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Hypothesis

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Is fever suppression involved in the etiology of autism and neurodevelopmental disorders?

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Abstract

Background: There appears to be a significant increase in the prevalence rate of autism. Reasons for the increase are unknown, however, there is a substantial body of evidence that suggests the etiology involves infections of the pregnant mother or of a young child. Most infections result in fever that is routinely controlled with antipyretics such as acetaminophen. The blocking of fever inhibits processes that evolved over millions of years to protect against microbial attack. Immune mechanisms in the central nervous system are part of this protective process.

Hypothesis: The blockage of fever with antipyretics interferes with normal immunological development in the brain leading to neurodevelopmental disorders such as autism in certain genetically and immunologically disposed individuals.

Testing the hypothesis: Epidemiological studies to determine associations between the use of antipyretics and neurodevelopmental disorders should be undertaken. Biochemical tests will involve the examination of fluids/serum by mass spectrometry and the determination of cytokine/chemokine levels in serum and cell culture fluids after stimulation with fever-inducing molecules from bacteria, viruses and yeast. Postmortem brain can be examined by immunohistochemistry or other methods such as fluorescent in situ hybridization (FISH) to determine altered expression levels of chemokines/cytokines and other molecules.

Implications of the hypothesis: 1) The use of antipyretics during pregnancy or in young children may be reserved for more severe fevers. 2) The perplexing genetic findings in autism may be better understood by categorizing genes along functional pathways. 3) New treatments based on immune, cell, pharmacological or even heat therapies may be developed.

Background

According to epidemiological studies, autism, a neurodevelopmental disorder, is increasing in the pediatric population [1]. In 1966 the prevalence rate was 4–5/10,000 births [2], while two recent studies show prevalence rates of 14.9/10,000 [1] and 34/10,000 [3]. Although there is no question that more clinical cases are being detected, the increase in prevalence of autism is in dispute as diagnostic practices have changed over the years and this heightened awareness has changed the evaluation of previously unrecognized cases [4]. Increased services have also contributed to the rise as clinicians are inclined to get individuals into autism programs that can help remarkably. Despite these considerations, there is still a concern about a real increase in the prevalence rate.

In 1943, Kanner [5] described autism as a neurodevelopmental disorder with impairments in social interactions, restricted stereotyped interests, and abnormalities in verbal and nonverbal behavior. Little is known about the etiology, and the diagnosis of autism is done by behavioral criteria as no biomarkers have yet been identified. There is a strong familial component to autism [6], and etiologies based on infectious [7], autoimmune [8–11], and cytokine factors [12,13] have been proposed.

About 40% of parents with autistic children report that their seemingly normal children experienced developmental regression after being vaccinated. However, the theory of vaccines or adjuvants being involved in the etiology [14] has little support as epidemiological studies have failed to show an association with the measles, mumps, and rubella (MMR) vaccine [15–17] and autism.

It has been reported that 43% of mothers with an autistic child experienced upper respiratory tract, influenza-like, urinary, or vaginal infections during pregnancy compared to only 26% of control mothers [10]. Studies show that in rats, maternal exposure to infection alters proinflammatory cytokine levels in the fetal environment, including the brain; it has been proposed that these changes may have a significant impact on the developing brain [18,19]. This suggests that certain cases of autism may be a sequela of pathogenic infections, especially those of a viral origin [20–23].

There is no overt pathological lesion in autism, however, subtle abnormalities in the cerebellum, hippocampal fields CA1–CA4, entorhinal cortex, amygdala, behavioral differences and imbalances in cytokines and brain growth factors suggest that abnormal brain development is important in the pathogenesis [24–26].

Pathological infections, including vaccinations, commonly result in fever. For example, 50–60% of young children develop fever after receiving the MMR vaccine [27]. Fever is rarely harmful and only extremely high fevers of 42.2C (108F) may cause brain damage. However, fevers of 41C (106F) should get immediate medical attention to examine the patient for severe infection [28].

Fever is defined as an increase in the normal set point of body temperature. During the rising phase of fever, normal body temperature is below the new set point and the body, being hypothermic, uses several heat conserving and heat generating physiological reflexes, as well as behavioral responses, to raise body temperature. The breaking of fever results in a variety of heat-losing reflexes and behavioral responses to lower body temperature.

There are two related fever pathways. The intraperitoneal injection of lipopolysaccharide (LPS), a potent pyrogen, results in the production of various cytokines from organs in the viscera. Cytokines are polypeptides that are involved in inflammation, immune activation, cell differentiation and cell death. These groups of polypeptides include interleukins, interferons, tumor necrosis factors, chemokines and growth factors. They generally have little or no known function in healthy tissue, but can be induced in a very rapid manner in response to tissue injury, inflammation or infection. A signal from IL-1β is thought to initiate afferent information traveling from the vagus nerve to the hypothalamus to increase hypothalamic IL-1β. This in turn causes an increase in hypothalamic IL-6, which raises the thermoregulatory set point. This pathway is mediated via prostaglandins and can be blocked by cyclooxygenase inhibitors (antipyretics). These two cytokines are also important in inflammation and are commonly labeled as proinflammatory cytokines.

The second fever pathway, also initiated in the hypothalamus by afferent signals from the vagus nerve, is mediated by locally produced macrophage inflammatory protein-1 (MIP-1), a chemokine. MIP-1 appears to act directly on the anterior hypothalamus via a non-prostaglandin mechanism and is not blocked by antipyretics [29].

Fever is metabolically expensive: every 1 °C rise in temperature increases the metabolic rate approximately 10% [30]. It stands to reason that a defense mechanism that evolved over millions of years and is so costly in terms of energy must be important. Numerous studies have shown that fever enhances the immune response by increasing mobility and activity of white cells, stimulating the production of interferon, causing the activation of T-lymphocytes, and indirectly reducing plasma iron concentrations [29–32]. Antiviral and antibacterial properties of interferon are also increased at febrile temperatures [33,34]. A decreased morbidity and mortality rate has been associated with fever in a variety of infections [35–39]. Newborn animals infected with a variety of viruses have a higher survival rate when febrile [40]. The use of antipyretics to suppress fever results in an increased mortality rate in bacterially infected rabbits [41] and an increase in influenza virus production in ferrets [42]. Brain hyperthermia markedly exacerbates neuronal injury [43]. There is anecdotal evidence that children with autism show behavioral improvement when febrile (D. Odell, personal communications, 2003).

Sequestering fever during pregnancy may have effects on the fetus. Goetzl et al. [44] have shown that the treatment of epidural fever with acetaminophen significantly decreased maternal and fetal serum IL-6 levels at the time of birth. This may be significant, as it appears that the

fetus is incapable of producing IL-6 at the time of birth and is dependent on maternal IL-6 [45]. Although the expression of cytokines in the CNS is very low, brain cells can produce specific cytokines as well as cytokine receptors under certain conditions [19]. For example, IL-6 and its specific receptor (IL-6R) are expressed on neurons and glial cells including astrocytes. There is mounting evidence that IL-6 is important in the development, differentiation, regeneration and degeneration of neurons in the central nervous system [46]. It is known that IL-6 promotes the differentiation of precursor cells to astrocytes and functions as a differentiation factor for neurons of the peripheral and central nervous system. IL-6 and sIL-6R have also been shown to be important in regulating the expression of specific neurotrophins in astrocytes [46].

Pathological conditions in the CNS have been observed in transgenic mice that have astrocyte-targeted expression of IL-6. High levels of IL-6 in these mice correlate with astrocytosis, microgliosis, angiogenesis and the up-regulation of several inflammatory genes including IL-1 α/β, TNFα, GFAP, ICAM, and complement C3. Transgenic mice expressing TNFα and INF-α also displayed significant neurological changes [47]. Projects such as these suggest that normal brain development requires a delicate balance of different cytokines.

Ozato et al. [48] described the response of cell-surface toll-like receptors (TLRs) upon binding to microbial pathogens. There are at least 10 TLRs that recognize ligands from bacteria, viruses, yeast, and nucleic acids from viruses. There is a high binding specificity of the different TLRs for each microbial structure referred to as pathogen-associated molecular patterns (PAMPs) [48]. The best studied is TLR4 that binds LPS from gram-negative bacteria. The ligation of LPS to cell surface TLR4 initiates a signal cascade that results in the activation of intracellular nuclear factor kappa beta (NF6B) and the transcription of numerous genes involved in immune responses. This signaling pathway appears to be common to all the TLRs whether the PAMPs originate from bacteria, virus, or yeast. TLRs are mainly expressed myeloid lineage cells including macrophages, granulocytes and dendritic cells.

The central nervous system exhibits a similar immune reaction to pathogenic infection. There is a broad expression of TLRs in human brain astrocytes, oligodendrocytes and microglia [49]. Astrocytes and oligodendrocytes express mRNA for TLR2 that recognizes fungal, gram-positive and mycobacterial components and TLR3 that recognize double-stranded RNA. Microglia cells express mRNA for a wide range of TLR family members (TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8 and TLR9) much like other cells of the monocytic lineage [49]. The binding of LPS to TLR on microglia cells (brain macrophage) leads to the innate expression of cytokines, chemokines, extracellular matrix proteins, proteolytic enzymes, and complement proteins in the brain parenchyma [50,51]. It is also well established that glial cells participate in innate immune responses in human CNS [49].

Fever is generally considered harmful by physicians and is treated with antipyretics as it may lead to febrile seizures, stupor, dehydration, increased breathing, discomfort, and tachycardia [52]. It is a common practice to treat even low-grade fevers of 101–102F with antipyretics. Home use of antipyretics upon the first signs of a fever is also common. These behaviors have lead to the ubiquitous use of aspirin, acetaminophen, nimesulide, and ibuprofen, which control temperature by inhibiting prostaglandin synthesis in the hypothalamus. Aspirin is not currently recommended in the pediatric population due to an association with Reye's syndrome [53].

Acetaminophen (AP), the most widely used medication, is considered safe when used at pharmacological doses. High doses of AP can lead to liver failure and death without proper emergency treatment. Although the hepatotoxic actions of AP have been extensively researched, there is evidence that it is also an immunosuppressive agent. Suppression of the delayed hypersensitivity response and mixed lymphocyte reaction occur in mice fed AP [54]. It has recently been shown that AP added directly to splenocyte cultures inhibited the *in vitro* antibody response without affecting cell viability [55]. Other immune effects include an impairment of TNFα release [56] and a 10–20-fold increase of monocyte chemoattractant protein (MCP-1) and chemokine receptor (CCR) from liver Kupffer cells (macrophages) [57]. These studies suggest that the AP directly affects immune cells and is not a secondary response to AP-hepatitis.

Presentation of the hypothesis

The premise of this theory is that the blockage of fever with antipyretics interferes with normal immunological development in the brain, leading to neurodevelopmental disorders in certain genetically and immunologically disposed individuals. The effects may occur in utero or at a very young age when the immune system is rapidly developing. Maternal infection is a risk factor for neurodevelopmental disorders including autism [20–23]. It has been shown that in rats, maternal exposure to infection alters proinflammatory cytokine levels in the fetal environment, including the brain; it has been proposed that these changes may have a significant impact on the developing brain [18,19]. Acetaminophen also interferes with IL-6 [44] levels as well as the release of TNFα [56], the same proinflammatory cytokines necessary for brain development.

Testing the hypothesis

The experimental avenues below can be used to test the theory:

1) Epidemiological studies can be undertaken to determine any association between the use of antipyretics and neurodevelopmental disorders.

2) Peripheral blood cells from subjects with neurodevelopmental disorders and controls can be examined in culture for chemokine/cytokine production after stimulation with bacterial, viral, or yeast PAMPs. The incubation of isolated white blood cells with bacterial or viral components (LPS, unmethylated DNA, dsRNA) that are known to increase cytokine expression may be useful to determine if there are genetically encoded differences in cells from subjects with autism and age- and sex-matched controls. It has been shown that the administration of low dose IL-1β to mice at birth suggests that long-lasting and perhaps permanent alterations occur in the CNS and peripheral neurotransmitter systems [58]. It would be important to know if individuals with autism are prone to be low or high producers of certain cytokines like IL-1β or IL-6.

3) The expression of chemokines/cytokines such as IL-1β and IL-6 can be examined in postmortem brain by immunohistochemistry, FISH, western/northern blotting or other molecular methods. These two cytokines play seminal roles in fever and are also important in the proinflammatory response. It has recently been shown that IL-1β, IL-6 and TNFα decrease in vitro survival of certain neurons and play important roles in the normal development of neurons including proliferation, survival, differentiation, axodendritic outgrowth and synaptic regulation [59].

4) Serum/plasma samples can be evaluated by analytical methods in an attempt to detect biomarkers for autism. Significant advances in mass spectrometry have been made in examining complex samples like serum for biomarkers for disease [60]. We have preliminary data examining plasma from subjects with autism and age-and sex-matched control samples by time-of-flight mass spectrometry. Examination of this data by multivariate analysis suggests that plasma from subjects with autism may have a unique peptide/protein profile.

5) Animal models can be tested in vivo to determine the neurodevelopmental effects of fever treatment. For example, brain tissue can be examined for cytokine/chemokine differences in mice treated/untreated with antipyretics after inducing fever with LPS.

Implications of the hypothesis

Several important changes may result from studies designed to test the theory:

1) The use of antipyretics during pregnancy or in young children may be reserved for more severe fevers.

2) Many of the perplexing genetic findings in autism may be better understood by categorizing genes along functional pathways. For example, the genes for TLR5, TLR9, TLR1, TLR4, and TLR7 are on different chromosomes (1,3,4,9, and X respectively). The binding of the respective ligand to a TLR causes the activation of a common transcriptional factor NF6B that results in the transcription of numerous immune related genes. This example clearly illustrates that genetic defects on different chromosomes may have a common result.

3) The discovery of specific immune defects may suggest new therapies for neurodevelopmental disorders. These treatments may be based on immune, cell, pharmacological or even heat therapies that alter the CNS immune system.

Competing interests

None declared.

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