CASE REPORT / OLGU SUNUMU

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Recurrent Psychotic Mixed Mania in a Child Triggered by Clarithromycin and Amoxicillin Use: A Rare Case of Pediatric Antibiomania

Klaritromisin ve Amoksisilin Kullanımı Sonrası Gelişen Tekrarlayıcı Psikotik Karma Mani: Nadir Bir Pediatrik Antibiyomani Olgusu

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ABSTRACT

The term antibiomania is used for manic episodes resulting from antibiotic use. Although some cases of antibiomania have been reported in the literature in various age groups, childhood cases of antibiomania are quite limited. In this article, a case of a 12-year-old boy with no previous mood disorder who developed mania with mixed and psychotic features after using clarithromycin or amoxicillin at three different times was presented. This case is a rare example of pediatric antibiomania that differs from previously reported antibiomania cases by having mixed and psychotic features of the manic episode. With this case report presentation, it was aimed to emphasize that mania can develop following antibiotic use without any genetic or organic risk factors, that antibiomania in children can have a recurrent nature, and that careful clinical evaluation and consideration of risk factors such as medication use are important for making a diagnosis in this age group.

Keywords: Antibiomania, clarithromycin, amoxicillin, psychotic mixed manic episode, child

ÖZ

Antibiyomani terimi antibiyotik kullanımına bağlı manik ataklar için kullanılır. Literatürde çeşitli yaş gruplarında antibiyomani olguları bildirilmiş olmakla birlikte çocukluk çağı antibiyomani olguları oldukça sınırlıdır. Bu yazıda, daha önce duygudurum bozukluğu olmayan 12 yaşında bir erkek çocukta üç farklı zamanda klaritromisin veya amoksisilin kullanımı sonrası karma ve psikotik özellikler gösteren mani tablosunun gelişmesi sunulmuştur. Bu olgu, manik atağın karma ve psikotik özellikler göstermesiyle daha önce bildirilen antibiyomani olgularından ayrılan nadir bir pediatrik antibiyomani örneğidir. Bu olgu sunumuyla, antibiyotik kullanımıyla maninin genetik veya organik risk faktörü olmadan da gelişebileceği, çocuklarda antibiyomaninin tekrarlayıcı bir yapıya sahip olabileceği ve bu yaş grubunda tanı koymada dikkatli klinik değerlendirmenin ve ilaç kullanımı gibi risk faktörlerinin göz önünde bulundurulmasının önemli olduğu vurgulanmak istenmiştir.

Anahtar Kelimeler: Antibiyomani, klaritromisin, amoksisilin, psikotik özellikli karma manik epizod, çocuk

Introduction

Mania that occurs after antibiotic use is called antibiomania. This rare phenomenon is gaining increased recognition due to a growing number of published case reports.[1] Antibiomania is most commonly observed with macrolide antibiotics, especially clarithromycin, and with fluoroquinolones such as ciprofloxacin and ofloxacin.[2-5] It generally develops within a few days of starting antibiotic use and resolves rapidly when the antibiotic is discontinued.

Although the precise pathophysiological mechanism of antibiomania remains unclear, proposed hypotheses include GABA-A receptor inhibition, disruption of inhibitory neurotransmission within the central nervous system, and alterations in prostaglandin levels leading to neuroinflammation.[6]

The cases reported in the literature to date are mostly occur in adulthood, and there are only a few case reports in children and adolescents.[7] In most cases, a single manic episode has been reported, and recurrent manic episodes are rare.

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Therefore, this case of antibiotic-induced recurrent manic episodes with psychotic features in the pediatric age group, without any genetic or psychiatric risk factors, is noteworthy.

This case report discusses three episodes of psychotic and mixed manic symptoms in a 12-year-old boy, each occurring after treatment with clarithromycin or amoxicillin. This case exemplifies that antibiotic-related neuropsychiatric side effects can also occur in childhood and can have a recurrent course.

Case Report

A 12-year-old patient diagnosed with attention deficit hyperactivity disorder (ADHD) who had not taken any medication, at the request of his family, presented to the Child and Adolescent Psychiatry Outpatient Clinic at the University of Health Sciences Türkiye, Erenköy Mental and Nervous Diseases Training and Research Hospital three times in the last three months, complaining of decreased need for sleep, excessive talking and increased energy. The patient first visited our clinic 10 days after the third attack, after the pediatric neurologist referred the patient to a child psychiatrist. When he applied to the clinic, the patient had no active complaints. A historical assessment was conducted.

The first attack occurred approximately three months before the outpatient clinic application. A diagnosis of upper respiratory tract infection was made based on complaints such as fever, nasal discharge and difficulty swallowing. The patient was prescribed clarithromycin 250 mg twice daily and ibuprofen/pseudoephedrine 200 mg twice daily after applying to the pediatrician. After using the medicines for one day, there was a decrease in the need for sleep and a significant increase in energy levels. He walked around all night. He laughed to himself at night and cried during the day. He was very angry and hostile towards the people around him. His speech became faster and more voluminous, and he had flight of ideas, saying that his power was enough for everything. He said that he was receiving a signal and that everything in the house smelt bad. The family did not seek medical attention during this period and discontinued the medication after four days. The complaints gradually decreased and there were no symptoms after one week. The retrospective Young Mania Rating Scale/Parents form (YMRS-P) total score was 47. This score is consistent with a manic episode.

Approximately one month after the first episode, a pediatrician prescribed oxymetazoline HCl 0.05% spray twice daily, benzydamine HCl + chlorhexidine gluconate mouth spray four times daily and amoxicillin-clavulanic acid 400/57 mg twice daily for an upper respiratory tract infection. The day after he started taking the medication, he needed less sleep and had significantly more energy. He was crying and unhappy, and he wasn't talking to people or interacting with those around him during the day. He did not want to go to school because he thought his classmates did not like him. At night, he was laughing for no reason. His speech speed and volume increased again. People around him found it difficult to follow his train of thought. He thought he was superior to others. The family used antibiotics for one and a half days. After discontinuing the antibiotic use, the symptoms decreased and ended after two days. Meanwhile, the YMRS-P was administered retrospectively based on parental reports, yielding a total score of 47. This score is consistent with a manic episode.

About one month after the second episode, he visited a pediatrician complaining of a sore throat, fever and cough. The pediatrician prescribed clarithromycin 250 mg twice daily for an upper respiratory tract infection. One day after taking the antibiotic, similar to previous episodes, there was a decrease in the need for sleep, an increase in energy levels, an increase in the speed and amount of speech, and aggressive behaviors appeared at night. He cried and felt upset during the day. The antibiotic was discontinued after three days due to symptom emergence. The symptoms persisted for approximately one week and resolved completely thereafter. There were no symptoms after a week. A retrospective YMRS-P total score of 36 was obtained based on parental reports. This score is consistent with a manic episode.

The patient underwent testing for a complete blood count, blood electrolytes, liver function, bilirubin levels, kidney function, thyroid function, blood glucose levels, C-reactive protein levels, and a complete urinalysis. The results revealed leukocytosis and an elevated C-reactive protein level, both of which are consistent with a bacterial infection. Following these episodes, the family consulted a pediatric neurologist, who could not identify any organic cause. No epileptiform activity was detected in the electroencephalography, and no lesions were found in the cranial magnetic resonance imaging scan.

The patient's first psychiatric visit occurred when he was in the first grade, when he was seven years old, due to a delay in learning to read and write. Following a psychiatric and psychometric evaluation, he was diagnosed with ADHD. He was gradually started on short-acting methylphenidate twice daily. He used the medication for approximately one and a half months. The family stopped administering the medication because the patient experienced emotional blunting as a side effect. Later, as the symptoms of ADHD persisted, he was started on a 27 mg long-acting dose of methylphenidate. After two to three months, when the observed benefit decreased, the dose was increased to 36 mg. However, after a teacher claimed that such medications are harmful to children, the family stopped using the medication.

The patient was born at term via C-section, weighing 3,500 grams, with no birth complications. He said his first words at nine months, formed his first sentences at two years of age, began walking at eleven months, and finished potty training at two years of age.

There was no known family history of psychiatric or mood disorders. Detailed questioning revealed that no one had been diagnosed with a mood disorder. His academic performance was age-appropriate, and no specific learning difficulties were reported.

He came to the interview at his mother's request. The patient reported no subjective complaints, and that he was angry with his mother for bringing him. Information was obtained from both the patient and his mother.

The patient's physical appearance and grooming were appropriate for his developmental age. The patient was fully oriented to time, place, and person. His mood was euthymic. He displayed an appropriate affect, congruent with mood and context. There were no suicidal or homicidal ideations, obsessions or delusions within his thought content. His thought process was normal. The patient's speech was spontaneous, with normal rate, rhythm, and volume. The patient's ADHD symptoms persisted, but his family said they did not want treatment.

It was thought that the patient, who had no history of mood disorders, experienced psychotic mania with mixed features induced by antibiotics.

Because the patient had no active symptoms when he arrived at our clinic and because his symptoms began shortly after he started taking antibiotics and subsided approximately one week after he stopped taking them, we did not initiate any medical treatment. The family received psychoeducation and information about risky antibiotic classes. They were also asked to inform their physicians about any previous manic episodes related to antibiotic use.

Because the manic episode was triggered by an antibiotic and the patient was young, he was referred to the child and adolescent psychiatry outpatient clinic for monitoring his risk of developing bipolar disorder.

Verbal assent was obtained from the child, and written informed consent was obtained from his parents.

Discussion

This case is of particular significance as it involves a rare adverse effect of antibiotic use, known as antibiomania, observed in a pediatric patient with psychotic and mixed manic features. While previous reports have described single episodes in adult patients, this case highlights that recurrent manic episodes related to antibiotic use may also occur in children without any underlying psychiatric or organic pathology.[7,8] The temporal association between the initiation of various antibiotics and the subsequent emergence of manic symptoms, followed by symptom resolution upon drug discontinuation, along with the absence of a family history of mood disorders, strongly supports a diagnosis of substance/medication-induced bipolar and related disorder rather than primary bipolar disorder. However, there are issues that need to be addressed in the differential diagnosis. When evaluating this case, it is important to consider not only the potential contribution of antibiotic treatment, but also that of a previous upper respiratory tract infection, to the onset of manic symptoms. Some researchers have suggested that viral infections, particularly respiratory infections, may indirectly affect the central nervous system and trigger manic episodes. This could occur through mechanisms such as neuroinflammation, increased cytokine levels, and activation of the hypothalamic-pituitary-adrenal axis. Indeed, the occurrence of manic episodes in individuals with no prior psychiatric history following a severe acute respiratory syndrome coronavirus 2 infection supports this view.[9] In each episode, the onset of manic symptoms occurred within 24 hours of starting antibiotic therapy. Although the patient had exhibited clinical signs of infection prior to treatment, no mood or behavioral changes were reported until antibiotic administration began. This consistent temporal pattern strengthens the argument for antibiotic-induced mania rather than a direct neuropsychiatric effect of the underlying infection; therefore, the episodes were considered to be associated with antibiotic exposure. The differential diagnosis should also consider any other medications the patient was taking during the episode. The patient used clarithromycin and pseudoephedrine together during the first episode and clarithromycin alone during the third. Although pseudoephedrine was co-administered during the first episode, the recurrence of a similar manic episode with clarithromycin alone, together with the consistent temporal relationship and symptom resolution after discontinuation, strongly supports clarithromycin as the primary precipitating agent.

Differential diagnosis should also include medications such as pseudoephedrine and nasal decongestants, which have previously been associated with manic episodes in children and adolescents.[10,11] Drug-induced mania related to various pharmacological agents has also been described in the literature.[12]

Clarithromycin, a macrolide-class antibiotic, has been reported as the agent most frequently associated with antibiomania.[2] Although the exact mechanism by which clarithromycin triggers mania is not known, there are some mechanisms suggested to explain this relationship. One of the mechanisms proposed to explain the relationship between clarithromycin and antibiomania is that clarithromycin causes negative allosteric modulation on GABA-A receptors. This results in a decrease in the GABA-mediated response.[13] Another proposed mechanism is that clarithromycin has an antagonistic effect on GABA-A receptors. The antagonistic effect reduces GABA-A receptor inhibition and reduces the entry of chloride ions into the neuron. This can lead to neuronal hyperactivity, increased dopamine and glutamate, and the emergence of manic symptoms.[14]

Although less frequent than clarithromycin, cases of antibiotic mania associated with the use of amoxicillin-clavulanic acid combination have also been reported in the literature. These case reports suggest that amoxicillin-clavulanate, like clarithromycin, may trigger mania through GABA antagonism.[8]

Beyond its effects on GABAergic neurotransmission, several alternative mechanisms have been proposed to explain the occurrence of antibiomania. These include elevated levels of cortisol, prostaglandin E1, pro-inflammatory cytokines, and C-reactive protein. Additionally, disruptions in glutamatergic signaling, mitochondrial dysfunction caused by antibiotic exposure, and alterations in gut microbiota composition have also been considered as potential contributing factors.[2]

Additional investigations are required to better understand the underlying mechanisms involved.

It has been suggested that repeated exposure to triggering factors might progressively lower the threshold for mood episodes, as conceptualized by the kindling hypothesis. This model further emphasizes the importance of psychiatric monitoring in such cases.[15,16]

Secondary etiologies should be considered when evaluating acute mood disturbances in pediatric populations. A thorough psychiatric history is essential for the identification of antibiotic-induced mania, allowing clinicians to avoid unnecessary psychopharmacological interventions.

Ethics

Informed Consent: Verbal assent was obtained from the child, and written informed consent was obtained from his parents.

Footnotes

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