

## Acetaminophen/Autism: Alarm?

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**Keywords:** Acetaminophen; Autism; N-acetyl-p-benzoquinoneimine (NAPQI)

Autism is a developmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that appear in early childhood [1]

Autism is complex and heterogeneous in origin and proposed to be due to interaction of genetic and environmental factors [2]. The incidence of autism has risen ~10-fold since the early 1980s, with most of this rise not explainable by changing diagnostic criteria. Is there any explanation for that? Clinical and epidemiological studies and post-market pharmacovigilance are of utmost importance in detection of unrecognized or missed drug-induced side effects. Acetaminophen (paracetamol) is a widely used over-the-counter (OTC) analgesic and antipyretic that was introduced since 1955 [3]. Unfortunately the recent mechanistic evidence suggests correlation between acetaminophen exposure and increased incidence and risk of autism [4-6]. Considerable evidence supports this contention, most notably the exponential chronological rise in acetaminophen consumption for infants and young children since 1980s when it began to replace aspirin [7]. For instance, this compound has been taken, at least once, by more than 85% of children under the age of 91 months in the UK [8]. Children who are poor metabolizers of acetaminophen may be at higher risk even under therapeutic doses [5]. There are four major pathways for acetaminophen detoxification namely; the major pathways of glucuronidation or deacetylation to a phenol, and sulfation catalyzed by phenolsulfotransferase, and the minor toxic pathway by the cytochrome P450 (CYP2E1) enzyme producing N-acetyl-p-benzoquinone imine (NAPQI) Glucuronidation is commonly present at low capacity in the fetus, newborns, and young infants, such that exposure to acetaminophen at these times leads to greater metabolism by other pathways [9]. One key piece of evidence came from the observation that sulfation pathway catalyzed by phenolsulfotransferase is proved to be deficient in autism. This leads to overproduction of the toxic metabolite NAPQI from acetaminophen with a subsequent depletion of glutathione the main source of sulfhydryl groups with reduction in the ability to detoxify a host of toxic chemicals in the environment, increasing oxidative stress, which leads to protein, lipid, and nucleic acid damage from free radicals [5]. The characteristic loss of Purkinje cells in the brains of autistic cases is consistent with depletion of brain glutathione and as of 2012; there are many articles that indicated an association between toxic chemical exposure and autism. For example, exposure to NAPQI derived from acetaminophen, competitively inhibits the reaction of metals (such as mercury) with the sulfhydryl groups in children with autism [10]. Importantly, NAPQI also inhibits the isomerase and the biological activities of macrophage migration inhibitory factor (MIF) [11]. Polymorphism of MIF has recently been associated with autism spectrum disorders (ASDs) [8]. In addition, oxidative damage of mitochondrial proteins and DNA by acetaminophen leads to activation of DNase (s) which is typically responsible for nuclear DNA fragmentation and apoptosis [12]. There are several studies had shown an association between mitochondrial dysfunction and apoptosis with autism [13]. Also, acetaminophen has been found to induce apoptosis-dependent neurotoxicity by increasing neuronal CYP2E1 enzymatic activity, leading to neuronal

death through mitochondrial mediated mechanisms that involve cytochrome c release and caspase-3 activation. One of the prominent features of autism is immune system dis-ceregulation [14]. Recently, acetaminophen has been postulated to provoke autism through neuro-immunomodulatory effect that may be mediated by activation of endocannabinoids system. Acetaminophen metabolite p-aminophenol can conjugate with arachidonic acid in the brain and spinal cord resulting in inhibition of the cellular uptake of anandamide, a naturally occurring endocannabinoid [15]. The cannabinoid CB2 receptors are primarily located in immune tissues and cells and may serve a regulatory function [16]. To this point of information, safety of acetaminophen becomes questionable and acetaminophen/autism alarm should be paid more attention.

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Received December 12, 2013; Accepted December 14, 2013; Published December 23, 2013

Citation: Abdin AA (2013) Acetaminophen/Autism: Alarm?. *Biochem & Pharmacol* 2:e148. doi:10.4172/2167-0501.1000e148

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