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Beyond malaria: A rare case of Tardive dyskinesia-like syndrome in antimalaria therapy

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Abstract

Tardive dyskinesia is an involuntary and iatrogenic hyperkinetic movement disorder triggered by the use of dopamine receptor antagonists or partial agonists. It significantly impacts and profoundly burdens the physical, psychosocial, and overall quality of life. Tardive dyskinesia is seen among those using antipsychotic medications and dopamine receptor-blocking medications. In recent times, it has been reported in those receiving non-antipsychotic and non-dopamine receptor-blocking medications, like antihistamine and antimalaria medications. The criteria for diagnosis of tardive dyskinesia is still debatable. Hence, the term tardive dyskinesia-like syndrome in those without the complete criteria as in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. We present a report of a female patient that received artesunate and amodiaquine for malaria therapy and subsequently developed tardive dyskinesia-like symptoms. The objective is to promote vigilance in identifying tardive dyskinesia-like syndromes in patients not on antipsychotic or dopamine receptor-blocking medications and encourage further researches on the topic.

Background

Tardive dyskinesia is a hyperkinetic movement disorder marked by abnormal involuntary movements, primarily triggered by dopamine receptor antagonists or partial agonists like antipsychotics, with significant functional impairment and biopsychosocial consequences [1]. These movements mainly manifest in the peri-oral region, presenting as chewing, tongue protrusion, or lip puckering. They may also involve neck, shoulder, and limb movements, including writhing or contraction [2]. While tardive dyskinesia is commonly linked to prolonged antipsychotic use, it can also emerge with shorter doses and durations, particularly among seniors [3]. Significant risk factors for tardive dyskinesia development involve older age, female sex, mood disorders, dementia, fetal alcohol syndrome, smoking, and substance use disorder [3]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V), diagnoses tardive dyskinesia by requiring the use of the offending medication for at least three months or one month in individuals aged 60 and above [4]. The Abnormal Involuntary Movement Scale is a widely accepted tool for assessing the presence and severity

of tardive dyskinesia [5]. It can be utilized both as a baseline assessment before initiating antipsychotic medications and for monitoring the clinical progression [6].

Tardive dyskinesia and other extrapyramidal symptoms can also arise from non-antipsychotic drugs, including antiemetics like metoclopramide, antihistamines, antimalarials, and, less commonly, certain anticonvulsants and oral contraceptives [7]. While research on these side effects from non-antipsychotic medications is limited and not as well understood, published data suggests a prevalence of tardive dyskinesia caused by non-antipsychotic agents ranging from 1% to 10% [2].

Linking tardive dyskinesia to non-antipsychotic drugs presents challenges such as unverifiable medical history, the presence of similar movement abnormalities in untreated populations with unknown etiology, and inadequate use of screening instruments [2]. Some studies even argue against non-antipsychotic medications directly causing tardive dyskinesia, suggesting instead that these medications may unmask or exacerbate underlying movement disorders [7]. However, emerging evidence implicates medicines used to treat malaria in causing the tardive dyskinesia-like syndrome [8], although the literature on this topic remains scarce. We, therefore, present a case of tardive dyskinesia-like syndrome in a patient treated with Artesunate and amodiaquine for malaria.

Case presentation

A 29-year-old woman presents to the emergency room of a tertiary health center with a complaint of uncontrollable facial muscle twitching around the eyes, mouth, and neck. It intermittently involved the lower extremities. The complaints commenced 6 hours prior to the presentation and have been persistent. There was no current fever, lightheadedness, altered consciousness, photophobia, or limb weakness. About three days earlier, a diagnosis of uncomplicated malaria with parasitological confirmation was made in a primary care center following physical symptoms of fever, myalgia, and headache. The patient was placed on Artesunate 100 mg plus Amodiaquine 270 mg, which came in a blister pack of 6 tablets. She took two tablets daily and had the last dose on the presentation day. The patient also received Tylenol 650 mg PO t.i.d. for two days before presentation. The patient denied any history of mental illness or use of psychotropic medication in the past. She also denied the use of any dopamine receptor blocker. The patient denied the use of herbal medication. There was no history of medication or food allergy. There is no family history of a similar illness. The patient denies social habits of alcohol ingestion, cigarette smoking, or use of any other substance.

An anxious middle-aged woman with persistent blinking of both eyes, facial muscle twitching, and twitching around the mouth and right side of the neck was noted on examination. There was an observed intermittent wiggling of both lower extremities. There were no remarkable components of the general examination. The central nervous system examination revealed a woman who was oriented to person, place, and time. Neither asterixis nor meningeal irritation was elicited. Both cranial nerve palsy and cognitive impairment were absent. Tone and deep tendon reflexes were also normal. Every other system was grossly normal. The vital signs trended within the reference limits.

Complete Blood Counts (CBC) revealed hemoglobin of 9.5 g/dl and hematocrit of 29%. Other components of the CBC were within normal limits. The serum electrolytes, creatinine and blood urea nitrogen, liver function test, random blood glucose, and serum lipid profile were also within normal limits. Her genotype was AA, and her ECG at rest was similarly normal. P. falciparum trophozoite and schizont forms were observed in a peripheral blood smear investigation for malaria parasites using light microscopy of thick and thin stained blood.

A provisional clinical diagnosis of an adverse drug reaction to Artesunate and amodiaquine was made. Intravenous access was secured and maintained with an intravenous infusion of isotonic saline. The patient was given intravenous hydrocortisone 200 mg. The patient was evaluated an hour later, and the symptoms were persistent. In a further interview, the patient endorsed similar symptoms in the past year but stated that they resolved within minutes after the onset. She was further evaluated with an Abnormal Involuntary Movement Scale (AIMS) 5. A total scale score of 3 was assigned. With a previous history of similar symptoms in the past, for over a year, a diagnosis of tardive dyskinesia-like syndrome was made. The patient was given intravenous diazepam 10 mg. The patient slept off and woke up after 4 hours. She became symptom-free on waking up, and the AIMS score was zero. The patient was observed for the next 12 hours and remained symptom-free with an AIMS score of zero. The patient was counseled to avoid the use of Artesunate and amodiaquine for malaria treatment in the future. She remained well after follow-ups with the primary care physician.

Discussion

There are reports of tardive dyskinesia arising from non-dopamine receptor blockers [7]. However, in some reports, some patients had histories of either prior use of dopamine receptor block medications or use of antipsychotic medications not ruled out [9,10]. In the index report, the patient denies any prior history of mental illness or use of antipsychotic medication in the past. She equally denies the use of dopamine receptor-blocking medication in the past. Tardive dyskinesia results primarily from dopamine receptor antagonism or partial agonism [1]. Artesunate is currently under evaluation for its potential interactions with dopamine receptors [11,12]. Previous research has shown that it exhibits significant inhibitory effects on prolactinoma, both in vitro and in living organisms in vivo, primarily through its antagonistic action on dopamine receptors [11]. In the index report, the patient was administered Artesunate in combination with amodiaquine, suggesting that Artesunate might exert some antagonistic effects on dopamine receptors.

According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V), tardive dyskinesia is confirmed when the offending medication must have been used for at least three months or one month in elderly adults 60 and above [4]. The diagnosis involves medications with dopamine receptor antagonism. However, a universal consensus on the definition of tardive dyskinesia is still being debated, yet reliance has been on DSM V criteria. A syndrome with a similar presentation and symptoms has been ascribed to non-dopamine receptor-blocking drugs [13]. The index case falls into this category.

The striking features in the index case are the similar symptomatology with tardive dyskinesia as defined by DSM V [4].

Her gender is female, which is a risk factor [3]. The patient also improved with the administration of benzodiazepine, with diazepam as the only available type in the facility at the time. Benzodiazepine is one of the medications with an efficacious effect on tardive dyskinesia [14]. Abnormal Involuntary Movement Scale (AIMS) [5], a widely used tool to determine the presence and severity of tardive dyskinesia, was employed in the clinical trajectory of the patient in the index report. A review of the tardive dyskinesia from non-dopamine receptor blocking medications prioritizes diagnosis in the form of tardive dyskinesia-like syndrome [15].

Malaria incidence continues to be common in individuals with genotype AA [16]. The genotype of the patient in the index report is AA, which might have accounted for several incidences of malaria the patient had experienced in the past with accompanying reports of tardive dyskinesia-like symptoms.

Conclusion

This paper presents a rare case of tardive dyskinesia-like syndrome initially attributed to a medication side effect from Artesunate and amodiaquine therapy for malaria. Subsequent treatment, in line with tardive dyskinesia management, proved crucial for the improvement. The study underscores the importance of clinicians' vigilance in recognizing tardive dyskinesia-like syndrome in patients displaying movement abnormalities, particularly in regions where antimalarial drugs are commonly used. Furthermore, it advocates for continued research into the mechanisms by which non-antipsychotic and non-dopamine receptor-blocking medications induce tardive dyskinesia. Such researches are essential for enhancing our understanding of tardive dyskinesia and tardive dyskinesia-like syndrome, ultimately facilitating the development of preventive strategies.

Declarations

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