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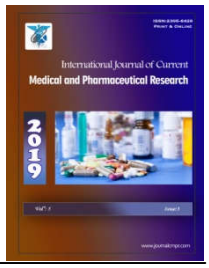

RABBIT SYNDROME: UPDATE ON AETIOLOGY AND MANAGEMENT FOR PHARMACISTS, PSYCHIATRISTS AND DENTISTS

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ABSTRACT

Rabbit syndrome (RS) is an involuntary movement disorder, characterized by fast and fine movements of oral and masticatory muscles along the mouth vertical axis in the absence of tongue involvement. RS prevalence varies between 2.3% to 4.4% and could result from the administration of antipsychotics and antidepressants. In case of second generation antipsychotics, there is a reduced risk of RS compared with first generation antipsychotics with mainly isolated literature case reports especially with the use of risperidone as antipsychotic. RS affects only the buccal region, with the possible involvement of the basal ganglia, in particular the substantia nigra. The management of RS include reduction or change of the psychotropic treatment and use of anticholinergic medications such as trihexyphenidyl. Although RS is rare and easily treatable, it is essential that dentists and psychiatrists could distinguish this syndrome from other movement disorders such as tardive dyskinesia.

INTRODUCTION

Rabbit syndrome (RS) is a vertical rhythmic dyskinesia of the mouth and lips with no tongue involvement. This involuntary movement disorder is characterized by fast and fine movements of oral and masticatory muscles along the vertical axis of the mouth, similar to chewing movements of a rabbit at a frequency of approximately 5 Hz (1). Fatigue, anxiety, attention, concentration, motor performances and stressful situations could intensify RS symptoms with an increase in muscle tone (2). RS is often misdiagnosed as tardive dyskinesia, the tongue-involving movement disorder (3), where the movements of the mouth are less regular and slower and involve the tongue (4).RS symptoms could be presented as the outcome of antipsychotics and/or antidepressants side effects, which are related to extrapyramidal side effects (EPSE). These well-known antipsychotics side effects are due mainly to the antipsychotic antagonist activity on the dopaminergic receptors (5).

In this review article, we describe RS clinical manifestations and prevalence, while focussing on the associated medications pharmacology and commenting on the literature clinical cases with discussion on the current management options.

Rabbit Syndrome and Antipsychotics

Rabbit syndrome is considered a rare side effect of prolonged antipsychotics treatment. Its involuntary movements could appear after prolonged treatment (months or years); however, in few cases absence of antipsychotic involvement was demonstrated. RS reported prevalence varies between 2.3% to 4.4% of patients managed with first generation antipsychotics (FGA) with elderly, female gender and previous brain injuries considered risk factors (4) as highlighted in a study following 266 chronic inpatients receiving antipsychotics, where 4.4%suffered RS, while co-administering anticholinergic medications such as procyclidine resulted in resolving RS signs/symptoms (6).

For second generation antipsychotics (SGA), there is a reduced risk of RS with mainly isolated case reports in literature (7)for amisulpiride, risperidone, levosulpiride and paliperidone as potential culprit for RS especially risperidone (8-14) such as the case of 38-year-old man with a major depressive disorder on 4 month treatment of risperidone, where RS responded to anticholinergic treatment (15). Although olanzapine and clozapine are antipsychotics with less risk of EPSE, RS was reported (16-18).In paediatric population, some reports of RS following antipsychotic administration were also reported (19)

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such as a bipolar patient, who suffered RS signs/symptoms following quetiapine administration (20,21). Some clinical cases were also reported for RS as a side effect of aripiprazole, a new dopaminergic agent with reduced EPSE. Aripiprazole pharmacological mechanisms of action include D2 receptor binding, low anticholinergic properties and dopamine hypersensitivity (22-24). Furthermore, co-administration of Ziprasidone (antipsychotic) with sertraline (antidepressant) or the combination of lithium and risperidone induced RSsymptoms/signs (25,26).

Rabbit Syndrome and Antidepressants

Some clinical cases of RS were induced by Serotonin Specific Reuptake inhibitors (SSRI) such as citalopram, escitalopram or paroxetine with discontinuation leading to symptoms improvement (27,28).Cases of tricyclic antidepressant (TCA) dose-related RS symptoms were reported; responding to antiparkinsonian agents or propranolol (29).

Pharmacology of the Medications Associated with rabbit syndrome

RS affects only the buccal region, with the possible involvement of the basal ganglia; in particular the substantia nigra pars reticulate - also implicated in oral dyskinesia (30). RS could be due to imbalance of the cholinergic and dopaminergic neurotransmission in the basal ganglia similar to the antipsychotic induced parkinsonian syndrome (31), with cerebral scans supporting these ideas by revealinga decreased basal ganglia perfusion in the presence of RS (32).

FGA such as haloperidol are dopamine (D2) receptors antagonists and block histamine, muscarinic and alpha-1 receptors (33), while SGA such as quetiapine are serotonin-dopamine antagonists (34). Serotonin antagonism could increase dopaminergic neurotransmission in the nigrostriatal pathway, which reduces the risk of EPSE such as dystonic reactions, akathisia and tardive dyskinesia (34). TCAs inhibit serotonin and norepinephrine neurotransmitter reuptake by pre-synaptic neurons, increasing their levels in the synapse. TCA possess also high affinity to muscarinic, cholinergic and adrenergic receptors, while SSR Is inhibit serotonin reuptake in the brain. Anticholinergic such as trihexyphenidy l and procyclidine are used to counter the hyper-cholinergic state in RS (35).

Management of Rabbit Syndrome

RS may be due to a hyper-cholinergic state resulting from the blockade of dopaminergic neurons in the extrapyramidal system (35). RS is easily treatable when recognized, but needs to be differentiated from tardive dyskinesia. Its treatment is empirical (7), with the first step to reduce/ stop the psychotropic medication. RS responded to anticholinergic drugs with the antipsychotic switch (36). Trihexyphenidyl as anticholinergic was used successfully in severe cases causing dysphagia (37,38) and in schizophrenic inpatients on long-term antipsychotics with a significant reduction in RS score and Simpson-Angus rating scale (31). Switching to a second generation antipsychotic with high anticholinergic properties, like olanzapine may be another possible management strategy as olanzapine has less risk to cause RS signs/symptoms compared to risperidone; however, care should be applied as some rare cases suggested that olanzapine itself could be a culprit (39,40). Quetiapine was effective as a mono-therapy for the management of both RS and psychotic symptoms (21). Use of an antiparkinsonian agent may be required (35,41), however, RS did not respond to levodopa or dopamine agonistsin some cases (42).

DISCUSSION

RS is a movement disorder affecting perioral muscles and has been traditionally associated mainly with first generation antipsychotics treatment. However, second generation antipsychotics such as risperidone and antidepressant medications could also be involved in the pathogenesis of RS. RS is considered a form of antipsychotic induced EPS Eoccurring late in treatment, even in the absence of other EPSE (18). RS differ from typical oral dyskinesia, where the tongue is involved and the movements could be suppressed voluntarily by the patient. This syndrome main management include reducing or stopping the culprit antipsychotic, while switching the medication and administering anticholinergic agents shown efficacy in reducing RS symptoms.

As RS signs/symptoms highly resembles oral dyskinesia and tardive dyskinesia- conditions that could become worse upon administering of anticholinergic medications, it is imperative for psychiatrists and dentists to ensure that they could confirm RS before starting treatment.

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