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Ifosfamide-induced Psychosis

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To the Editor:

Intravenous administration of ifosfamide has been associated with encephalopathy or mild toxicity of the central nervous system (CNS) ranging from 5 to 30% (1). Hallucinations are the most common symptom, but patients can develop somnolence, coma and, sometimes, even death. The onset of these complications is generally acute and recovery usually occurs within a few days after discontinuing therapy. However, up until now, psychiatric disorders have not been described in association with either ifosfamide or other chemotherapy agents. We report on the first case of psychosis induced by ifosfamide therapy.

Lung carcinoma stage IV was diagnosed in a 67-year-old man who was then treated with a regimen of sequential doublets of gemcitabine/vinorelbine (days 1 and 8 for 3 cycles) followed by ifosfamide 3 g/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1 and 8, for 3 cycles. After the start of the fourth cycle (the first of ifosfamide/vinorelbine), the patient developed episodes of anxiety alternating with depression. Progressive worsening of psychological symptoms was observed during the chemotherapy. After the 6th cycle, the patient presented visual hallucinations, anxiety, insomnia, unjustified fear and delusions of persecution. The patient described how he thought that people were 'spying him', that he heard 'footsteps on the roof' and when a car parked in front of his house he thought that someone was going to harm him or steal his money and belongings. Metabolic disorders were ruled out. A brain CT scan was negative to tumour and the thoracic CT scan showed a partial response of the tumour. Treatment with 1 mg haloperidol, twice daily, was prescribed. The following week the persecution mania continued. The patient experienced delusions, hallucinations, disorganized speech and behaviour and negative symptoms and he was admitted to the Psychiatry Unit. Mental status testing revealed signs of decreased attention and alterations of memory and writing. An MRI scan was negative to brain metastases or meningeal enhancement. The patients was prescribed 4 mg risperidone twice a day, resulting in improvement in the symptoms and parameters of the Mini Mental Test. Exacerbation was observed one and a half months later with the suppression of neuroleptics. Risperidone was reintroduced until the patient's death 4 months later, due to thoracic progression of disease without evidence of cerebral disease. Necropsy was not authorized.

Substance-induced psychotic disorder is associated with several drugs that cross the blood–brain barrier. The most common agents implicated are drugs of abuse. However, epidemiologic studies evaluating the incidence and prevalence of this disorder have not yet been published. The 'Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (Text Revision)' has integrated several diagnoses of the previous editions in the category, 'Substance-Related Disorders' (2). This category includes psychiatric disorders caused by alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives (sleeping pills, barbiturates, etc.) and others drugs (ifosfamide could be one of these) (2). When psychotic symptoms such as delusions and hallucinations are present, the disorder is referred to as 'Substance-Related Psychosis'. The level of consciousness is not generally affected; confusion could be present and delusions of persecution are common. The speech is disorganized, and hypoactivity may alternate with hyperactivity and insomnia. Differential diagnoses have to be done with some disorders with similar or even the same symptoms, such as: delirium (acute, reduced level of consciousness); dementia (impairment of memory and intellect) and major depressive disorder accompanied by psychotic symptoms (mood congruent delusions and hallucinations are the most common) (3).

Substance-related delirium with the administration of ifosfamide has been described elsewhere (4, 5). The onset of hallucinations and confusion is acute (1–5 days) after infusion of the drug, and recovery usually occurs within a few days after discontinuing therapy. Our patient is the first reported case of ifosfamide-related psychosis, with persistent symptoms until his death 4 months later. The case fulfils the causality criteria described by both Hill and Susser (6, 7): association, temporariness and a possible cause–effect relation. Moreover, the aetiologic relation could be explained following the algorithm described by Karch & Lasagna (8). In addition, the exclusion of metabolic alterations and the negative results of the CT and MR scans rule out general medical or tumoral conditions that could explain these disorders.

In conclusion, we believe that the incidence of psychiatric disorders due to the administration of drugs that cross the blood–brain barrier is unknown. On the basis of these observations, we think that psychosis should be considered as a potentially toxic effect of ifosfamide administration.

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