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Neuropsychiatric Complications of Voriconazole and Steroids: Case Reports

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Case Report

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Abstract

Background:

Medication-induced psychotic disorder is characterized by the emergence of hallucinations or delusions temporally related to exposure to a pharmacological agent, in the absence of primary psychotic illness or delirium. Corticosteroids and voriconazole are widely used in clinical practice but are recognized to precipitate neuropsychiatric adverse effects. We report two cases of medication-induced psychosis associated with intravenous methylprednisolone and voriconazole.

Case presentation:

An 80-year-old man with acute exacerbation of interstitial lung disease (ILD) developed second-person auditory hallucinations and persecutory delusions on the third day of intravenous steroid therapy. Metabolic, infectious and structural causes were excluded. Discontinuation of steroids and initiation of low-dose risperidone led to complete resolution within two weeks.

A 56-year-old post–bone marrow transplant recipient treated with voriconazole for invasive aspergillosis developed agitation, auditory hallucinations and delusion of reference within 24 hours of voriconazole therapy initiation. Laboratory parameters were normal. Symptoms resolved completely within 48 hours following voriconazole cessation and short-term haloperidol administration.

Conclusions:

These cases highlight the importance of recognizing temporal associations, excluding alternative etiologies and promptly discontinuing the offending agent in medication induced psychosis. Early identification prevents unnecessary investigations, reduces morbidity and ensures patient safety. Clinicians should exercise caution, particularly in elderly with multiple comorbidities.

BACKGROUND

Medication-induced psychotic disorder is diagnosed when hallucinations or delusions develop during or soon after taking or withdrawing from a medication known to cause such symptoms, are not better explained by a primary psychotic disorder or delirium, and cause clinically significant distress or functional impairment [1]. Psychiatric manifestations caused by therapeutic agents range from subtle mood changes to frank psychosis. We describe two cases of medication-induced psychosis following intravenous (IV) steroids for interstitial lung disease (ILD) exacerbation and IV Voriconazole for invasive aspergillosis.

CASE PRESENTATION

Case 1

An 80-year-old man presented with progressive breathlessness and a cough of two months' duration. On admission, his peripheral oxygen saturation was 70% on room air. Chest auscultation revealed bilateral “velcro” crackles. High-resolution computed tomography (HRCT) of the thorax demonstrated bilateral honeycombing and fibrosis with a usual interstitial pneumonia (UIP) pattern, consistent with ILD. The patient was diagnosed with an acute exacerbation of ILD and initiated on supplemental oxygen, IV antibiotics, IV Methylprednisolone 40 mg three times daily, and bronchodilator nebulization. Baseline blood investigations, including electrolytes, renal and liver function tests, were within normal limits. On day 3 of admission, the patient developed new-onset psychotic symptoms. The patient was seen to be muttering to himself and appeared fearful and suspicious. He mentioned hearing the voices of his neighbours talking to him. Mental status examination showed second-person auditory hallucination and delusion of persecution. He was oriented to time, place, and person. There was no associated fever, hypoxia-related confusion, or metabolic abnormality. He sustained a minor fall resulting in a head injury; however, computed tomography of the brain was unremarkable. Given the temporal relationship between steroid initiation and symptom onset, a diagnosis of steroid-induced psychosis was made. IV Methylprednisolone was promptly discontinued, and oral Risperidone 0.5 mg daily was initiated. In two weeks, psychotic symptoms disappeared, and Risperidone was slowly reduced and discontinued. The patient was still psychiatrically stable on follow-up.

Case 2

A 56-year-old man came with a cough, breathlessness, and sputum. His history included treatment of leukaemia with bone marrow transplantation two years ago. On observation, he was oriented and alert. Bilateral consolidations were observed in the chest computed tomography, which is suggestive of pulmonary infection. Bronchoscopy and bronchoalveolar lavage showed fungal elements on potassium hydroxide (KOH) mount, which were typical of Aspergillus species. Invasive aspergillosis was therefore diagnosed. The patient was initiated on voriconazole 400 mg twice a day on day 1, 200 mg twice a day on day 2. He experienced a sudden behavioural change within 24 hours of taking Voriconazole: he was observed to be agitated and suspicious that people in the ward were talking about him. Mental status examination revealed augmented psychomotor activity, second-person auditory hallucination, delusion of reference, and irritable affect. He was afebrile and hemodynamically stable, and lab studies, such as renal and liver functions, arterial blood analysis, and electrolytes, were normal. Agitation was treated with intravenous Haloperidol 5mg, and oral Haloperidol was given in the following 2 days. Voriconazole was discontinued, and psychotic symptoms were completely resolved in 48 hours without further antipsychotic treatment. The diagnosis of Voriconazole-induced psychosis was made based on the temporal association, the exclusion of metabolic causes, and a rapid recovery of the symptoms following the discontinuation.

DISCUSSION

The occurrence of steroid-induced psychosis has been reported to be all over the place, with a range of 2% to 60% [2]. Along with psychosis, steroids are linked with various affective, behavioural, and cognitive disorders, the most common of which are the affective ones [3]. The review of Sirois [4] found that the most frequent affective symptoms were euphoria, irritability, and anxiety; depression and mania were the most frequent mood disorders. In their review, Grace Huynh et al. [5] considered 13 cases where delusions (n = 6) and hallucinations (n = 5) were common presentations. Differences between acute and long-term steroid exposure have also been observed; Bolanos et al. [6] found that while short-term therapy was more often associated with mania or hypomania, prolonged prednisone use (> 7.5 mg/day for 6 months) was more frequently linked to depressive symptoms. Stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to corticotropin releasing factor secretion, adrenocorticotropic hormone release, and subsequent cortisol production. Cortisol exerts genomic and rapid nongenomic effects via mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). MRs regulate stress appraisal and initiation, while GRs mediate stress termination and recovery; a physiological MR–GR balance is essential for neural homeostasis. GRs and MRGR imbalance: Synthetic glucocorticoids selectively activate GRs and inhibit endogenous cortisol. This imbalance is a contributor to cognitive dysfunction, emotional dysregulation, and central neurotoxicity. Long-term high doses lower the glucose levels in the hippocampal, lower neurotrophic factors, impair neurogenesis, and weaken the synaptic plasticity [7]. Corticosteroids also increase the level of tyrosine hydroxylase, which raises the level of dopamine and causes schizophrenia-like alterations and disrupts serotonin and glutamate neurotransmission between neurons, causing mood swings and perceptual disturbances [5]. Steroid induced psychiatric syndromes can be treated by reducing or stopping the use of corticosteroids, as well as pharmacological therapy with antipsychotics, antidepressant and mood stabilisers. Grace Huynh et al. [5] also reported that the majority of the cases were treated with antipsychotics along with steroid withdrawal, most commonly Haloperidol, followed by risperidone. The literature on the topic of voriconazole-induced psychosis is limited to case reports, and the neurobiological mechanisms of this disorder are poorly understood, which creates the necessity to recognise the problem at the earliest possible stage to prevent unnecessary research and provide patient safety. Voriconazole, a widely used antifungal for invasive fungal infections and empiric therapy in febrile neutropenia, has been rarely linked to hallucinations and psychosis, with onset typically within one day to one week of initiation and resolution up to 5 days after discontinuation [8]. Rekha HS et al. [9] described a man in his late 70s with rhino-orbital invasive aspergillosis who developed persecutory and referential delusions with intense fearfulness and disruptive behaviour, which resolved after discontinuation of intravenous voriconazole and initiation of haloperidol. Zonios DI et al. [8], in a prospective cohort of 72 Voriconazole-treated patients, reported hallucinations in 12 patients, most occurring within 2 days of initiation (though some developed symptoms after 6–8 days); all of whom improved following drug cessation. Agrawal AK [10] reported a 78-year-old man with acute myelogenous leukemia who developed musical auditory hallucinations on the second day of therapy, which resolved completely within three days of discontinuing Voriconazole. The mechanism of psychosis induced by Voriconazole is not entirely known, but it is probable and most likely multifactorial, and it includes altered pharmacokinetics and central nervous system penetration. High levels of Voriconazole (> 5 mg/L) in serum are closely linked to

psychotic symptoms in the form of delusions, hallucinations, and fearfulness. This is because of its nonlinear pharmacokinetic and hepatic metabolism through cytochrome P450 enzymes, in which genetic polymorphisms and drug interactions (e.g., proton pump inhibitors) can result in drug build-up [11]. Immunosuppression, old age, underlying infections (e.g., aspergillosis), and immunomodulatory effects of the drug increase the susceptibility of vulnerable people further [9].

CONCLUSION

The incidence, risk factors, clinical manifestations, definitions, implicated dosages, and study populations of drug-induced psychosis differ significantly throughout the literature. Certainly, clinicians are strongly advised to be extra cautious when prescribing corticosteroids and Voriconazole to elderly patients, especially those who experience hepatic or renal comorbidities and polypharmacy. The cornerstone in management is dose reduction or discontinuation of the agent in question and short-term and low-dose antipsychotics when clinically determined.

DECLARATIONS

Ethics approval and consent to participate : Written informed consent was obtained from the patient for publication of this case report

Consent for publication : Written consent taken

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