Case Report

Clozapine-responsive cluster headache

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Headaches are commonly associated with various psychiatric disorders. The comorbidity of migraine and psychiatric disorders has been well documented. Here we present a case of schizophrenia with comorbid headache treated with clozapine. The patient’s headache fulfilled the diagnostic criteria for cluster headache (CH). To our knowledge this is the first report of CH responding to clozapine therapy. The relationship of headache and psychiatric disorders is a matter of debate and there has been very little research on the aspect of causality or direction of causation. The response of both the conditions to a serotonin-dopamine antagonist such as clozapine might be important in giving newer insights into the pathogenesis of these disorders. It also has the clinical implication of being useful in patients with dual diagnosis.

Key words: Cluster headache, clozapine.

Introduction

Patients with headache commonly suffer from comorbid psychiatric illnesses. The association of migraine and psychiatric illness is well-known. Headache in the context of psychiatric disorders has given rise to newer interesting classification and newer categorisation. Here we present the probable role of clozapine in reducing and remitting the attacks of cluster headache (CH) in an adolescent. The drug was started in this individual, as she also had a comorbid diagnosis of schizophrenia and had history of severe extrapyramidal side effects with lower doses of typical and other atypical anti-psychotics. Recent research has disclosed the involvement of 5HT-1, 5HT-2, 5HT-3 and 5HT-7 receptors in the pathogenesis of migraine headache and these could be the targets of clozapine too. To our knowledge this is the first case report of a person suffering from cluster headache (CH), responding to clozapine.

19-year-old girl presented to our outpatient department with history of episodic severe left sided unilateral (frontal and temporal regions) headache for the past eight years. All these episodes were preceded by flashes of light in no specific distribution, which lasted for approximately 10 minutes. Patient did not report any paresthesia or aphasia. Episodes of headache occurred mostly in evenings and occasionally in mornings, at a frequency of 5-6 per month. Headache usually started at 5-6 PM and occasionally patient woke up with headaches. The duration of active clusters was 5-6 weeks, occurring 2-3 times per year. The duration of headache-free period was 2-3 months. The patient or caregivers did not identify any other specific precipitant for these episodes of headache. She also used to become irritable during the episodes of headache and often was found to tear off her scalp hair and hold her head with her hands. These episodes were associated with photophobia and phonophobia. They were often associated with nausea and vomiting but not invariably. The headache had a throbbing quality and was aggravated with physical stress. The patient had occasional rhinorrhea and nasal congestion associated with the headache but did not have any other autonomic symptoms during the periods of headache as eyelid ptosis, conjunctival injection. The headache usually lasted for 15-30 minutes. She could resume her regular activities following the bout of headache. She had full recall of the happenings of the period of headache and no history of falls, incontinence, tongue bite or altered sensorium suggestive of a seizure phenomena. Patient had a family history of similar headaches in her maternal grandmother. There was no family history of psychiatric disorders. Patient was a non-smoker.

This patient had also been diagnosed to have schizophrenia for the past 5 years, which had been treated with typical and atypical anti-psychotic medications. The various drugs tried included haloperidol, trifluperazine, risperidone, olanzapine, Quitiapine and ziprasidone. The dosage range varied between 400 mg to 800 mg.

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clozapine equivalents. The reason for not increasing the drug dosage beyond that which was used was due to appearance of drug induced acute dyskinesia. This patient was particularly prone to drug induced acute dyskinetic side effects, which were extremely disabling even at low doses of both typical and atypical drugs. She had both positive and negative symptoms of schizophrenia in the inter-morbid headache-free period. The headache frequency and severity were independent of the severity of the psychotic symptoms and their treatment. She had not received any prophylactic therapy for headache. Patient had become socio-occupationally dysfunctional to a significant degree for the past 8 years. Patient’s disability could be attributed to her psychotic symptoms and regular bouts of severe episodic headache.

General and systemic examination of the patient during episodes of headache showed mild nasal congestion during some of the episodes of headache. The examination in the inter-morbid period was normal. A detailed neurological examination was normal. We had considered the differential diagnosis of cluster headache, migraine, short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome, paroxysmal hemiergia and seizure disorder. The headache duration did not qualify for the diagnosis of migraine (too short for migraine) or SUNCT syndrome (too long for this). The frequency of headache, even at most difficult periods over the past eight years, was around once a day and thus went against paroxysmal hemiergia. There was nothing to suggest a diagnosis of seizure disorder other than the episodic nature of the illness. Provisionally a dual diagnosis of episodic CH and schizophrenia was made. However, it should be mentioned that the patient had several atypical features for CH, such as female sex, short duration of attacks, positive family history and history of aura and intermittent frequency of attacks.

Investigations including blood counts, serum electrolytes and blood biochemistry were all within normal limits. A normal Magnetic Resonance Imaging of her brain and Electroencephalogram ruled out any structural pathology and seizure activity. The two disorders seemed to be independent of each other and the dual diagnosis was retained.

After evaluation of the patient, it was decided to start her on clozapine because of her poor tolerance of typical and other atypical antipsychotic drugs and inadequate response of psychotic symptoms with other atypical agents. It was decided to abort any acute attacks of CH with sumatriptan nasal spray as and when necessary.

This patient gradually improved with the commencement of clozapine therapy. The dosage of clozapine was titrated slowly over a 3-week period. She was maintained on only 100 mg of clozapine because of her excellent response and past history of severe extrapyramidal side effects even with lower doses of other atypical antipsychotic drugs. After completing four weeks of treatment, she stopped having any further headache and her psychotic symptoms had remarkably reduced. At discharge, on Brief Psychiatric Rating Scale[4] she scored 3 as compared to a baseline score of 20. She had become functionally much improved and appropriate rehabilitation measures were planned.

**Discussion**

The pathogenesis of CH is not well understood. Clozapine alone was sufficient to treat both conditions (schizophrenia and CH). Initially though, our goal was to control the psychosis and meanwhile try to abort the acute attacks by using sumatriptan. To our surprise, we saw the patient improving as regards both psychotic and headache symptoms with clozapine alone. The commonality in treatment response of psychosis and CH may be based on serotonergic or dopaminergic mechanism. Clozapine blocks both dopamine D2 and serotonergic receptors. Further research in this direction might give newer insights into the pathophysiology of these disorders. Limitation of this report is that it is based on anecdotal experience of a single case. Earlier there have been case reports of patients of CH responding to other serotonin-dopamine antagonists, namely olanzapine[5] and chlorpromazine.[6] For treatment-resistant CH, the efficacy of clozapine needs to be further studied. This case is unlikely part of the newer category of headache associated with psychiatric disorders as she had onset of headache much earlier to the onset of schizophrenia.

**References**


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