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Hypothesis

Aminoglycoside antibiotics and autism: a speculative hypothesis

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Abstract

Background: Recently, it has been suspected that there is a relationship between therapy with some antibiotics and the onset of autism; but even more curious, some children benefited transiently from a subsequent treatment with a different antibiotic. Here, we speculate how aminoglycoside antibiotics might be associated with autism.

Presentation: We hypothesize that aminoglycoside antibiotics could a) trigger the autism syndrome in susceptible infants by causing the stop codon readthrough, i.e., a misreading of the genetic code of a hypothetical critical gene, and/or b) improve autism symptoms by correcting the premature stop codon mutation in a hypothetical polymorphic gene linked to autism.

Testing: Investigate, retrospectively, whether a link exists between aminoglycoside use (which is not extensive in children) and the onset of autism symptoms (hypothesis "a"), or between aminoglycoside use and improvement of these symptoms (hypothesis "b"). Whereas a prospective study to test hypothesis "a" is not ethically justifiable, a study could be designed to test hypothesis "b".

Implications: It should be stressed that at this stage no direct evidence supports our speculative hypothesis and that its main purpose is to initiate development of new ideas that, eventually, would improve our understanding of the pathobiology of autism.

Background

Autism is a devastating neurodevelopmental syndrome characterized by difficulties in social interaction, pragmatic language, and repetitive behaviors or obsessive interests, which usually begins in infancy and is still largely untreatable [1,2]. It appears that there may be a genetic component in the predisposition to autism; there are probably a few genes that interact and cause the autism phenotype [3]. Recently, it has been suspected based on an uncontrolled study that there is a relationship between therapy with various antibiotics and the onset of autism; but even more curious, some children benefited transiently from a subsequent treatment with a different antibiotic, vancomycin [4]. Thus, a link between antimicrobial use and the onset of autistic symptoms was first noticed by parents of children with regressive-onset autism. An attempt to help these children by treatment with vancomycin was based on the following hypothesis: the first antimicrobial treatment led to the colonization of the intestines by a neurotoxin-producing microbial species that was responsible for triggering autism; hence, improvement could be expected by treating this

intestinal infection with vancomycin. Inspired by these findings, we propose a speculative hypothesis on how antibiotics might be associated with autism.

Presentation of the hypothesis

Modulation of RNA function by antibiotics

As important as the genetic code itself is the decoding that takes place at ribosomes via translation of mRNA into proteins. Antibiotics may significantly interfere with this process [5]. Particularly important is the ability of aminoglycosides (e.g., gentamicin) to suppress premature stop mutations in mammalian mRNA and to restore physiological amounts of protein that otherwise could not be translated and synthesized. This action of antibiotics such as gentamicin can be used for therapeutic purposes in genetic diseases that arise from point mutations which introduce premature stop codons (UAA, UAG, UGA) into coding sequences [6,7]. For example, aminoglycoside antibiotics are currently being considered for treatment of Duchenne's muscular dystrophy patients who carry a nonsense mutation in the dystrophin gene [8] as well as for the treatment of cystic fibrosis (CF) patients [9]. In CF patients, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, containing a premature stop codon, are responsible for decreased production of CFTR chloride channels. In vitro, aminoglycoside antibiotics were shown to be capable of restoring the appearance of functional CFTR channels in mutant cells, and in a pilot study with nine patients carrying stop mutations, local gentamicin application produced improvement in a physiologic parameter measured in nasal epithelia [9]. Interestingly, recent studies of autism patients confirmed previous evidence that linked autism to a region of chromosome 7q near the CFTR gene [10].

We now hypothesize that antibiotics could a) trigger the autism syndrome in susceptible infants by causing the stop codon readthrough, i.e., a misreading of the genetic code of a hypothetical vulnerable gene, and/or b) improve autism symptoms by correcting the premature stop codon mutation in a hypothetical polymorphic gene linked to autism.

These speculative hypotheses are inspired by the observations by Sandler et al. [4] who linked the onset of autism symptoms to previous antimicrobial therapy and the improvement of these symptoms to treatment with vancomycin. These authors did not specify whether aminoglycosides were used in children prior to onset of autism in their study; they primarily focused on antimicrobial therapy-induced diarrhea which they thought might relate causally to the onset of autism symptoms. Thus, our hypothesis that aminoglycoside antibiotics may precipitate autism in genetically susceptible individuals would be supported if a link could be established between amynoglicosides and the onset of autism symptoms, or if it could be found in a post-hoc analysis of existing clinical data from a larger pool of autism patients. Genetic susceptibility is a known factor in the occurrence of side effects of aminoglycosides, which produce lasting, sometimes permanent alterations despite even a transient use. For example, inherited susceptibility to aminoglycoside ototoxicity is based on a mutation in mitochondrial DNA (i.e., 12S rRNA) [11]. It is possible that similar aminoglycoside-sensitive mitochondrial mutations could be involved in autism as well; namely, an autistic phenotype was recently observed in a child from a family with the mitochondrial DNA G8363A transfer RNA mutation [12].

Paradoxically, our hypothesis postulates that in some cases, i.e., premature stop codon mutation in a hypothetical autism-linked gene, antibiotics might be helpful in treating autism symptoms. Sandler et al. [4] found a transient improvement of autism symptoms in children treated with vancomycin. Since vancomycin is poorly absorbed (and it is not an aminoglycoside), these authors concluded that it must have produced a local effect (i.e., on the intestinal flora) and they proposed the existence of a "gut-brain" connection in autism. We hypothesize that aminoglycoside antibiotics might be helpful because they would correct a premature stop codon mutation in a hypothetical autism-linked gene product. This effect could not only be achieved in the central nervous system (CNS), i.e., for a CNS-specific RNA, but also in the periphery. For example, insulin-like growth factor (IGF-1), a growth-promoting peptide hormone that has neurotrophic properties in the CNS and is synthesized in the periphery including the intestine [13], has been shown to cross the blood-brain barrier; when injected systemically IGF-1 increases the proliferation and survival of neurons in the CNS of adult rats [14]. Thus, if a similar peripherally-synthesized protein plays a role in autism when mutated, the premature stop codon mutation in the RNA that is responsible for its synthesis might be susceptible to correction by local (e.g., enteric) administration of an effective antibiotic.

Testing the hypothesis

Relatively simple but rather extensive studies would be required to investigate whether a link exists between aminoglycoside use (which is not extensive in children) and the onset of autism symptoms (hypothesis "a"), or between aminoglycoside use and improvement of these symptoms (hypothesis "b"). Even if a positive correlation were found, this would be a first step, not definitive proof of our concept. Whereas a prospective study to test hypothesis "a" (e.g., investigate the effect of aminoglycosides in children at risk for autism) is not ethically

justifiable, a study could be designed to test hypothesis "b", i.e., whether aminoglycosides could ameliorate the clinically symptomatic disease.

Implications of the hypothesis

If a link between aminoglycoside antibiotic use and autism could be clearly established, either positive or negative, further studies could be designed to elucidate the mechanisms involved, including genetic analyses. It should be stressed, however, that at this stage no direct evidence supports our speculative hypothesis and that its main purpose is to initiate development of new ideas that, eventually, would improve our understanding of the pathobiology of autism.

List of abbreviations

CF, cystic fibrosis

CFTR, cystic fibrosis transmembrane conductance regulator

CNS, central nervous system

IGF, insulin-like growth factor

mRNA, messenger RNA

Competing interests

None declared

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