: dav4601@aol.com

Abstract

A little over a year ago, a new viral disease appeared worldwide. Much like earlier pathologic RNA viruses, Covid-19 can cause distinctive harmful effects on pregnant women and their offspring. Because of the coexistent fever associated with a rise in pro-inflammatory interleukins in the most severe cases, there is a serious concern about the baby's neurologic development. Although not yet observed in many Covid-19 pregnancies, it is anticipated particularly that the onset of autism in the child may be realized in a year or more postpartum. Prior studies have reported that exclusive breast-feeding which provides a good source of IGF1 for the baby may well reduce the incidence of autism in such cases.

Keywords: Cytokine storm; Interleukins; Respiratory distress; Pro-inflammatory; Alveoli

Introduction/Background

In the intrauterine development of a baby, the fetal stage is marked by varying levels of blood interleukins and IGF1 (insulin-like growth factor-1). If the baby is developing normally, without adverse influences in its environment, the trend over time is for serum interleukins to decrease and IGF1 to increase until delivery. On the other hand, if a maternal febrile cytokine storm occurs during the pregnancy, an overproduction of interleukins and reduction of IGF1 can take place. Such a phenomenon in the past has been associated with various bacterial and viral infectious diseases including cytomegalovirus, hemophagocytic lymphohistiocytosis, group A streptococcus, variola virus, influenza virus, SARS-CoV-1 (severe acute respiratory syndrome – a coronavirus), and avian H5N1 virus. Without fever, adverse manifestations are reduced [1-10].

Since 1918, orthomyxoviruses [single-stranded RNA viruses], such as influenza, have been the cause of epidemics and pandemics every few years. These viruses are spherical with distinctive surface spikes made of Hemagglutinin (HA) or Neuraminidase (NA) protein. Beginning with 2020, Covid-19, the newest member of this pathologic microbial group, has exhibited aspects of cytokine excesses in many cases. Much like the earlier pandemics of Spanish flu and H5N1, such a flare-up is characterized by fever, lethargy, and dyspnea. These zoonotic viruses are increasingly proliferative as the human population grows [3,6].

A consistent finding in patients with pulmonary complications is the overproduction of specific pro-inflammatory interleukins. Cytokines can elicit responses in cell proliferation and inflammatory reactions. Interleukin 1 (IL1), IL6, IL17, and TNF (tumor necrosis factor) in particular are central to the overt harmful features of acute viral diseases [7,11,12]. Especially with Covid-19, the most serious damage appears to be localized in the lung alveoli, where the viral spikes attach to ACE2 receptors. As the pathogenesis progresses, lung injury can lead to Acute Respiratory Distress Syndrome (ARDS) [6-11,13].

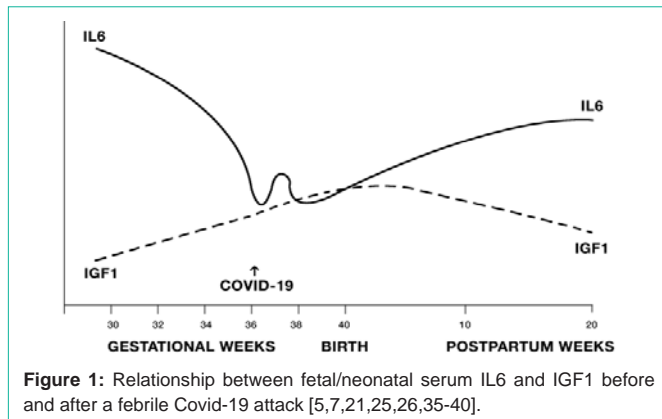Current therapy protocols for difficult cases of COVID-19 include drugs such as Tocilizumab (TCZ), a monoclonal antibody against IL6 receptor in patients with life-threatening cytokine storm [14-16]. In combination with methylprednisolone, this therapeutic agent is reported to successfully reduce cardiovascular collapse and major organ dysfunction in a number of severely ill coronavirus patients. Another relatively new agent, Allocetra, is effective in reprogramming macrophages and dendritic cells [17]. Under normal postpartum conditions, the serum IGF1 level rises until the early teen years, after which it slowly decreases over time. In contrast, when a fetus had faced a fever-generating antepartum state such as a severe maternal coronavirus attack, the levels of serum IGF1 of the newborn are diminished and of pro-inflammatory Interleukins (e.g., IL6) are increased [18,19]. In a postmortem examination of human autistic brains, increased cytokines and pathologic signs of inflammation have been detected [1].

Maternal death often follows a failure to recover from immune paralysis and irreversible lung injury. As in similar cytokine enhancing events with other febrifacient viruses, one would anticipate an upsurge in the number of autistic children in the coming months or years with mothers who experienced febrile antepartum Covid-19 [12,20-23]. Antipyretics in gravidas have been somewhat successful in lowering the autism rate in viral illnesses [11].

Proposed Therapy

It has been reported with previous viral pandemics that gravidas suffering from microbe-induced fevers give birth to children who are more likely to exhibit autistic traits later. From various studies, this is apparently related to a deficiency of IGF1 and a persistence of enhanced IL6 in the baby after birth [5,7]. Such an IGF1 deficit reduces the rate of myelination and functional assembly of neo-neuronal circuits in the baby's brain (dysconnectivity) [24].

In laboratory fetal mice, increased serum IL6 is concomitant with low IGF levels *in utero*. In unaffected humans born at a mean gestational age of 27.8 weeks, for example, the average serum concentration of IGF1 is 46.6 ng/l, whereas the concentration of IGF1 is approximately double in full term neonates. In otherwise normal

Figure 1: Relationship between fetal/neonatal serum IL6 and IGF1 before and after a febrile Covid-19 attack [5,7,21,25,26,35-40].

pregnancies, the serum IL6 at term is about a quarter of what it was in the middle of the gestation [25,26].

In pregnancies where the gravida had suffered a serious ARDS event before delivery, the newborns sustain IL6 levels at birth and beyond which are much higher than normal. Similarly, children with overt autism are typically found to have elevated serum IL17 [23,26,27]. In other words, autism is more likely to arise postpartum if the serum IGF1 level is depressed concurrently, as in severe COVID-19.

The hypothetical diagram (Figure 1) displays the typical fall in serum IL6 and the rise of IGF1 preceding the infected phase of a pregnancy, as well as the opposite trends following a Covid-19 infective/febrile event. Gross symptoms of autism in the baby usually become evident after the first year of postpartum life [23,26-28].

An efficacious means for supplying IGF1 to the affected newborn currently is breast-feeding. Human breast milk typically contains larger concentrations of IGF1 than milk from other sources [29-31]. In general, autism is less common in children who have been fed breast milk only for up to one full year initially. It has also been reported that the higher the serum IGF1 level of the gravida, the lower is her own risk of Covid-19 death [32]. The spontaneous lowering of IGF1 with age might explain why older people have an increasing chance of dying once COVID-19 is contracted [33].

Such observations would suggest that virally affected pregnant women could also be treated with supplemental IGF1, especially at the critical time of a harsh attack. Vertical transfer of COVID-19 from the mother to the unborn child is very uncommon [23]. It is now accepted practice in the U.S. to fortify very premature neonates with IGF1, leading to improved states in the first weeks after delivery [34].

As Covid-19 appeared around the beginning of 2020, it will be of interest to evaluate the veracity of this model once the babies of infected parturients reach an age of 1-3 years.

Conclusions

The past [41] and present reports are intended to provide an encompassing conceptual basis for elucidating the biochemical phenomena underlying the origin and prevention of autism. Prior research work in this subject has defined our understanding of what causes some, many, or all cases of autism. In this way, our current studies are sharpened as follows:

- Autism and IGF1 deficiency: IGF1 directly affects the rate at which oligodendrocytes promote myelination and neural circuitry development in the infantile CNS. Factors which reduce the production or availability of IGF1 could retard normal nerve programming in the fetus or neonate, leading to autism or schizophrenia.

- Breast-fed babies possess increased IGF1 and less frequent autism: The emergence of autism in young children appears to result from dysmyelination and dysconnectivity of brain neurons related to inadequate supply of IGF1 in the newborn. Breast-feeding for the first year following birth promotes the decreased incidence of autism [42,43].

- Prevention of later autism tendency in fetuses/neonates of febrile gravidas: Risk of autism is raised when the fetus is carried by a febrile infected mother with elevated IL1, IL6, IL17, and TNF pro-inflammatory interleukins. Few antiviral medications have sofar been tested rigorously to avoid fetal/neonatal side-effects, thereby limiting their use in pregnant cases. Immediate postpartum treatment with IGF1 supplementation is feasible (e.g., IV infusion) when umbilical cord blood testing indicates need.

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