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RABBIT SYNDROME INDUCED BY ATYPICAL ANTIPSYCHOTICS: A RARE EXTRAPYRMIDAL SIDE EFFECT

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Abstract:
Rabbit syndrome (RS) characterized by rapid, fine, rhythmic movements of the perioral muscles along a vertical axis at a frequency of about 5 Hz, mimicking the chewing and puckering movements of a rabbit with no Rabbit syndrome (RS) is a rare extra pyramidal symptom (EPS) caused by a prolonged neuroleptic medication, RS is characterized by rapid, fine, and rhythmic movements with the involvement of the tongue. Patients using antipsychotics found to have a rabbit syndrome prevalence that ranges from 1.3 to 4.4%. Polypharmacy and long-term neuroleptic use are the risk factors in developing this syndrome. RS is typically thought to be caused by first-generation antipsychotics. Nonetheless, second-generation antipsychotics like Riserpidone, which have a strong serotonin blockade and a lessened dopaminergic blockade also causes RS more frequently. Differential diagnosis include tardive dyskinesia in which movements are slow and irregular which does not follow rhythmicity and involves tongue movement. Management usually involves the reduction in the dose or changing to alternative atypical antipsychotics. Anticholinergics and anti-parkinsonic medications are also helpful to treat RS.

Keywords: Rabbit Syndrome, Antipsychotics, Tardive Dyskinesia, Riserpidone, Anticholinergics.

INTRODUCTION:

Rabbit syndrome is a rare extra pyramidal symptom (EPS) caused by prolonged neuroleptic medication, characterized by rapid, fine, and rhythmic movements of the perioral muscles along a vertical axis at a frequency of about 5 Hz, mimicking the chewing and puckering movements of a rabbit with no involvement of the tongue [1]. In most cases, months to years of neuroleptic therapy is required before the involuntary movements linked to RS become noticeable [2]. The antipsychotic drugs also called as neuroleptics are first line drugs to treat psychoses. These drugs believed to cause

extra pyramidal effects as adverse effects/side effects, and they include akathisia, dystonia, parkinsonism, malignant neuroleptic syndrome, and tardive dyskinesia [3]**.** Second generation antipsychotics are associated with fewer extra pyramidal side effects as compared to typical or first-generation antipsychotics. But they do cause RS which is different from that of dyskinesia. The unusual extra pyramidal adverse effect of atypical antipsychotics, RSwas the subject of this review [3].

Antipsychotic drugs: The antipsychotic drugs [also called neuroleptics] are primarily used to treat schizophrenia, are also effective in other bipolar and mood disorders.

Classification: The antipsychotic drugs are divided into first and second generation antipsychotics.They are classified based on their affinity for the dopamine D2 receptors.

First-generation antipsychotics (FGAs): Also called as typical or conventional or traditional antipsychotics and have potent dopamine D2 receptor blocking action. They include chlorpromazine, triflupromazine, fluphenazine, haloperidol, penfluridol, levosulpiride and flupenthixol.

Second-generation antipsychotics (SGAs): Also called atypical or newer antipsychotics that have a weak D2 receptor action risk potent 5-HT2 antagonistic activity. Atypical antipsychotics include clozapine, olanzapine, quetiapine, aripiprazole, riserpidone and ziprasidone [3].

Clinical pharmacology of atypical antipsychotics:

When compared to conventional antipsychotics, atypical antipsychotics exhibit robust of 5-HT2 antagonistic activity that moderate D2 blocking, and hence are more likely to cause metabolic side effects such as diabetes, hypercholesterolemia, and weight gain.

Mechanism of action:

The mechanism of action of second-generation antipsychotic medications has been revealed to be heavily dependenton 5-HT2A-receptor blockage.

Serotonin receptor blocking activity: It has been discovered that the primary class of second-generation antipsychotic medications' mechanism of action includes a crucial role for 5-HT2A-receptor blockage. These substances block the 5-HT2A receptors constitutive activity because they are inverse agonists of the receptor. These receptors control the release ofseveral neurotransmitters in the cortex, limbic area, and striatum, including dopamine, norepinephrine, glutamate, GABA, and acetylcholine. Thus the dopamine release from the limbic system and cortexis inhibited by stimulation of 5-HT2C receptors [5].

Dopamine antagonism: some of the atypical antipsychotics blocks D2 dopamine receptors in the brain and the periphery.

Table01: Pharmacology of atypical antipsychotics [06]

Drug	Action	Metabolised by	t-1/2	Anti cholinergic activity
Clozapine	Weak D2 action, relative selectivity for D4 receptor, 5-HT2 and alpha adrenergic blockade	CYP1A2,CYP 2C19& CYP 3A4	12 hours	Potent
Olanzapine	Similar to clozapine with additional Muscarinic and H1 receptor blockade.	CYP 1A2 & Glucuronyl transferase	24-30 hours	Potent
Quetiapine	D2 blocking activity is low but has potent effect on 5-HT2, 5-HT1A, H1 receptor and alpha adrenergic blockade	CYP 3A4	6 hours	Moderate
Aripiprazole	Partial agonist at D2 and 5-HT1Areceptors but Antagonistat 5-HT2 receptors.	CYP2D6 & CYP3A4	3 days	Moderate
Riserpidone	Risperidone shows high affinity for serotonin 5-HT2,adrenergic and dopamine D2 receptors [7]	CYP 2D6	3 hours to 20 hours	Low
Ziprasidone	Combined D2, 5-HT2, H1 and alpha adrenergic blockade.	CYP 3A4 & CYP 1A2	8 hours	Low

How Riserpidone differs from other SGAs:

- Among atypical antipsychotics the hierarchy of anti cholinergic action clozapine >> olanzapine >> quetiapine > riserpidone/ziprasidone [7].
- After oral administration, risperidone is quickly and thoroughly absorbed; less than1% of it is eliminated in the faeces unaltered. 9-hydroxyrisperidone was found to be the main metabolite. In poor metabolizers the half-life of riserpidone was about 19 hours compared with about 3 hours in extensive metabolizers. The action of 9-hydroxyriserpidone is similar to that of riserpidone, thus the half-life is about 20 hours in extensive poor metabolizers [6].

DISCUSSION:

Definition: 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.

- Rabbit syndrome is a rest tremor [8] and was first described in1972 by Villeneuve [9].
- It is an iatrogenic syndrome[11]

Prevalence:

Rabbit syndrome prevalence varies between 2.3 to 4.4% [9] [12] [13] and is more common in Geriatrics and women being more vulnerable [14].

Risk factors:

- Long term use of neuroleptics [12].
- Poly pharmacy in elderly patient

Ex: using two antipsychotics

- An antipsychotic with antidepressant
- An antipsychotic with Lithium [16].
- Stress/during work (intensifies)[17][14].
- RS is exaggerated by stress and anxiety and works requiring attention and concentration [13]
- Oldage, female, sex and brain injury [14].
- Risk is more with (FGAs) but among (SGAs) riserpidone has more risk compared to other atypical antipsychotics [12] [13].

Riserpidone specific risk factors:

- Increase in the dose of riserpidone is associated with rabbit syndrome [9][16].
- Patient specific polymorphism such as poor metabolism by the cytochrome P450 2D6 isoenzyme. Some authors believes that in poor metabolisers increase in the dose leads to increase in adverse reactions [9] [10].

Pathophysiology:

- Dysbalance in the cholinergic and dopaminergic neurotransmission in the basal ganglia seems to be the cause but it is not clear [18].
- Antipsychotics acts by blocking dopaminergic and 5-HT2 receptors along with alpha adrenergic blockade.
- This anti-dopaminergic action leads to hypercholinergic state in the basal ganglia[13] A state of dopaminergic hypersensitivity charecterised by cholinergic hypofunction which is supported by clinical evidence because rabbit syndrome responds to anticholinergic treatment [19][9].

Investigations : No specific investigations required but a drug history including OTC should be taken [8].

Differentiating RS from tardive dyskinesia : Differentiating the RS from tardive dyskinesia is important because of similar features [9]. As prevalence of rabbit syndrome is rare compared to tardive dyskinesia, there can be a possibility of misdiagnosis.

Table 02: Differentiating of Rabbit Syndrome from Tardive Dyskinesia

Rabbit syndrome		**Tardive dyskinesia**
Rabbit syndrome (RS) ischaracterized by rapid, fine, rhythmic movements of the perioral muscles along a vertical axis.	**[1]**	Tardive dyskinesia is a slow, irregular movements that occurs in all directions(no rhythmicity).[9]
No tongue involvement [20]	**[2]**	Tongue is involved
Persistent in stage I NREM sleep [20]	**[3]**	Tardive dyskinesia is not persistent (or) ceased in stage INREM sleep [9] [16]
RS subsides by anticholinergics	**[4]**	Anticholinergics worsens tardive dyskinesia [9][21]

Management: Although rare, rabbit syndrome is easily treatable if recognised early [22].
Strategies to manage RS:

- Management include reduction in the dose (or) changing to another atypical antipsychotic.
- Usually in riserpidone induced RS ,second generation antipsychoticswith high anticholinergic activity are used. Ex: clozapine, olanzapine and quetiapine [12].
- "Rabbit Syndrome and akathesia in a patient treated with riserpidone: A casereport; C Lay" *et al* described A 28 year-old woman was being treated for OCD with riserpidone, quetiapine, and venlafaxine. Risperidone was stopped in due of RS, which she developed. The symptoms vanished after quitting risperidone and switching to a higher dosage of quetiapine.
- Anticholinergics are the drugs of choice which include trihexyphenidyl, Benztropin, Benzotropinemesylate [23] and Bisperiden [24].
- "Aropiprazole associated RabbitSyndrome: A Rare Case Report; Mahendra Kumar R" *et al* described A 47-year-old male patient arrived at the out patient clinic complaining of trembling hands, uncontrollable perioral motions,and slurred speech for the past week. .The patient was on aripiprazole 20 mg daily and 400 mg of sodium valproate daily. Aripiprazole was stopped, and lorazepam andtrihexyphenidyl tablets were introduced. The patient reported improvement in RS after a 5-day follow-up [14].
- After being given neuroleptics for several months, a 28-year-old man began to experience delicate and rhythmic perioral involuntary movements.The benztropine significantly decreased them [25].
- According to a study, antiparkinsonic medications does improve rabbit syndrome thus it is a strong evident that rabbit syndrome is similar to drug induced parkinsonism [26].
- Dopamine agonists (or) levodopa are not effective [02].

Conclusion:

Although there is a lesser risk of developing EPS and RS when using atypical antipsychotic medicines, it is never the less advised that doctors use caution when administering such drugs. If detected early, rabbitsyndrome is not a serious side effect and is easily treatable. The trick is to distinguish between the rabbit syndrome and tardive dyskinesia.

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