

Clozapine-induced rabbit syndrome: a case report

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Abstract

Rabbit syndrome (RS) is an antipsychotic-induced rhythmic motion of the mouth/lips resembling the chewing movements of a rabbit. The movement consists of a vertical-only motion, at about 5 Hz, with no involvement of the tongue. Long-term exposure to typical antipsychotics has clearly been associated with RS, but little is known of the risk of RS due to exposure to newer atypical antipsychotics. There have been isolated reports of RS in patients treated with the atypical agents risperidone, aripiprazole, olanzapine, and clozapine. We present the case history of a 44-year old female patient treated for paranoid schizophrenia for 22 years and RS during her last 10-month clozapine treatment. Background information from the literature is also discussed.

Introduction

Rabbit syndrome (RS) is a rare movement disorder generally associated with prolonged use of antipsychotics and characterized by involuntary, rhythmic, fast, and fine movements of the oral and masticatory muscles along the vertical axis of the mouth.¹ It takes its name from an unusual resemblance to the chewing motions of rabbits. The pattern of movement differs from tardive dyskinesia (TD), another form of oral dyskinesia, in which the tongue is involved in making slower and less regular movements.² Usually, the involuntary movements associated with RS appear after a long period (in most cases months or years) of antipsychotic treatment.³ Gender and age are also thought to be related to the development of RS. This syndrome is found predominantly in middle-aged and elderly patient populations; women are also thought to be at higher risk of developing RS than men.⁴ The reported prevalence of RS ranges from 2.3-4.4% of patients treated with typical antipsychotics.³ To the best of our knowledge, no prevalence study has been published to date on the relationship between RS and atypical antipsychotics. Of particular interest and importance is the risk of RS with exposure to newer atypical antipsychotics. Risperidone is considered the atypical antipsychotic with the

highest incidence of extrapyramidal symptoms (EPS).⁵ An extensive literature search revealed 11 cases of RS related to newer antipsychotic studies reported by Dell'Osso *et al.*⁶ Eight of the 11 reported cases of RS are linked to risperidone.⁶⁻¹² The 3 remaining cases occurred with clozapine, olanzapine, and aripiprazole, respectively.¹³⁻¹⁵ These atypical antipsychotics are characterized by a relatively low incidence of EPS. It is interesting that, in the case induced by clozapine, TD preceded RS which developed after treatment for approximately two years with chlorpromazine, haloperidol, and fluphenazine decanoate, either in monotherapy or in combination.⁶ In addition, there are 3 new case reports concerning EPS, which include RS associated with aripiprazole and olanzapine.¹⁶⁻¹⁸

It has been postulated that the underlying mechanism of RS is supersensitivity of dopamine receptors, possibly due to an underlying predisposition.¹⁶ Treatment of RS is empirical, reflecting poor understanding of neuropathology. The first step is to reduce the dose of antipsychotic treatment as much as possible. The next stage of treatment involves specific drugs aimed at controlling the syndrome. Anticholinergic drugs are the best known treatment. RS does not respond to treatment with levodopa or dopamine agonists.³ The most striking aspect of this syndrome is its specificity. RS only affects the buccal region, and within this area it involves a highly stereotyped involuntary movement. This immediately focuses attention on the basal ganglia, in particular the substantia nigra pars reticulata, which is also implicated in oral dyskinesia.³

Case Report

MO was a 44-year old single woman born in Artvin in Turkey. She was unemployed and had dropped out of university in her sophomore year. She was brought into our hospital by her family against her will. She was complaining of paranoia and introversion. In addition, she refused to speak, eat or leave her house. She also rejected other people's company and preferred to stay on her own. She could not sleep.

According to her family, her first complaint had started at the age of 22 before she went to university in Ankara. Based on information from her family, we learnt that she had begun to skip classes and this had had a negative impact on her academic achievement. Also her family said that she was hearing strange noises. Since then she had been treated in different hospitals and cities, being given various medications based on the diagnosis of paranoid schizophrenia. It was reported that in the first 15 years of her treatment she was pre-

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scribed with haloperidol (20 mg) irregularly and then she was prescribed with anti-psychotics such as fluphenazine decanoate (25 mg), trifluoperazine (5 mg), thioridazine (100 mg), zuclopentixol (200 mg). It was also said that in the last five years of her treatment she was prescribed with olanzapine 20 mg/day and risperidone 6 mg/day irregularly. Some side effects, such as a frequent sensation of slowing down, limited movements, tremor in her hands and dryness in her mouth, were observed during the period of medication. The family pointed out that there had been some improvement in her condition while she was taking her medications, but their side effects compromised continuity of treatment. Her symptoms worsened and her family brought her to the hospital. On presentation she had not taken prescribed medication for seven months.

MO was the youngest of 3 children and had an older brother and sister. Her mother was a 68-year old housewife who had finished elementary school. Her father had died in an accident 20 years earlier. There was no history of any neurological or psychiatric disease in the family. She had been successful at school and had gone to Ankara to study at the university after passing the entrance exam. In the first year, she had stayed in a dormitory with her friends but in the second year she began to live alone in a flat. She had to drop out of university in the second year because of her illness. She had not had any medical problems before her illness. She had been smoking one packet of cigarettes every three days. However, this amount had increased over the previous few months. Six months before presentation she had begun to suffer from eating disorders and insomnia, although she had had no previous history of either. She refused meals prepared by her mother, believing them to be poisoned. According to her family, the patient had been extrovert, more talkative, and generally happy-

er and livelier before her illness. She had subsequently become introverted and never wanted to leave the house. She was still living with her mother and her unmarried sister, six years older than herself.

Physical examination and laboratory findings

Vital findings, neurological and other system examinations were all normal.

Laboratory findings, hemogram, EFG, and brain magnetic resonance image (MRI) were also all normal.

At her first psychiatric appointment, the female patient, who looked older than her years, looked well groomed and behaved with respect. She kept looking around, didn't speak spontaneously, and replied hesitantly only when asked questions. During the interview she was agitated, her attention and concentration were poor, and she did not always seem to understand what was being asked of her. She showed no emotional response to the conversation and admitted to hearing voices that discussed her actions, ridiculed her, and at times warned her not to interact with family members. She had a persecution complex and expressed illusions of grandeur.

Clinical course

At the first psychiatric evaluation of the event it was confirmed that the patient had used classic and atypical antipsychotic, anticholinergic drugs for various periods over 22 years. During these periods she had experienced serious side effects such as akathisia, tremors, and deceleration in her activities, and these had not been completely resolved by the medication received. The patient was diagnosed with treatment-resistant schizophrenia and was treated with clozapine. Drug dose was gradually increased over six weeks (started at 12.5 mg/day and titrated up to a target dose of 450 mg/day). About 20 months after the initiation of clozapine, the patient developed involuntary movements of her mouth. Signs of typical RS were evident. The movements were fine, rhythmic, and rapid, along the vertical axis, and without lingual involvement. The patient and her family reported that dyskinetic movements of the patient's lips occurred during the examination, performed in the 16th month of her treatment, and that her social activities and communications with others had improved. The patient and her family were informed about the progress of the illness. Clozapine was stopped and treatment was changed to quetiapine. After four weeks of quetiapine treatment (starting dose of 100 mg/day and titration up to 700 mg/day) her RS symptoms diminished significantly with further improvements during the follow-up period. Her *Abnormal Involuntary Movement Scale*

(AIMS) score dropped from 14 to 8. The most prominent, albeit controversial, treatment agents for RS are benzhexol and biperiden. We were anxious to avoid aggravation or TD by the addition of anticholinergic agents.

Discussion

Increased knowledge about neurobiology has improved our understanding of the pathophysiology of schizophrenia. These improvements have led to the development of new generation antipsychotics with fewer side effects and more therapeutic effectiveness. Clozapine is considered an atypical antipsychotic drug. Atypical antipsychotics differ from typical antipsychotics in their effectiveness in schizophrenia and their profile of side effects. Clozapine may reduce the signs and symptoms of schizophrenia in a large proportion of treatment-resistant schizophrenic patients who do not respond to typical antipsychotics. Moreover, the drug is less likely to cause tardive dyskinesia and other EPS than typical antipsychotics.^{19,20} Frequent side effects of antipsychotic drugs are well known. RS is believed to be a rare condition affecting only a small fraction of the psychiatric population using antipsychotics. In the recent past, RS was also observed in patients treated with the newer antipsychotics.^{6,13} RS responds well to treatment with anticholinergic agents.³ RS typically disappears a few days after the introduction of an anticholinergic agent, but can, on occasion, reappear after stopping anticholinergic medications.² Researchers adopted a new treatment strategy after evidence was found that some patients with RS treated with an anticholinergic agent later developed TD.^{3,6} The availability of the newer atypical antipsychotics has led to the implementation of additional treatment strategies. Durst successfully treated RS triggered by the typical neuroleptic zuclopenthixol by switching the patient from zuclopenthixol to olanzapine.²¹ After the administration of olanzapine (started at 5 mg/day and titrated up to a target dose of 10 mg/day), both the RS and the psychotic symptoms showed significant improvement. In the presentation of the case a different atypical antipsychotic treatment was applied in a similar way. Switching to a new atypical antipsychotic with high anti-cholinergic properties, like olanzapine or quetiapine, may be another possible treatment strategy for RS.⁶ Continuing neurophysiological and pharmacological research of the basal ganglia holds the key to better understanding and improved treatment of this syndrome in the coming years. In particular, it agrees with the fact that RS is usually observed in females older than 40 and is seen twice as often in females as in

males. Moreover, different antipsychotic drugs were used before clozapine and the fact that EPS symptoms emerged is remarkable. This shows the importance of individual factors in RS. For this reason, it is important to diagnose the side effects emerging during antipsychotic drug treatment to determine which individuals are at risk of being exposed to EPS and to prevent possible negative results. Furthermore, increased awareness in medical practice that atypical antipsychotics cause RS, albeit rarely, will be beneficial in both patient compliance with treatment and in providing data for more comprehensive models to explain RS progress.

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