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Can antibiotics cause a psychosis?: Case report and review of the literature

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ABSTRACT

It is relatively unknown that some of the possible side effects of antibiotic treatment can be transient psychotic episodes and other encephalopathies such as seizure disorders. Since these are rare events, there have not been many studies about them, nor is there a clear understanding of the underlying basis for these symptoms. This phenomenon was recently brought to our attention by a patient whose case history is discussed here. For the past few years, he has been diagnosed at different times with schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, temporal lobe epilepsy, and psychogenic nonepileptic seizures. He was seen by a neurologist and placed on carbamazepine, which by his admittance helped him tremendously. During this same time period, psychiatrists placed him on various antipsychotic medications as well. The patient researched many medical conditions and came to the conclusion that his symptoms are caused by a large dose of an "antibiotic" given to him on his first day of basic training for the military, the so called "peanut butter shot", although he has not been able to convince his physicians of this theory. Whether or not this patient has a chronic schizophrenia-like illness or an adverse reaction to antibiotics, this case is presented so that clinicians are aware that neurological and psychiatric side effects can occur as rare reactions to antibiotic therapy and that treatment with an anti-seizure drug concurrently used as a mood stabilizer may be warranted in such cases.

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1. Introduction

Inflammation and the immune response have received much attention recently as possibly underlying the onset of a psychotic illness (Lizano et al., 2016), and may be a reaction that is occurring during the prodromal stage of illness (Zeni-Graiff et al., 2016). This process may also initiate a relapse and be dissipated by some antipsychotic medications (Kao et al., 2016). In fact, treatment with anti-inflammatory drugs has been suggested for schizophrenia early in the course of the illness (Koola et al., 2016). On the other hand, some people treated with antibiotics for various inflammation-producing infections, such as urinary tract infections (Mostafa and Miller, 2014), have long been observed to have transient psychotic symptoms and sometimes seizures as a rare side effect of beginning antibiotic treatments (Bhattacharyya et al., 2016). Early on, it was known that penicillin could cause psychotic reactions, such as visual and auditory hallucinations and multiple delusions. This was named "Hoigné syndrome" after the clinician who first observed this reaction (Hoigne and Schoch, 1959). More recently, antibiotic induced mania (initiated by treatment with a return to a euthymic condition after treatment discontinuation) has similarly been termed "antibiomania" (Abouesh et al., 2002). Mostafa and Miller (2014) did a comprehensive literature search of all English language reported cases of UTI and possible antibiotic-induced psychosis in order to determine the probability that an antibiotic was causing the psychosis. Of all the reports they examined, only 15 independent cases were found that could be studied in detail. The cases were mixed sex, varied in age from 18 to 88, included different classes of antibiotics, and 3 of the cases had a recurrence of the psychosis when re-challenged with the same antibiotic. The psychosis in each case began within a week of the initial antibiotic dose and resolved within a week after the medication was terminated. Although the number of cases were small, it was also interesting to note that the males seemed to have a prior psychiatric history as well, suggesting the possibility of an underlying vulnerability. The different classes of antibiotics associated with this response included fluoroquinolones, cephalosporins, penicillins, and trimethoprim-sulfamethoxazole drugs (reviewed in Mostafa and Miller, 2014). Several possible mechanisms for this relatively rare reaction have been proposed, such as reaching toxic levels of antibiotics in the bloodstream, anti-inflammatory properties of antibiotics perhaps inhibiting prostaglandin E-2, GABA antagonism by specific antibiotics, and *N*-methyl-D-aspartate (NMDA) receptor hypofunctioning, the latter two of which have been discussed as bases for schizophrenia in general

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(e.g. reviewed in Cohen et al., 2015). However, it should be noted that urinary tract infections, which are more frequently seen in the elderly, can also lead to psychotic symptoms and delirium when left untreated (Chae and Miller, 2015). Nevertheless, it is unknown whether individuals with these rare responses to antibiotics may be more vulnerable, perhaps genetically, to eventually develop a schizophrenia-like chronic illness regardless of treatment with antibiotics. A connection may be possible between the immune abnormalities seen in schizophrenia and the mechanism for causing a psychosis in antibiotic treated individuals.

There is a condition described in the literature as Antibiotic-Associated Encephalopathy (AAE) and was recently extensively reviewed by Bhattacharyya et al. (2016). AAE includes psychotic reactions, seizures, and myoclonus, as well as MRI and EEG changes. These authors found 292 articles describing 391 individual cases. Psychosis, defined as delusions or hallucinations, was present in 47% of the cases and was most commonly associated with sulfonamides (68%), quinolone (67%), macrolides (63%), and penicillin IM (68%) treatment. Psychosis was much less common in cases of AAE with cephalosporins (13%) and metronidazole (24%). A seizure disorder occurred in 14% of cases overall and was most common in association with penicillin (38%) and cephalosporins (35%).

MRI of the brain was abnormal in all cases of metronidazole-associated encephalopathy, but normal with the other antibiotics (Bhattacharyya et al., 2016). The MRI changes in association with metronidazole-treatment were T2 hyperintensities in the dentate nuclei of the cerebellum, and in some cases included the brainstem, corpus callosum, or other regions.

An EEG, when performed, was abnormal in 70% of cases, with nonspecific abnormalities reported such as slowing and generalized periodic discharges. EEG abnormalities were common with penicillin (83%), ciprofloxacin (83%), and isoniazid (69%), but performed in only a small number of cases associated with these antibiotics.

Based on their review, the authors have divided the AAE syndrome into 3 types:

Type I has an abnormal EEG and normal MRI with common myoclonic seizures. This type they relate to penicillin and cephalosporin treatment and suggest that it may be caused by disruption of inhibitory synaptic transmission that will thus lead to excitotoxicity. The most commonly implicated receptor is the ligand-gated ion channel g-aminobutyric acid class A receptor (GABAAR). Activation of GABAAR by endogenous GABA leads to an intracellular influx of chloride ions which in turn produces an inhibitory postsynaptic potential (IPSP) that increases the threshold for production of an action potential (Chow et al., 2005). Thus, inhibiting neurotransmission at the GABAAR, causing central excitotoxicity.

Type II, Hoigné syndrome, appears to predominantly have a psychosis that is rarely associated with a seizure disorder. Patients with this syndrome tend to have normal MRI scans and if an EEG is abnormal, it is reported as "nonspecific" (reviewed in Bhattacharyya et al., 2016). This is the clinical picture reported that is associated with procaine penicillin, sulfonamides, and fluoroquinolone antibiotics. It is suggested from some older literature that type II might be related to abnormalities produced in the dopamine (Thomas and Reagan, 1996) and NMDA pathways (Schmuck et al., 1998).

Type III was found to be associated with only metronidazole. It has been characterized by rare and nonspecific EEG abnormalities and an abnormal MRI, particularly in cerebellar regions, brain stem and splenium of corpus callosum (Kim et al., 2007) with psychosis occurring much less frequently compared to the others. The cause of type III is thought to be related to free radical formation and altered thiamine metabolism based on animal studies showing that derivatives of 5-nitroimidazole, such as metronidazole, form free radicals that can in turn be neurotoxic (Rao and Mason, 1987).

In addition, there is some evidence from one retrospective record review of an association of antibiotic exposure to development of depression and anxiety. Whether these episodes met criteria for major depression or anxiety disorder, nor how long they lasted subsequent to antibiotic treatment, was not determined (Lurie et al., 2015).

The above literature was uncovered following an encounter with a patient admitted to our inpatient service who claimed that all his symptoms were directly caused by antibiotic administration and he challenged us to look into it because he said that all previous physicians dismissed his claims as "crazy". We thus, present the following report about this young man who dates his illness onset to the injection of an antibiotic "cocktail" given to military recruits during their first days in basic training, which likely consisted of a penicillin G benzathine injection. The patient gave the co-authors written consent to publish this report.

2. Case report

Mr. S is a 33-year-old, single, male Veteran of the USA military who presented to the psychiatric emergency room for admission for depression, hypersensitivities to light and sounds, weakness, and a mild headache. He denied suicidal thoughts, although later admitted that in the previous few days, he had thoughts of jumping from a high building or getting a gun to shoot himself. He also reported trouble sleeping, low energy, and feeling hopeless. He maintained a flat affect when he recounted all that happened to him and attributed his symptoms to being in a postictal period. He had an unwitnessed seizure consisting of legs and arms shaking a few days prior to this admission and was treated in a local hospital emergency room and sent home. He associated the seizure to having discontinued carbamazepine that he was taking for the past 4 years before running out of medication 3 days prior to the seizure.

On mental status exam, when seen on admission, he was dressed and groomed appropriately, although he was restless and squirming in his chair. His speech was coherent, logical and with normal rate, rhythm and volume. His thought processes were linear and no disorganization or thought blocking noted. His thought content contained some fleeting suicidal ideation with no plans. He did not express any current delusionary material with the exception of claiming to have a previous psychotic reaction with multiple delusions, perceptual experiences and seizures subsequent to antibiotic treatment. He denied any current hallucinations of any kind. His mood was mildly depressed and his affect appropriate to this mood. His cognition appeared intact with good memory, attention and concentration, but he appeared to exhibit poor insight. He did admit in the past to having had some hallucinations (visual, gustatory, tactile, but not auditory), and delusions (religious, paranoid, grandiose, and somatic), affective symptoms (suicidal), and impulsivity (agitation), while attributing all of this to antibiotic treatment.

He was certain that his symptoms began when he acquired what he called a "Traumatic Brain Injury (TBI)" about eight years prior to this admission during his first few days in basic training for military service. The TBI he believed was that he "suffered damage to his temporal lobes when he was given antibiotics", particularly "beta-lactam" antibiotics, during his first couple of days after induction into the military. He had not been in combat or suffered any physical injury. He had received the "peanut butter shot", a slang expression for a very painful thick injection administered in the gluteus, given to recruits on entry to the military. This likely consisted of a penicillin G benzathine injectable suspension, to protect against infections that may occur when recruits train together, although a heavy suspension of IgG to prevent hepatitis has also been referred to as the "peanut butter shot" (personal communication: Jay Montgomery MD, Captain, Medical Corps, US Navy (Ret), Chief, Clinical Operations Office, Defense Health Agency, Immunization Healthcare Branch, Bethesda, Maryland). He had never had a depressive, psychotic or seizure disorder prior to this.

He then continued basic training for only a short period of time as he developed an extreme anxiety disorder, became agitated and paranoid,