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Acetaminophen Misuse: A Possible Risk Factor of Autism

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ABSTRACT

Autism Spectrum Disorder (ASD) represents a major public health concern as a prevalent neurodevelopmental disorder with pronounced risk for failure of adaptation across social, educational, and psychological outcomes. The exact etiology of autism is unclear. However there is a lot of research work giving some insights about the possible predisposing factors that enhance chance of autism. Several lines of evidence suggest that prenatal and/or early life acetaminophen exposure may adversely affect neurodevelopment increasing incidence of autism. Since 1980 acetaminophen greatly has replaced aspirin as an analgesic and anti-pyretic following reports indicating that aspirin use was associated with Reye's syndrome. Notably acetaminophen use has been associated with at least a 10-fold rise of autism epidemic since the early 1980s. Several mechanisms have been suggested to implicate the role of acetaminophen in pathogenesis of autism as altered immune function and impaired hepatic detoxification capacity resulting in accumulation of potentially neurotoxic metabolites. In early life, maturational compromises to the glucuronidation pathway in combination with the compromises to the sulfation pathway that typify autistic children, may lead to utilization of the suboptimal secondary metabolic routes with the potential for adverse neurological effects in susceptible individuals. Acetaminophen use during pregnancy has also been associated with altered metabolism increasing autism rates in born infants. The use of acetaminophen may also trigger autism by activating the endocannabinoid system thereby interfering with normal development. Accumulating evidence linking significantly increased rates of autism with prenatal and early life acetaminophen exposure strongly suggests its cautious use during these critical times.

Keywords: Autism, acetaminophen, sulfation, immunity, cannabinoid system.

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INTRODUCTION

Autism Spectrum Disorder (ASD) is a severe developmental disorder defined by social and communication deficits, repetitive behaviors and fixated interests that appear in early childhood. [1,2] Despite a large and rapidly expanding body of literature, the etiology of ASD remains poorly understood. There is substantial evidence implicating oxidative stress, inflammation and immune dysregulation, although no single coherent explanation has emerged. [3] Two of the prominent features of autism are immune system dysregulation and abnormal brain neuron organization.[4,5] Recent studies provide evidence that susceptibility to ASD may have significant environmental components, in addition to genetic heritability. [6,7]

Several lines of evidence suggest that medication use in pregnancy and early childhood may play a role in ASD etiology. Specifically, some authors have hypothesized that paracetamol (acetaminophen, N-acetyl-p-aminophenol) has increased ASD risk. [2,8-10] In 2008, Schultz et al reported an association between autism and acetaminophen (Tylenol®) given children for fever, pain, and other adverse reactions to the measles-mumps-rubella (MMR) vaccine which is usually administered between 12 and 15 months of age. [9] Children given acetaminophen after the MMR vaccine were significantly more likely to become autistic than children given ibuprofen. Although distribution studies detected no association, the MMR vaccine has long been suspected of provoking autism, especially by parents whose seemingly normal child regressed into autism not long after receiving the vaccine. [11] Schultz et al (2008), however, raised the intriguing question whether the trigger for autism is not the MMR vaccine, but acetaminophen given for its subsequent fever and pain. [9] This review will discuss the possible role of acetaminophen misuse in the pathogenesis of autism.

Synchronicity of Acetaminophen use and the Autism Epidemic

There are several theories about possible environmental triggers for autism including childhood vaccinations, mercury exposure, and viral infections. When Rimland founded the Autism Research Institute in 1967, parents were already reporting that their child deteriorated into autism soon after the diphtheria, pertussis, tetanus (DPT) vaccine. [12] Rimland suspected the increase in autistic regression at 18 months was due to wider use of the MMR vaccine – part of an accelerated effort to eradicate measles that began in 1978. [13] Descriptive clinical studies have suggested a link between MMR vaccination and autism/pervasive developmental disorder. [14-16] Epidemiological studies have not supported the relationship between prevalence of autism and the MMR vaccine.[17-19]

The link between the MMR vaccine and an elevated risk for autism is controversial. However, children are often given acetaminophen if they have symptoms such as fever or irritability, and the MMR vaccination can cause these symptoms.[20] One study showed that administration of acetaminophen after the MMR vaccination is associated with increased risk for autism. [9] A further report compared the features of autism with asthma and suggested a link to acetaminophen use. [10]

Paracetamol is one of the most common antipyretic analgesic medicines worldwide. In 1980, paracetamol essentially replaced aspirin as the primary treatment of fever in children and pregnant women after sufficient evidence emerged of an association between salicylates and Reyes syndrome, a rare but often fatal disease in young children after a bout of flu or chicken pox. [21-23] Since that date, paracetamol consumption throughout the world has increased dramatically. [24] Paracetamol sales in the United States (US) have had a continual upward trend. In 1982, US paracetamol sales were approximately $400 million; by 2008 they had risen to $2.6 billion.[25]

Surprisingly, decreased sales of children's aspirin and increased sales of children's acetaminophen products beginning about 1980 were associated with an increased number of children with autistic disorders born after 1980. The incidence of autism has risen 10-fold since the early 1980s. [13] Until about 1980, approximately 50-60 percent of autistic children were abnormal from birth, and 40-50 percent regressed into autism at approximately 18 months. [11] Around 1980 the total frequency of occurrence doubled, doubled again, and by 1995 was approximately 10 times that of 1980. Furthermore, while the onset-at-birth type had increased 3 to 4 times, the onset-at-18-months type had skyrocketed to considerably more than 10 times its 1980 level. [13] Theoharides and colleagues (2009) reported prevalence prior to 1980 as approximately 4/10,000, while Baio et al. (2012) estimated that US autism/ASD prevalence to have risen to about 110/10,000. [26,27]

Interestingly, in 1982 and again in 1986, product tampering led to a few bottles of a leading brand of paracetamol tablets being contaminated with cyanide. In each case, a rapid and brief decline in paracetamol sales occurred, with the long term upward trend recovering within a year. In three populations for which good data are available, Becker and Schultz (2010) noted that brief dips in the rising autism prevalence curves mirrored these sales anomalies. [10] The prevalence curves continued their upward trend after 1988. [25] More interesting, a recent investigation found transcriptomic changes in full-genome human miRNA expression indicating, for the first time, immune modulating effects and oxidative stress responses to paracetamol even

at low doses.[28] Studies in animals have shown paracetamol to induce apoptosis and neurotoxicity. [29] Several studies hypothesize increased apoptosis in the autistic brain. [30,31]

Metabolism and Toxicity of Acetaminophen

As parents may not realize children's cold remedies often contain acetaminophen, acetaminophen overdose in young children is not uncommon. [32] Paracetamol has four important metabolic pathways namely glucuronidation, sulfation, cytochrome P-450 system and deacetylation. The two main pathways are glucuronidation and sulfation. Paracetamol is mainly metabolized in the liver via conjugation with glucuronide and sulfate and then excreted. Both these metabolic routes yield inactive, non-toxic final products. Glucuronidation is the primary metabolic pathway in adults, while sulfation by the liver is the primary pathway to detoxify and excrete acetaminophen in children younger than 10. [2,9] Neonates, in general, have lower capacity to metabolize drugs due to the underdevelopment of the glucuronidation pathway and inefficiency and immaturity in renal function. [33] Low birth weight and bilirubinemia have also been found to reduce glucuronidation capacity, both of which have been associated with autism.[34]

Secondary metabolic pathways of acetaminophen

Autistic children usually show abnormal sulfate capacity and a specific inability to sulfate paracetamol causing them to process acetaminophen differently. [35,36] Parents of autistic children may also exhibit abnormal trans sulfuration metabolism.[37] Actually it is possible that children predisposed to developing autism have a sulfation deficit which may lead to increased blood levels of acetaminophen after administration of therapeutic doses. [2] The American Academy of Pediatrics warned that clinical signs of liver disease – fever and abdominal pain – are often treated with acetaminophen. Many cases of severe liver poisoning in children have been attributed to cumulative toxicity from repeated therapeutic doses of acetaminophen rather than acute toxicity from a single massive overdose. [32] Notably, evidence indicates that acetaminophen, although an effective analgesic does not reduce fever significantly.[38]

When the capacity to metabolize acetaminophen through the primary pathways is depleted or saturated, the fraction of the dose converted to reactive metabolites increases and the secondary metabolic pathways become increasingly involved.[39] One of the two secondary pathways is oxidation by cytochrome P-450 (CYP P-450), forming a highly reactive metabolite, n-acetyl-p-benzoquinoneimine (NAPQI) which reacts with cellular glutathione (GSH) to form a non-toxic conjugate, which is subsequently excreted. [40] Once GSH is exhausted, NAPQI binds to cellular proteins, including mitochondrial proteins reducing the ability to detoxify, which can lead to

oxidative stress, immune system activation, hepatocellular death, nephropathy and asthma.[28,41] It has been shown that paracetamol treatment induces greater glutathione depletion in male mice[29] Alterations in GSH homeostasis have been a consistent observation among autistic children and their mothers.[42,43] Also, decreased glutathione levels have been associated with preeclampsia. [44] Paracetamol use during the third trimester of pregnancy might be associated with increased risk of preeclampsia. [45] In the meantime, maternal preeclampsia has been associated with increased risk of having a child with ASD.[46]

A fourth metabolic pathway, accounting for about 6% of paracetamol metabolism, has been identified that is believed to be related to the mechanism of analgesic action. [47] This pathway involves deacetylation of paracetamol in the liver producing p-aminophenol that conjugates with arachidonic acid in the brain and in the spinal cord. [48,49] P-aminophenol is recognized to be involved in paracetamol nephrotoxicity. [50] Recently, P-aminophenol has been shown to produce a significant loss in mouse cortical neuron viability at therapeutic concentrations. [25] This suggests another possible pathway for a neurotoxic effect of paracetamol when the principle metabolic routes are exhausted.

Abnormal sulfate metabolism in children with autism

Parents and autism support groups commonly report that autistic episodes are triggered when these children eat wheat, corn, sugar, apples, bananas, chocolate, cheese, and other dairy products. **[35]** Because many of these "trigger" foods are high in phenolic amines (e.g., dopamine and serotonin) that depend on sulfate for excretion**,** sulfate metabolism in children with autism has been investigated. **[51]** The liver uses sulfate derived from the amino acid cysteine to make a variety of foreign and domestic substances soluble for excretion. **[51]** The liver also uses cysteine to synthesize the antitoxin and antioxidant glutathione as well as metallothionein, which transports zinc and copper and binds mercury and other toxic metals.**[52,53]** Liver detoxification is almost universally impaired in children with autism. **[51]** Autistic children may have significantly reduced plasma levels of methionine, cysteine, and glutathione. They also show reduced methylation capacity with plasma cysteine severely reduced in more than 65% of cases. [54]

Autistic children intolerant of certain foods and chemicals were found to have very low levels of phenolsulfotransferase (PST), an enzyme that sulfates phenols and amines for excretion. Such children are more susceptible to adverse effects of acetaminophen given relatively freely for minor illness. **[55]** Reduced ability of autistic children to sulfate phenols and amines might lead to accumulations of un-metabolized catecholamine neurotransmitters (dopamine, norepinephrine, and epinephrine) in the brain, with neurotoxic effects.**[35]**

Sulfation and acetaminophen in mothers of autistic children

During pregnancy a women's sulfation capacity is reduced which may precipitate activation of immune responses, via the P-450 pathway. [56] The activation of immune response and pro-inflammatory cytokine interleukin signaling has recently been detected even at therapeutic doses of paracetamol. [28] Converging evidence highlights the important role of many of the same cytokines in mediating maternal immune activation effects on the neurodevelopment of autistic offspring. [57-59]

One critical sulfation reaction during pregnancy converts the adrenal androgen and estrogen precursor dehydroepiandrosterone (DHEA) to its sulfate DHEAS, a reservoir form of DHEA that takes 15 times longer to clear from the blood. [60,61] DHEAS from the fetal adrenal cortex is the most common precursor of the placental estrogens so vital to fetal growth and maturation. [62] Geier and Geier, 2006 found that children with autistic spectrum disorders had higher levels of serum/plasma DHEA and testosterone, and lower levels of methionine, cysteine, glutathione, and other cysteine metabolites. They noted that DHEA can convert to androstenedione and then testosterone, or be sulfated to the "normally favored storage molecule" DHEAS. Because sulfation of DHEA requires glutathione as a cofactor, they proposed that glutathione deficiency in these children causes less DHEA to convert to DHEAS and more to androstenedione and testosterone.[63]

A similar shift of adrenal steroid synthesis occurs in mother and fetus during complications of pregnancy, and in adults under stress, increasing cortisol at the expense of DHEAS. [64] Strous et al., 2005 found plasma DHEAS significantly low in adults with autistic spectrum disorders. [65] Croonenberghs et al., 2008 detected a high ratio of plasma cortisol to DHEAS in autistic adolescents. [66] Sulfation is also important for the excretion of steroids, including DHEA and testosterone.[51] Mothers of autistic children commonly suffer more bacterial and viral infections and fevers during pregnancy, for which they commonly take acetaminophen.[8,67,68] If their babies are born cysteine-deficient, newborn boys may be more vulnerable because their uptake of cysteine takes longer to mature. [69] Acetaminophen given infants before the MMR vaccine may also set the stage for autism, notably when given for reactions to the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at ages two, four, and six months – a vaccine with the most fever/pain. [13]

Acetaminophen impairing sulfation before and after birth may explain why children with autism have smaller brains at birth (estrogen deficiency), then an accelerated and prolonged growth

spurt of males specific brain structures within a few months of birth (androgen excess). [70,71] The testosterone-dependent amygdalae are larger than normal in these children and the estrogen-dependent corpus callosum disproportionately smaller. [71,72] These anomalous brain structures in autism, and the characteristic personality, behavior, and aptitudes they beget, have been termed the "extreme male brain" by Baron-Cohen et al., 2005. [71] Impaired sulfation of DHEA to DHEAS before and after birth, reducing estrogens and increasing testosterone, together with impaired sulfation/excretion of testosterone, may explain these anomalies. [13]

ACETAMINOPHEN-INDUCED ANALGESIA AND CANABINOID RECEPTOR ACTIVATION

Although acetaminophen has been used as an analgesic for more than a hundred years, its mechanism of action has remained elusive. It has been shown by two independent groups that acetaminophen produces analgesia by potentiating cannabinoid receptors in the brain. [47,48] These observations have been confirmed by Mallet and colleagues (2008). [49] Hogestatt and colleagues have shown that acetaminophen is deacetylated to p-aminophenol which is conjugated with arachidonic acid in the brain and spinal cord by fatty acid amide hydrolase (FAAH). [47] The resulting compound, N-arachidonoylphenolamine inhibits the cellular uptake of anandamide, a naturally occurring endogenous cannabinoid or endocannabinoid. The result is increased levels of endocannabinoids which produce an analgesic effect. [47] Bertolini and colleagues (2006) noticed a similarity in the effect of acetaminophen and cannabinoids. [48] Cannabinoids and acetaminophen both have an analgesic action and lower body temperature. They were able to show that blockage of cannabinoid receptor 1 (CB_1) completely prevents the analgesic activity of acetaminophen. [48]

Interference with normal development through modulation of the canabinoid system

The endocannabinoid system plays an important role in the development of the central nervous system and its activation can induce long-lasting functional alterations. [73] Use of cannabis (an exogenous cannabinoid) in the still-maturing brain may produce persistent alterations in brain structure and cognition. [74] Animal models have revealed the danger of both cannabis abuse and exposure to cannabinoid drugs during brain development. [75] Developmental problems associated with the endocannabinoid system may occur through either of the two known cannabinoid receptors, CB_1 or CB_2. [2] CB_1 receptors are located in the central nervous system (CNS), peripheral nervous system, and peripheral organs. In the CNS, CB_1 receptors are concentrated in the cerebellum, hippocampus, and the basal ganglia which are areas in the brain implicated as dysfunctional in autism. [5, 76,77]

During fetal life, CB_1 receptors and their associated endocannabinoids are important for neuron differentiation and proper axonal migration. [78] In addition, recent studies suggest that CB_1 cannabinoid receptors define synapse positioning. [79] Modulation of CB_1 cannabinoid receptors could trigger autism by interrupting normal brain development. CB_2 receptors are primarily located in immune tissues and cells and may serve a regulatory function. CB_2 receptors have been shown to control the movement of inflammatory cells to the site of injury, and CB_2 receptors' reverse agonists may serve as immune system modulators. [80] The activation of CB_2 receptors stimulates beta-amyloid removal by macrophages which may slow the progression of Alzheimer's disease. [81] CB_2 receptor agonists attenuate transendothelial migration of monocytes and monocyte-endothelial adhesion. [82]

Monocytes are one of the primary cells of the immune system and differentiate into macrophages and dendritic cells. If the evidence is correct that acetaminophen acts as an activator of cannabinoid receptors then activating CB_2 receptors could influence the growth of monocytes. Lab evidence indicates that acetaminophen in the media inhibits the cell division of monocytes in a dose dependent manner. [2] Inhibition of growth is noted even at the therapeutic concentrations. If as proposed, children with autism are poor metabolizers of acetaminophen, higher than normal therapeutic levels could be possible with recommended doses and could lead to a greater inhibition of monocytes.

It has been shown in several studies that children with autism have immune system dysregulation. [83-85] This dysregulation includes differential monocyte responses, abnormal T helper cytokine levels, decreased T cell mitogen response, decreased numbers of lymphocytes, and abnormal serum immunoglobulin levels. Many studies have shown that children with autism exhibit autoimmunity, in particular antibodies against brain and central nervous system proteins. [86-88] It is proposed that the immune dysregulation in children with autism is due to the influence of acetaminophen on CB_2 receptors during gestation or in early childhood.

PRENATAL/PERINATAL ACETAMINOPHEN EXPOSURE: POSSIBLE EXTRA LINKS TO AUTISM

A common neonatal medical procedure is circumcision, which typically occurs during the postpartum hospital stay, within the first two days of life for a vaginal delivery and first four days for a cesarean section. [89] Prior to the 1990's circumcision was generally performed without analgesics. A 1994 study by Howard et al. found that when paracetamol is given regularly every 6 hours for at least the first 24-hour postoperative period, infants demonstrated decreased responses to pain. [90] This study led to the development of circumcision pain management

guidelines by the American Academy of Pediatrics (1999) and others. [91-93] These guidelines include the suggestion of a first dose of paracetamol two hours prior to the procedure, and doses every 4–6 hours for 24 hours following the procedure. Thus newborn males often receive 5–7 doses of paracetamol during the developmentally vulnerable initial days of life. This might explain the approximately 4.6 times higher prevalence of autism in males compared to females.[27]

Prenatal exposure trends

Previous research has identified paracetamol usage trends that curiously coincide with the rise in prevalence and population demographics of autism/ASD. In the US Slone Epidemiology Center Birth Defects study paracetamol was the most commonly used medication amongst all subjects with usage higher during pregnancy than before pregnancy. In the early 1980's about 42% of women used paracetamol during the first trimester of pregnancy. The rate climbed to over 65% in the early 1990's, where it has essentially remained through 2004. [21]

Maternal viral infection requiring hospitalization during the first trimester and maternal bacterial infection in the second trimester have been associated with diagnosis of ASD in the offspring.[94] Maternal self-reported influenza was found to be associated with a twofold increased risk of infantile autism and a febrile episode lasting more than seven days was associated with a threefold increased risk. [95] Each of these maternal infections or a prolonged febrile episode would likely increase the exposure to paracetamol. In the U.S., usage of paracetamol by pregnant women mirrors the population demographics of women whose children develop ASD, by race, age and education. [96] The population demographics for mothers who circumcise their children are also very similar, with rates increasing with socio-economic status and insurance coverage rates. [97,98] Studies have shown that a parent's own usage rates of paracetamol and other medications correlate with what they give to their children, so a similar demographic usage pattern would be expected for childhood exposure.[99] This synchronous U.S. pattern may be suggestive of an additive nature of both prenatal and early life exposure to paracetamol and a relationship to autism/ASD.

Early life exposure trends

Paracetamol is the most common drug administered to US children and the predominant analgesic/antipyretic drug among children up to 24 months of age. [100] Paracetamol is suggested for pain management following vaccinations. In 1983 the average U.S. child received 8 immunizations before age 2. In 2011, the average was 25, a 313% increase. [25] This represents increased opportunities for paracetamol exposure in pain management (although administering several vaccines at once means analgesia may not increase proportionally). A recent study

representing one-fifth of all paediatric hospital admissions in the U.S., identified paracetamol as the most common drug administered to children over one year of age and the second most common drug administered for those under one year; more than 40% of hospital stays in both groups include paracetamol. [101]

POTENTIAL THERAPIES

Because autistic children lack capacity to metabolize and excrete foreign and native toxins of all kinds, the most effective general countermeasure may be to increase their sulfur substrate, e.g., via magnesium sulfate (Epsom salts) in bathwater and/or careful doses in orange juice. Oral magnesium sulfate, which is poorly absorbed, draws water into the intestines, potentially causing diarrhoea; whereas, well absorbed magnesium taurate provides magnesium as well as sulfur from taurine.[102]

Almost half of autistic children and adults benefit when given oral vitamin B_6 plus magnesium (optimal daily dose on average: 8 mg vitamin B_6/lb body weight plus 4 mg magnesium/lb) [103]. Other good sources of sulfur are cabbage, onions, garlic, dried fruit oral supplements like whey protein and methylsulfonylmethane (MSM) and a high-protein diet.[53,104,105] Cysteine supplements, however, appear unsafe. Quig, 1998 noted that high doses of cysteine (e.g., 500 mg 3 times daily) may transport mercury into the brain. [53] Pangborn, 2002 warned that a sudden influx of cysteine may mobilize toxins the body is not ready or able to excrete.[11]

When acetaminophen overdose depletes the liver's supplies of sulfate and glutathione and toxicity develops, N-acetylcysteine is used to replenish intracellular glutathione.[106] N-acetylcysteine and oral glutathione are safer than oral cysteine, while ascorbate (vitamin C) may protect against glutathione depletion. [13]

Torres, 2003 recommended that fever suppressants be reserved for severe fevers in young children, on grounds that fever helps mature the immune system. [8] Large trials have shown that low-dose aspirin during pregnancy is relatively safe for mother and child. [37] Giving aspirin to children with autism, however, may tax the liver as much as acetaminophen, although salicylates are usually metabolized as glucuronides. [107] Alberti et al, 1999 noted that salicylates are primary biochemical offenders in autistic children, and high dose aspirin inhibits the sulfating enzyme PST. [35] The Feingold Association has received parent reports of significant improvements in behavior of autistic children after removing gluten (wheat) and casein (dairy) products from their diets, as well as salicylates naturally present in fruits and vegetables. For a child with autism it might be wise to stay off salicylates for a longer period of time since these kids are likely to be very sensitive. [13]

CONCLUSIONS

The synchronicity detected between the onset of the autism epidemic and the surge in acetaminophen use after the warning by Centers for Disease Control and Prevention (CDC) in 1980 against aspirin seems unlikely to be artifact or coincidence. The Autism Research Institute also concluded that autism rates began to multiply around 1980, especially regression after the MMR vaccine. Schultz et al found that children given acetaminophen for reactions to the MMR vaccine were more likely to become autistic than children given ibuprofen.[13] Acetaminophen most probably induces immune system dysregulation and depletes the liver's supplies of detoxifying agents. Notably impaired sulfation of DHEA and testosterone before and after birth may explain the extreme male brain. Further, the use of acetaminophen may trigger autism by activating the endocannabinoid system thereby interfering with normal neurological development. Children who are poor metabolizers of acetaminophen may be at higher risk since normal therapeutic doses may lead to higher blood levels in these children. It has been proposed that the blockage of fever with antipyretics (as acetaminophen) could lead to autism by interfering with normal immunologic development. [8] Autistic children may show temporary improvement of autism symptoms when they have a fever. [8, 108] It is interesting to note that activation of CB_1 receptors, in addition to providing an analgesic effect, causes a decrease in body temperature.[109] This type of effect may be further evidence of endocannabinoid disruption in children with autism. Acetaminophen taken during pregnancy may provoke autism present at birth, while acetaminophen given after birth (e.g., for vaccine reactions) may provoke autistic regression. Prenatal acetaminophen exposure may trigger maternal immune activation with possible effects on fetal brain development. In early life, maturational compromises to the glucuronidation pathway e.g. at the time of the circumcision related exposure, in combination with the compromises to the sulfation pathway that typify autistic children, may lead to utilization of the suboptimal secondary metabolic routes with the potential for adverse neurological effects in susceptible individuals. [25] In conclusion, acetaminophen exposure during pregnancy and early childhood should be better avoided as a prophylactic measure against autism, a disorder that remains greatly so far as a multi-etiological illness with no clear-cut conclusive cure.

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