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Case Report

Low-dose clozapine monotherapy for recurring episodes of depression, hypersomnia and behavioural disturbances: a case report

Havaki-Kontaxaki BJ, Ferentinos PP, Kontaxakis VP, Kontaxaki M-I V, Geronikola X, Armeniakos I, Papadimitriou GN. Low-dose clozapine monotherapy for recurring episodes of depression, hypersomnia and behavioural disturbances: a case report.

Case Report: We present a 27-year-old woman who manifested recurrent episodes of hypersomnia, compulsive hyperphagia, hypersexuality, impulsive behaviours, irritability and depressive mood since the age of 13 after a viral febrile infection. She had 3–4 episodes/year lasting from a few days to 2–3 weeks which were managed with various psychotropics. During her last episode, she was admitted because of persistent behavioural disturbances. Brain 99m-Tc-ethyl cysteinate dimer single-photon emission computed tomography scans showed bilateral mesiotemporal and thalamic hypoperfusion, more significant in the right hemisphere. While hospitalised, she developed neuroleptic malignant syndrome following haloperidol administration. She was discharged on clozapine 100 mg/day. Over the following 30 months, she remained symptom free on clozapine 50–100 mg/day.
Discussion: Differential diagnosis included either an atypical recurrent mood disorder with hypersomnia and behavioural disturbances or Kleine–Levin syndrome.
Conclusion: Low-dose clozapine monotherapy may worth being further investigated for the management of recurring episodes of depression, hypersomnia and behavioural disturbances.

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Case report

In this case report, we present an atypical syndrome of recurring episodes of depression, hypersomnia and behavioural disturbances and discuss its differential diagnosis. Finally, we highlight the potential efficacy of low-dose clozapine monotherapy in the short- and long-term management of this clinical syndrome.

T. is a 27-year-old woman with a family history of major depression (mother). At the age of 13, she had a viral infection with high fever and associated confusion. She has since presented with recurrent episodes of hypersomnia, compulsive hyperphagia, hypersexuality, impulsive behaviours, irritability and depressive mood. She had 3–4 episodes/year, lasting from a few days to 2–3 weeks; eventually, she was fired from her job. The episodes were managed with various treatment combinations (antidepressants, antipsychotics and antiepileptics). Between the episodes, the patient was symptom free without any medication.

During her last episode, she presented with social and sexual disinhibition, excessive irritability and aggression. She was prescribed carbamazepine (400 mg/day) and ziprasidone (80 mg/day) with no response; a few days later, haloperidol (titrated up to 40 mg/day) was added. She was finally admitted to our hospital because of persistent behavioural

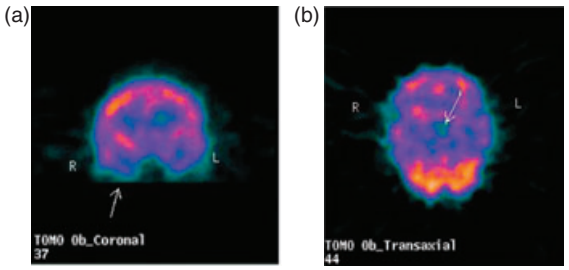

Fig. 1. Coronal (a) and transaxial (b) brain 99m-Tc-ECD SPECT scans showing more marked right mesiotemporal (a) and thalamic (b) hypoperfusion.

disturbances. A detailed history of past episodes was recorded through contacts with her family and previous therapists; physical and neurological examinations, total blood count, blood chemistry, urine and thyroid function tests were normal. Electroencephalogram (EEG) showed diffuse theta waves. Computed tomography (CT) and magnetic resonance imaging (MRI) scans were normal; brain 99m-Tc-ethyl cysteinate dimer (ECD) single-photon emission computed tomography (SPECT) scans showed bilateral hypoperfusion in the medial temporal lobes and thalami, more significant in the right hemisphere (Fig. 1).

Five days post-admission, the patient developed severe hypertonia, 'cogwheel' rigidity, tremor, tachycardia, tachypnoea, diaphoresis, fever (37.7°C), serum creatine phosphokinase elevation (755 U/l) and leucocytosis (WBC 10 400/μl). A diagnosis of neuroleptic malignant syndrome (NMS) was made. All psychotropics were stopped and over the next week only diazepam 20 mg/day was administered (1). NMS symptoms progressively disappeared but behavioural disturbances persisted. Clozapine was started and titrated up to 100 mg/day. Symptoms gradually abated in the following 10 days and finally disappeared. She was discharged on clozapine 100 mg/day. Over the following 30 months, she was receiving clozapine 50–100 mg/day and reported no relapse of mood, sleep or behavioural symptoms.

Discussion

The clinical presentation of our patient is compatible with a differential diagnosis of either an atypical recurrent mood disorder with hypersomnia and behavioural disturbances or Kleine–Levin syndrome (KLS), a rare disorder characterised by periodic episodes of hypersomnia, hyperphagia, hypersexuality and cognitive or behavioural disturbances often triggered by a viral infection during early adolescence in young males (2). KLS is a heterogeneous and as yet unexplained clinical syndrome for which several biological aetiologies have been suggested: post-infectious autoimmunity, genetic susceptibility, implication of frontotemporal and diencephalic regions (3,4). It is often under- or even misdiagnosed (5). In about 50% of cases, mood symptoms are prominent during episodes (6) and similarities between KLS and mood disorders have urged speculations that KLS may be a variant of bipolar disorder (7,8). In our patient, SPECT findings during the episode were consistent with previous reports in KLS patients (4). However, a diagnosis of KLS would be firmly established if thalamic hypoperfusion receded after episode remission but a SPECT repeat was not performed in our patient.

The addition of haloperidol (an agent with high affinity for D2 receptors) seems to have triggered NMS in our patient (9). Our report is compatible with organic brain dysfunction and affective symptomatology being known NMS risk factors (10). Once NMS receded, our first concern was the management of persistent behavioural disturbances with a drug that would not re-trigger NMS. Clozapine has a low affinity for D2 receptors and is unlikely to induce full-blown NMS (11). Clozapine has proved helpful in managing impulsive and aggressive behaviours in psychiatric patients (12). Besides, clozapine (dosage not reported) was effective in controlling acute psychotic-like behavioural disturbances in a KLS patient although a new relapse followed 3 months later (13). However, one cannot safely attribute short-term improvement of our patient to clozapine alone; spontaneous remission of the episode cannot be excluded.

Our patient had a persistently high frequency of episodes (3–4 episodes/year) and relapse prevention was an inevitable concern after remission of the acute episode. Our first thought was to replace clozapine with lithium which had never been administered before and which has a documented long-term efficacy in mood disorders and may show some benefit in up to 40% of KLS cases (6,14). However, clozapine was finally continued as it was excellently tolerated and risk of agranulocytosis is known to decrease with time (15). Finally, clozapine seems to have prevented recurrence for more than 2 years in contrast to all previous years. Again, spontaneous disappearance of episodes cannot be excluded. Data on atypical antipsychotics in the short- and long-term management of KLS are scarce (6) while atypical antipsychotics, including clozapine, are increasingly useful as monotherapy in affective disorders (16,17).

In conclusion, despite the limitations of a single case report with a restricted follow-up period we suggest that low-dose clozapine monotherapy may worth being further investigated for the short- and long-term management of recurring episodes of depression, hypersomnia and behavioural disturbances.

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