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Similarities in features of autism and asthma and a possible link to acetaminophen use

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Abstract

Autism and autism spectrum disorders are enigmatic conditions that have their origins in the interaction of genes and environmental factors. In this hypothesis, genes statistically associated with autism are emphasized to be important in inflammation and in innate immune pathways, including pathways for susceptibility to asthma. The role of acetaminophen (paracetamol) in an increased risk for asthma is described and a possible similar link to an increased risk for autism is suggested.

Keywords

autism; asthma; acetaminophen; innate immunity

Introduction

Autism is a complex and heterogeneous disorder, and the etiology is unknown. Although numerous theories of early initiating events in the development of autism have been proposed, two areas of active scientific interest are immune dysregulation and genetic predisposition. In this report we compare immune and genetic aspects of autism. We then describe acetaminophen's link to asthma and suggest a link with acetaminophen to immune anomalies in autism.

Immune and inflammatory observations in autism

There are an increasing number of reports that anomalies in the immune system may play a role in autism. This has been found at the molecular, pathological, and epidemiological level. Altered levels of immunoglobulins¹⁻³, cytokines⁴ and, inflammatory markers have been identified in the serum⁵, cerebral spinal fluid⁶, and autopsy brain tissues² of autistic

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patients. Gastrointestinal inflammation in autism⁷ as well as pathological evidence of neuroinflammation involving activation of brain microglia has been shown⁸. An increase in head circumference in autistic children⁹, a consistent finding in autism, may involve neuroinflammation. Abnormalities in macrophages^{8,10} and mast cells in autism have also been noted¹¹. Differential monocyte responses to Toll-like receptors have been found in children with autism spectrum disorders suggesting involvement of innate immune pathways¹². Interestingly, activation of TLR2 has been shown to inhibit embryonic neural progenitor cell proliferation resulting in cortical dysgenesis *in vitro* and *in utero* in a mouse model (unpublished).

In addition, epidemiological evidence of immune involvement has been shown through an increased frequency of autoimmune disorders in family members of autistic patients¹³⁻¹⁵. Comparisons to early events between childhood asthma and autism have been suggested, including an increase in head circumference and male preponderance, among others¹⁶. There is no evidence of T cell mediated autoimmune tissue destruction as found in classical autoimmune disorders. Immune involvement in autism has recently been reviewed¹⁷⁻¹⁹. Interestingly, alterations in fever have been hypothesized to be involved in the etiology of autism²⁰ and fever has recently been shown to transiently improve both behavior and language in autistic patients²¹. Also, low levels of breastfeeding could decrease immune protection in infants by decreasing mother to child transfer of IgA. Breastfeeding has been linked to autism risk in the authors' previous work²².

Genes implicated in autism and asthma: macrophages, mast cells, and innate immunity

Although autism has been shown to be highly heritable, the genetic underpinnings of autism are complex and unclear^{21,23}. The relationship of genetic findings to the etiology, pathobiology, disease incidence in the population, or clinical course of the disease is obscure and speculative. While several important genes identified in genetic association studies in autism are often discussed in the context of synaptogenesis and brain development, a number of these autism candidate genes are central to the genetics or immunobiology of inflammatory disorders, including asthma and macrophage or mast cell dysfunction^{23, 24}. These genes include *PTEN*^{25,26}, *MET*^{23,27}, *SERPINE1*²⁸, *PLAUR*^{29,30}, *ITGB3*^{30,31}, *ADRB2*^{32,33} and *MIF*³⁴⁻³⁶.

PTEN, phosphatase and tensin homolog, is an important regulatory checkpoint in the inhibition of the PI3K/Akt/mTOR pathway²⁴ which is central to innate immunity as well as mast cell²⁵ and macrophage biology²⁶. *PTEN* has been associated with autism spectrum disorders and macrocephaly²⁷ and autism related phenotypes in a mouse model²⁸.

MET, the met proto-oncogene also known as hepatocyte growth factor receptor, has been associated with autism in multiple studies^{29,30}. *MET* has also been shown to be a regulator of mast-cell activation as a co-receptor with $\alpha 2\beta 1$ integrin³¹. In addition, both *SERPINE1* and *PLAUR*, two genes involved in the *MET* signaling cascade and in the fibrinolytic system, have both been genetically associated with autism³² and asthma³³. Both *PLAUR* (*uPAR*) and *SERPINE1* (*PAI-1*) have been shown to be highly expressed in macrophages, activated brain microglia³⁴, as well as in mast cells³⁵. Both *PLAUR* and *SERPINE1* may play an important role in the pathogenesis of asthma^{36,37}.

Integrin beta 3 (*ITGB3*) on chromosome 17 codes for a cell surface molecule involved in cell-surface mediated signaling and cell adhesion. Polymorphisms in *ITGB3* have been associated with multiple disorders including autism³⁸ and asthma^{33,39} in genetic association studies. *ITGB3* (CD61) is found on the surface of mast cells where it is involved in binding vitronectin and mast cell activation^{40,41} and cell signaling in macrophages⁴².

ADRB2, the beta-2 adrenergic receptor, is a G protein-coupled receptor that is expressed ubiquitously and influences many pathological states including asthma, obesity and Type 2 diabetes. The Glu27 allele of *ADRB2* been associated with autism⁴³ in the AGRE⁴⁴ cohort as well as in dizygotic twins⁴⁵. This polymorphism of *ADRB2* is also associated with asthma disease severity and drug response⁴⁶.

MIF, or macrophage migration inhibitory factor, codes for a cytokine involved in immunoregulation and inflammation⁴⁷ in T lymphocytes, pituitary cells, astrocytes, macrophages, smooth muscles cells, endothelial cells, and mast cells⁴⁸. Polymorphisms in the promoter of *MIF* have recently been associated with autism spectrum disorders⁴⁹, as well as in allergic asthma⁵⁰, and have been shown to be required for allergic inflammation in a mouse model of asthma⁵⁰. In addition, polymorphisms in *MIF* have been associated with Hereditary Periodic Fever (HPF) syndromes as well as regulating serum MIF concentrations⁵¹. Interestingly, in all three cases, autism, asthma, and HPF, the – 173G/C promoter polymorphism which alters levels of *MIF* gene transcription was an associated allele. Importantly, the metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI), inhibits the isomerase and the biological activities of MIF⁵².

The genes described above having been commonly identified in autism, asthma, and inflammation suggests an overlap in genetic susceptibility factors between these disorders. This raises the possibility that environmental factors acting through gene-environment interactions may act in similar ways in both disorders.

Acetaminophen

Acetaminophen (paracetamol) is a widely used over-the-counter pain reliever and fever reducer (antipyretic) that was introduced in the US in 1955²²⁵⁶. Acetaminophen largely replaced aspirin for the treatment of pediatric fever after the CDC advisory in 1980 to physicians and parents regarding an association between aspirin and Reye's syndrome. Acetaminophen overdose is a leading cause of hepatotoxicity and acute liver failure. Activation of liver Kupfer cells (phagocytic macrophages of the liver) by acetaminophen metabolites have been shown to activate cytokines and alter innate immunity in liver injury⁵³. Acetaminophen has been suggested to alter the Th1/Th2 cytokine balance in acetaminophen induced liver injury⁵⁴ and to act through TLR4⁵⁵ and TLR9⁵⁶. In addition, acetaminophen has recently been shown to alter protein levels and phosphorylation of PTEN and S-nitrosylated Akt in a chronic rat model of muscle aging⁵⁷.

Most importantly, acetaminophen use in the first year of life has been strongly associated with a later increased risk of asthma, and related phenotypes of asthma⁵⁸. This association was recently found to have a dose dependent risk of childhood asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years, in a large multinational study⁵⁹. Moreover, increased risk of asthma due to acetaminophen use in late pregnancy has also been shown⁶⁰. The exact molecular mechanism of this increased risk of asthma and allergic disorders due to acetaminophen use is not known⁶¹, although mechanistic theories include alterations in glutathione levels, effects on serotonin, suppression of COX2, and specific effects of acetaminophen breakdown products⁶² such as NAPQI. Importantly, acetaminophen use after MMR vaccination has recently been associated with autism in a small case controlled study⁶³; this association was not seen with ibuprofen.

Moreover, acetaminophen affects glutathione levels as well as pathways involved in transsulfuration. Glutathione metabolism is fundamental to many biological processes and alterations in glutathione homeostasis are implicated in numerous human diseases including immune and inflammatory disorders⁶⁴. Polymorphisms in glutathione pathways have been associated with both autism and inflammatory disorders⁶⁴⁻⁶⁷. Glutathione reductase has

been shown to be inhibited through acetaminophen-glutathione conjugates⁶⁸. The transsulfuration pathway converts cysteine to homocysteine through the intermediate cystathione. Transsulfation metabolism has been shown to be altered in children with autism⁶⁹ and parents of children with autism⁷⁰.

Interesting inflections in disease prevalence curves

Numerous studies have attempted to measure the prevalence of autism and asthma in the population⁷¹⁻⁷³. Both asthma and autism have had a similar apparent rise in the number of cases since approximately 1980, over the past 30 years, and in both disorders these have been repeatedly referred to as “epidemics”. In autism, this apparent rise in cases is highly controversial⁷⁴ and may be whole or in part due to increased disease awareness and/or expansion and reclassification of diagnostic criteria.

The following discussion is not intended to judge the validity of disease prevalence studies in asthma or autism; it is simply to point out interesting minor anomalies in those curves. In disease prevalence curves of both autism and asthma in the US, the sharp rise in cases began in approximately 1980. In the period from 1980 to 1990 there were two slight downturns in the slope of the curves, after 1982 and after 1986. Both curves continue markedly upward after 1988 into the 1990s (see Figures 1 and 2). In addition, there are similar slight downturns in slopes of the curves at the same times from independent and geographically disparate studies in both asthma and autism including: hospitalizations⁷⁵, autism cases in Minnesota⁷⁶, autism in north east London⁷⁷, and autism in an urban area in Sweden⁷⁸ (see supplemental figures 1-4).

Four significant events related to acetaminophen use occurred between 1980 and 1990. The first was the CDC caution in 1980 concerning the relationship of aspirin to the risk of Reyes Syndrome which was followed by a public and professional warning by the United States Surgeon General regarding a possible Reyes Syndrome-aspirin association⁷⁹. These cautions against the use of aspirin as a fever reducer in children were largely responsible for the replacement of aspirin by acetaminophen as a pediatric antipyretic⁸⁰.

In 1982 and again in 1986 there were product tampering cases where acetaminophen tablets were laced with cyanide resulting in eight deaths. Acetaminophen sales collapsed after each tampering event, but recovered in less than a year in each case⁸¹⁻⁸³. These dates roughly correspond to the slight downturns in asthma and autism cases mentioned above.

Hypothesis

The discussion above provides multiple lines of evidence for overlap in genetic susceptibility, molecular pathways, and other features associated with early preclinical etiological events in autism and asthma. A number of these features including biological, genetic, and epidemiological evidence may converge in aspects of inflammation or innate immunity, often involving macrophages or mast cells.

There is strong epidemiological evidence that acetaminophen use in late pregnancy and/or in the first year of life increases the risk of subsequently acquiring childhood asthma and related allergic disorders. This may be due to direct effects on immunological pathways or secondary effects such as through alterations in blood serotonin, glutathione, or transsulfuration. Fever has been shown to have a modifying effect on behaviors in autism, and acetaminophen is widely used to treat childhood fever as well as symptoms associated with childhood infections and childhood vaccines. Acetaminophen use has been shown to be associated with autism in a preliminary study⁶³.

It is proposed that widespread use of acetaminophen in late pregnancy or early childhood may significantly alter subtle immune processes, through direct or indirect mechanisms, increasing the risk for autism. It is suggested that a large scale population based epidemiological study be conducted to determine the role, if any, of acetaminophen in the risk for autism.

Limitations

No evidence is presented here that acetaminophen in any way causes autism. Readers of this hypothesis should not conclude that acetaminophen is central to the etiology of autism or speculate beyond what is presented here. This hypothesis is largely based on multiple lines of often weak evidence. It is hoped that further research can clearly strengthen or disprove the ideas presented here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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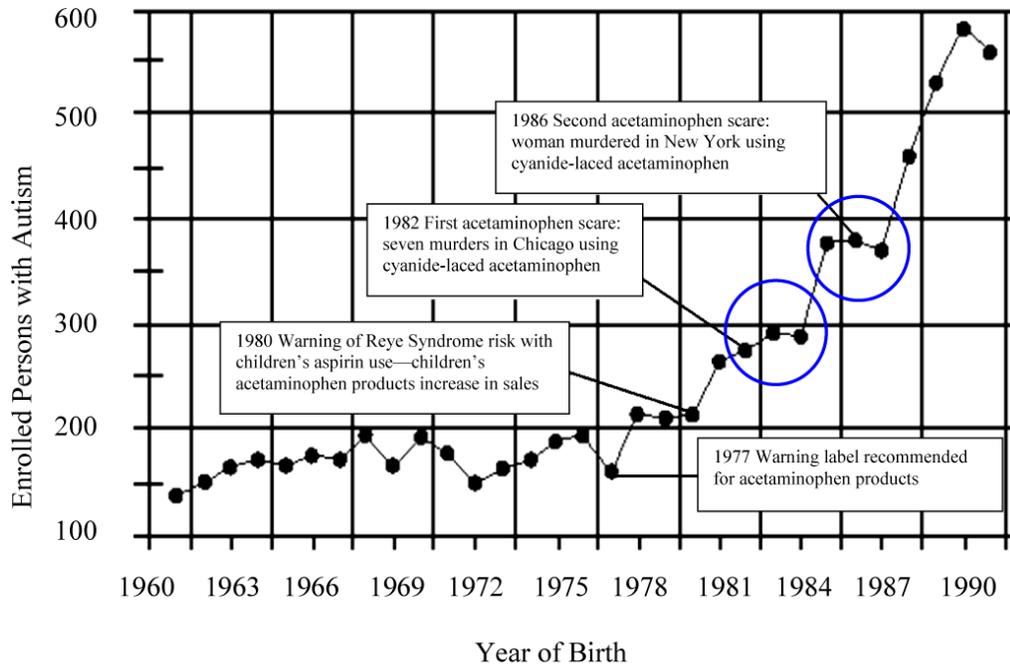


Figure 1. Number of enrolled persons with autism in California by year of birth* with addition of events in the history of acetaminophen. The post-1982 and post-1986 downward inflections are circled.

*Adapted from: Changes in the population of persons with autism and pervasive developmental disorders in California's developmental services system: 1987 through 1998. A report to the legislature (DDS, 1999). Figure 1, page 8. Available at: http://www.dds.cahwnet.gov/Autism/docs/autism_report_1999.pdf

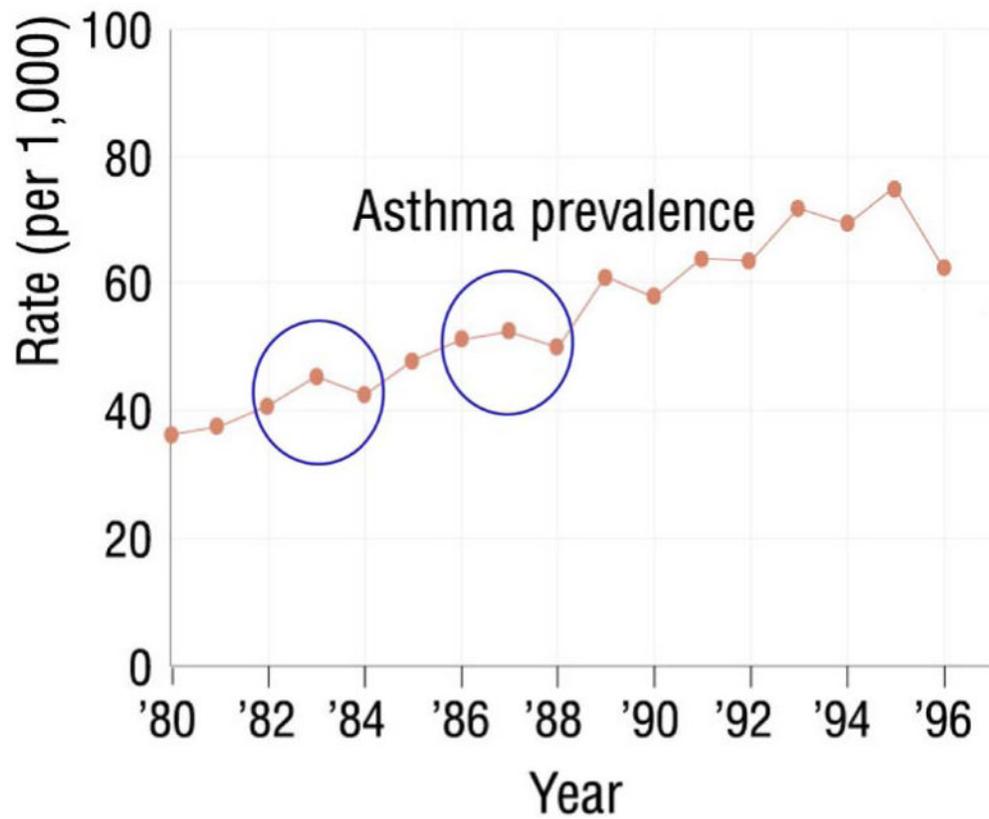


Figure 2.

Asthma prevalence in US children 0-17 years, 1980-2007. The post-1982 and post-1986 downward inflections are circled.

Adapted from: US EPA-Report on the environment. Exhibit 5-31 Asthma prevalence in US children 0-17 years, 1980-2007⁸⁴; Adapted from Akimbami, 2006; NCHS, 2007b; NCHS, 2008.