Asterixis (Flapping Tremors) As an Outcome of Complex Psychotropic Drug Interaction

To the Editor: Asterixis (flapping tremors) is an important clinical sign. It is not pathognomonic of any condition, but gives a clue to serious underlying disease processes. A few psychotropic drugs are also known to cause asterixis, especially when used in combination. Here, we report on a patient who developed asterixis on a combination of psychotropic agents: clozapine, sodium valproate, and risperidone. Asterixis (flapping tremors) is a motor disturbance marked by intermittent lapses of an assumed posture, as a result of intermittency of sustained contraction of groups of muscles. It was first described by Adams and Foley in 1949; it usually manifests as a bilateral flapping tremor at the wrist, metacarpo-phalangeal, and hip joints. It may also be seen in tongue, foot, and any skeletal muscle. Except for the facial muscles, the tremors occur in an asynchronous fashion on either side of the body.[1] The exact mechanism by which asterixis occurs remains unknown. A leading theory suggests interruption of the posture pathway in the rostral reticular formation and abnormal joint proprioception. The lapse of posture has been termed "negative clonus" because, during tonic muscle contraction (i.e., posture), a short EMG silent period precedes the tremor. In essence, the patient struggles to maintain posture while posture-control repetitively vanishes.[2] It is best demonstrated by extending the hand and dorsiflexing the hand. Common causes of asterixis are hepatic encephalopathy, renal failure, metabolic encephalopathy, CO_2 toxicity, and Wilson's disease. A few psychotropic drugs are also associated with asterixis, and, most of the time, it is the combination of psychotropic drugs that can lead to asterixis. Here, we report on a patient who developed asterixis on a combination of psychotropic agents: clozapine, sodium valproate, and risperidone.

Case Report

A 35-year-old married woman from a middle-class family reported with third-person auditory hallucinations, thought-alienation phenomena, and bizarre delusions for the past 2 months, and was diagnosed with paranoid schizophrenia. Initially, a fair trial of olanzapine tablets up to 30 mg/day and trifluperazine tablets up to 20 mg/day were given for 8 weeks each, resulting in little improvement. Later, she was started on clozapine tablets 25 mg/day, and was slowly titrated to 400 mg/day over a period of 2 months. Clinical improvement in the symptoms was noticed at that dose. She developed one episode of generalized tonic–clonic seizure within a month of starting clozapine 400 mg/day tablets. The dose of clozapine was reduced to 200 mg/day. An EEG was done shortly thereafter, which revealed mild abnormality, with diffuse slowing of waves, for which sodium valproate tablets 1,000 mg/day was started by the neurophysician. As she showed worsening of psychotic symptoms after a month, risperidone tablets 4 mg/day was started concurrently as an augmenting agent. Within 2 weeks of starting the drug, she developed asterixis, with dropping of objects, which gradually increased in intensity, irrespective of emotional stimulus. General physical examination and systemic examinations did not reveal any abnormalities. Investigations for hepatic, renal function, and serum electrolytes were within normal limits. CT brain did not reveal any abnormalities. Three months later, EEG was repeated and did not show any abnormalities, and sodium valproate was tapered off. Simultaneously, risperidone was tapered, in view of the asterixis. Later, as the patient had worsening of psychotic symptoms, risperidone 4 mg/day alone was reintroduced, along with clozapine tablets 200 mg/day. This time, asterixis was not seen, even after 6 weeks of observation. From the above case, it is clear that asterixis occurred only when the patient was on all the three drugs: clozapine, sodium valproate, and risperidone.

Discussion

There are reports that asterixis is a complication of clozapine, especially when used in combination with other psychotropic medications, such as lithium and carbamazepine. A study on 10 patients, most with affective spectrum disorders being treated with combination therapy where the drugs most often used were clozapine (eight cases), lithium (seven cases), and carbamazepine (seven cases); but there were neither metabolic disorders nor structural brain lesions that could explain the occurrence of asterixis. The dosages were moderate, and serum levels were

within therapeutic boundaries in most cases. The symptom seemed to have been caused by an interaction of drugs, rather than by a single agent.[3] A similar report of asterixis was noted with the combination of lithium, clozapine, and zuclopenthixol.[4] Asterixis rarely occurs with sodium valproate. A study report on two patients with asterixis who were taking sodium valproate had serum levels within the therapeutic range. Neither patient had clinical or laboratory evidence of hepatotoxicity. Asterixis seems to be due to a central effect of the drug unrelated to hepatotoxicity or sedation.[5] The most common side effect of sodium valproate is dose-related tremor, occurring in as many as one-quarter of chronically treated patients. Less often, asterixis, chorea, sensorineural hearing loss, and encephalopathy have been reported.[6] Desarkar et al.[7] described a case of cataplexy with a clozapine-and-valproate combination. In response to this case, Butler et al.[8] argued that it could be negative myoclonus, rather than cataplexy. Cataplexy is specific to narcolepsy and is characterized by a sudden drop in muscle tone, triggered by emotional factors. Asterixis is also a potential explanation for Desarkar et al.'s patient, whose valproate, either alone or in combination with clozapine, could have contributed to a subtle toxic-metabolic encephalopathy.[8] In our case, asterixis was not observed when clozapine was used alone, even at 400 mg/day. It appeared within 2 weeks of initiating risperidone treatment (4 mg/day), with a combination of clozapine 200 mg/day and sodium valproate 1,000 mg/day. Asterixis was not observed when risperidone treatment-alone was reinitiated in the same dosage because of worsening of psychotic symptoms. In the absence of any identifiable metabolic abnormalities and structural abnormalities in the brain, it is likely that there was some other, unknown, drug interaction by which asterixis might have been caused. This observation is in line with previous reports that combinations of psychotropic drugs and clozapine are frequently involved in the etiology of asterixis. Asterixis is an important clinical sign and an invaluable clue for serious underlying disease processes. It is not pathognomonic of any condition, and therefore a list of possible differential diagnoses tailored to the patient's clinical presentation must be considered. The treatment of asterixis is the treatment of the underlying condition. Asterixis is a prognostic marker of severity of underlying disease in some conditions, and its cause should therefore be meticulously sought. The early detection of asterixis can help to initiate effective treatment that may help avoid complications in these patients.[9] In conclusion, careful observation of patients who are on combinations of psychotropic agents is needed. Combination of clozapine, sodium valproate, and risperidone may rarely cause asterixis because of an unknown complex drug interaction.

Raghavendra Nayak, M.D.
Aditya Pandurangi, M.D.
Govind Bhogale, M.D.
Nanasaheb Patil, M.D.
Sameeran Chate, M.D.
Dept. of Psychiatry
J N Medical College
KLE University
Belgaum Karnataka
India
Correspondence: Dr. Nayak; rbn.psych@gmail.com

References

1. Adams RD, Foley JM: The neurological changes in the more common types of severe liver disease. Trans Am Neurol Assoc 1949; 74:217–219
2. Young RR, Shahani BT: Asterixis: one type of negative myoclonus. Adv Neurol 1986; 43:137–156
3. Rittmannsberger H: Asterixis induced by psychotropic drug treatment. Clin Neuropharmacol 1996; 19:349–355
4. Rittmannsberger H, Leblhuber F: Drug-induced asterixis. Dtsch Med Wochenschr 1994; 119:585–588
5. Bodensteiner JB, Morris HH, Golden GS: Asterixis associated with sodium valproate. Neurology 1981; 31:194–195
6. Zadikoff C, Munhoz RP, Asante AN, et al: Movement disorders in patients taking anticonvulsants. J Neurol Neurosurg Psychiatry 2007; 78:147–151
7. Desarkar P, Goyal N, Khess CR: Clozapine-induced cataplexy. J Neuropsychiatry Clin Neurosci 2007; 19:87–88
8. Butler T: Clozapine-induced negative myoclonus is not cataplexy. J Neuropsychiatry Clin Neurosci 2009; 21:345–346
9. Gokula RM, Khasnis A: Asterixis. J Postgrad Med 2003; 49:272–275