Review Article

Understanding Rabbit Syndrome: Clinical Insights, Pathophysiological Mechanisms, and Management Strategies: A Mini-Review

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Rabbit syndrome (RS) is a rare extrapyramidal side effect of long-term neuroleptic use, marked by rhythmic, fine rhythmic movements of the perioral muscles resembling a rabbit's chewing. Its subtle presentation often leads to misdiagnosis, confusing it with other movement disorders. It has a rare incidence in long-term neuroleptic therapy and is more common with higher doses and extended use. It shows distinctive perioral movements without tongue involvement, unlike tardive dyskinesia. Precise diagnosis is vital to distinguish rabbit syndrome from other movement disorders. Treatment typically involves reducing or stopping the dosage of neuroleptic agent, sometimes with anticholinergic medications. For this mini-review, relevant literature was identified through searches of PubMed, Google Scholar, and Scopus, focusing on studies describing clinical features, pathophysiological mechanisms, and management approaches. This article presents an in-depth clinical review of rabbit syndrome, covering its prevalence, symptoms, risk factors, differential diagnoses, and treatment options.

KEYWORDS: Antipsychotics, extrapyramidal symptoms, rabbit syndrome, risk factors

Introduction

Rabbit syndrome (RS) is a rare extrapyramidal symptom that occurs after long-term use of neuroleptic medication. It is characterized by fast, precise, and rhythmic movements of the perioral muscles around the mouth in an up-and-down motion, resembling a rabbit's chewing and puckering movements. These movements occur at a frequency of approximately 5 Hz with no involvement of the tongue. This is a rare disorder that only affects few psychiatric patients who are being treated with antipsychotic medication. Typically, involuntary movements associated with RS manifest after several months to years of neuroleptic medication.

It is a rare extrapyramidal adverse effect that occurs in 2%-5% of patients who have been receiving long-term neuroleptic treatment. Typically, this condition is more common in females over 40 and is twice as prevalent in females as in males. Villeneuve initially

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characterized it in 1972. Antipsychotic medications, also referred to as neuroleptics, are the primary treatment for psychotic disorders. Despite their effectiveness, they are associated with extrapyramidal side effects, such as akathisia, dystonia, Parkinsonism, neuroleptic malignant syndrome, and tardive dyskinesia. Second-generation antipsychotics exhibit a lower incidence of extrapyramidal side effects as compared to typical or first-generation antipsychotics. However, they do induce RS, which is distinct from dyskinesia. Second-generation antipsychotics.

MATERIALS AND METHODS

A literature search was conducted using Google Scholar, PubMed, and Scopus databases up to April 2024. Keywords such as "Rabbit Syndrome," "extrapyramidal

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side effects," "antipsychotic-induced movement disorders," and "neurological side effects of antipsychotics" were used. The initial search retrieved 134 articles, and after removing duplicates, 108 remained. Titles and abstracts were reviewed independently by two researchers, leading to the exclusion of 80 articles. Fulltext analysis was performed on 28 articles, of which 13 met the inclusion criteria for this review. The inclusion criteria were studies explicitly investigating RS, discussing its pathophysiology, clinical manifestations, and treatment, as well as case reports and systematic reviews. Articles unrelated to RS, those with insufficient data or unclear diagnostic criteria, and non-English publications without translations were excluded. Any disagreements in the selection process were resolved through discussion with a third reviewer.

Prevalence of rabbit syndrome

RS is considered to be a rare illness that only affects few individuals in the psychiatric population who use neuroleptics. In 1986, Yassa and Lal conducted a study on the prevalence of RS in the inpatient population of a psychiatric institution. They discovered that 2.3% of the 266 patients receiving older neuroleptics, either alone or in combination with anticholinergic agents, had RS.[4] The prevalence rate of RS in individuals who only use neuroleptic medications was 4.4%.[4] A subsequent investigation into the occurrence of RS among patients receiving neuroleptic treatment in a geriatric mental health clinic reported a prevalence of 1.5%.[5] A relationship between gender, age, and the development of RS is known to exist. The condition is primarily observed in middle-aged and older patients, with women being considered more susceptible to acquiring RS compared to males.^[6,7]

Clinical features of rabbit syndrome

RS primarily develops from prolonged use of older neuroleptic medications. However, recent findings indicate that newer antipsychotics can also contribute to its onset. Several studies have established a link between older antipsychotic drugs and the development of RS. High-potency neuroleptics, such as haloperidol, which have minimal anticholinergic effects, are most commonly associated with induction of RS. The condition is typically observed over an extended period of therapy and is particularly noticeable when using potent medications such as haloperidol, fluphenazine, and pimozide. RS incidence is rare in patients taking drugs such as thiodazine, clozapine, olanzapine, and aripiprazole, as well as in those taking low doses of risperidone. [8]

In RS, oral and masticatory muscle movements are involved, but the tongue is not.^[9] The chewing action

has a resemblance to that of rabbits, which is why it is referred to as "Rabbit Syndrome." RS has distinct characteristics compared to tardive dyskinesia since it is characterized by slower and less consistent motions. [10] RS only affects the buccal region, specifically causing stereotyped involuntary movements. RS presents features characteristic of Parkinson's disease and tardive dyskinesia, as evidenced by studies conducted by Schwartz and Hocherman^[2] and Sovner and Dimascio.^[11] The study conducted by Jus *et al.*^[12] found that the movements characteristic of the RS increase during periods of exhaustion, anxiety, and stressful situations.^[12]

Although the underlying mechanisms remain unclear, the exact pathophysiology of this syndrome is unknown.^[13] RS is caused by a hypercholinergic state that results from the blocking of dopaminergic neuronal activity in the extrapyramidal system.[10] RS may happen because there are more serotonin type 2 and dopaminergic type 2 receptors than usual, and anticholinergic muscarinic receptors are less active. The symptoms of RS closely resemble those of Parkinson's disease, while the cessation of symptoms is comparable to that of tardive dyskinesia. RS may be distinguished from typical oral dyskinesia because it involves slower and less regular movements by the tongue, which can be suppressed by patients voluntarily. RS differs from other forms of oral dyskinesia, such as buccolingual and buccolingual-masticatory syndromes, in that the patient cannot consciously control it.[14]

Risk factors of rabbit syndrome

Prolonged use of neuroleptics can lead to several consequences, particularly in elderly individuals. Polypharmacy, the simultaneous use of multiple medications, is common in such cases. This can involve combinations like two antipsychotic drugs, an antipsychotic with an antidepressant, or an antipsychotic used alongside lithium, as noted by Mendhekar.[15] Stress has the potential to amplify symptoms, and symptoms are frequently magnified by stress and anxiety when engaging in tasks that demand focus and concentration.[16,17] Old age, being female, and having undergone brain injury are risk factors for developing symptoms. First-generation antipsychotics (FGAs) have a greater risk compared to second-generation antipsychotics (SGAs), and risperidone has a higher risk compared to other atypical antipsychotics. [3,17] Levin and Heresco documented the first occurrence of RS caused by risperidone in 1999.[18] This established risperidone as the predominant atypical antipsychotic linked to RS and was confirmed by Catena et al.[8,9] Because some atypical antipsychotics have better serotonin-to-dopamine receptor affinity ratios, they may be linked to a lower incidence of RS. RS is linked to a higher dosage of risperidone.^[15,19]

The patient exhibits particular polymorphisms, such as a diminished metabolization ability by the cytochrome P450 2D6 isoenzyme. According to some researchers, individuals with weak metabolisms may experience more unpleasant responses when the dosage of a substance is increased.[19,20] The underlying reason appears to be an imbalance in the cholinergic and dopaminergic neurotransmission in the basal ganglia; however, the exact mechanism is not yet fully understood.[8,9] Antipsychotics function by inhibiting dopaminergic and 5-HT2 receptor activity, as well as blocking alpha-adrenergic receptors. The inhibition of dopamine receptor activity results in an increase in the cholinergic activity in the basal ganglia.[17] A condition of heightened sensitivity to dopamine, known as dopaminergic hypersensitivity, is marked by reduced activity of the neurotransmitter acetylcholine, a phenomenon known as cholinergic hypofunction. Clinical data confirm this relationship, as evidenced by the positive response of individuals with this condition to anticholinergic medication.^[21]

Differential diagnosis of rabbit syndrome

Although tardive dyskinesia (TD) has been discussed previously in the context of differential diagnosis, it is essential to underscore its distinguishing features. TD is typically marked by irregular, involuntary movements involving the tongue, face, and limbs. In contrast, RS is characterized by rhythmic, vertical movements restricted to the mouth, without tongue involvement. This distinction is critical for ensuring an accurate diagnosis and appropriate treatment approach. Distinguishing between tardive dyskinesia and RS is undoubtedly challenging. Idiopathic oral dyskinesia, Parkinsonism, untreated schizophrenia, and dental dyskinesia can all cause buccal movements that resemble those observed in RS. Patients diagnosed with RS are frequently misidentified as having oral tardive dyskinesia. When dealing with these situations, the crucial factor for making an accurate diagnosis is the presence of tardive tongue movements, which are not present in RS. A simple differentiation between the two conditions may be achieved by instructing the patient to protrude their tongue for approximately 10s. During this stage, people with tardive dyskinesia have tongue-twisting, whereas those with RS have a stationary tongue. The direction of lip movements can distinguish RS. In RS, these movements are limited to the vertical axis, but in tardive dyskinesia, they can occur in any direction. The speed and rhythm of the movements, which are rapid and rhythmic in RS but slower and less consistent in TD, also aid in distinguishing between these conditions. Furthermore, choreoathetotic movements in the face and other body regions are significantly higher in tardive dyskinesia compared to RS.

Ultimately, a patient can have both tardive dyskinesia and RS simultaneously. Idiopathic oral dyskinesia, a condition that occasionally affects older individuals, can be misdiagnosed as RS. In such cases, the irregular and non-rhythmic nature of such movements may help distinguish them from RS. In individuals with schizophrenia, buccal involuntary movements might exist before the initiation of antipsychotic medication, whereas RS is often observed only after exposure to antipsychotics. The incidence rate of lip movements in RS is comparable to that of tremors in Parkinson's disease. Furthermore, individuals diagnosed with RS may have symptoms of Parkinsonism, including muscle stiffness, bradykinesia, slow movement, and reduced facial expression.[22] Casey concluded that RS and drug-induced Parkinsonism are comparable, and both are part of the same pathology, along with idiopathic Parkinson's disease. They are positioned at various locations along the physiological continuum of this disorder.[22] However, it would be erroneous to define RS and Parkinsonism as manifestations of the same condition, given that RS does not exhibit a response to therapy with dopamine agonists.[23]

Long-term outcomes and quality of life of patients with rabbit syndrome

Rabbit syndrome is a rare movement disorder characterized by compulsive, rhythmic mouth movements resembling a rabbit's chewing. It typically occurs as a side effect of prolonged antipsychotic medication use. Because of its social stigma and functional disability, this condition may have a substantial negative influence on one's quality of life. Krishnan et al.[24] carried out a meta-analysis of anticholinergic medications' efficacy in treating RS, concluding that although the illness often resolves with therapy, long-term psychological effects remain possible.[24] Research has demonstrated that treatment compliance and mobility abnormalities like RS may impact the quality of life associated with overall health. [24] Pinto et al. [25] conducted research emphasizing the significance of patient adherence to therapy to optimize long-term results and quality of life, even while dealing with chronic diseases and side effects such as RS.[25] Bonam (2021) provided a thorough analysis of RS, emphasizing the importance of early detection and effective treatment to improve long-term outcomes.^[26] Kaufman *et al*.^[27] examined the safety and long-term effects of rabbit antithymocyte globulin induction in comparison to other treatments. Their findings may have implications for treating RS.^[27] Management of long-term side effects and conditions, such as mobility impairments, is essential for maintaining quality of life on elderly patients after stem cell transplantation.^[28]

Age and gender differences in rabbit syndrome

To effectively identify at-risk groups and adjust treatment strategies, clinicians need a thorough understanding of how age and gender influence RS development and presentation. Research by Fornazzari et al.[29] suggests that RS is more prevalent in middleaged and older patients.[29] This vulnerability may be attributed to prolonged antipsychotic use, agerelated brain changes, and the increased likelihood of polypharmacy, which increases the risk of movement disorders and extrapyramidal side effects (EPS).[30,31] While RS is less common in younger individuals, high dosages or long-term antipsychotic use can increase their risk. Early identification and intervention are vital to preventing chronic conditions in these patients.^[32] Gender differences in RS risk are less well-documented compared to age. Wada^[33] suggested that women might be more prone to RS than men.[33] This could be due to estrogen's influence on dopamine receptor sensitivity and variations in drug metabolism between genders, which may alter drug levels and side effect profiles.[34,35] Despite the potential for gender-related differences, both men and women should be closely monitored, especially if other risk factors are present.^[35]

Rabbit syndrome and stigma

In social settings, individuals with RS may experience significant distress due to their visible motor symptoms. Violating social norms regarding expected motor skills can lead to fears of negative evaluation and emotions such as shame and guilt, often resulting in embarrassment and avoidance behaviors. These emotional responses can exacerbate functional disability, limiting the individual's ability to engage in social and occupational activities.^[36] Self-stigma, which refers to the internalization of negative societal attitudes and stereotypes, is particularly prevalent in neuropsychiatric diseases, including RS. This internalized stigma can have several detrimental consequences.

Social isolation may occur as individuals withdraw from interactions to avoid negative judgments. The fear of stigma can also lead to delayed seeking of medical help, resulting in a progression of symptoms and potentially worse outcomes. Additionally, individuals with RS may

exhibit non-adherence to treatment regimens due to feelings of hopelessness or futility, further complicating their condition. In severe cases, self-stigma can contribute to increased suicide rates as individuals may feel overwhelmed by their symptoms and the perceived lack of societal acceptance.^[37,38] Interestingly, while self-stigma is common in RS, its prevalence tends to decrease as the disease progresses. This decrease may be due to individuals gradually adapting to their condition or the development of coping mechanisms over time. However, depression remains a significant associated risk factor for self-stigma in RS. Addressing depression through targeted interventions could be an effective strategy to mitigate self-stigma and improve overall outcomes for individuals with RS.^[39]

Treatment of rabbit syndrome

The treatment of RS focuses on two main steps. First, the dose of the antipsychotic medication that caused the symptoms should be reduced as high doses can often trigger RS. Second, specific medications are given to help relieve the symptoms and improve the patient's overall condition.^[2] One of the most common treatments for RS involves using anticholinergic drugs. These include medications such as benztropine, biperiden, procyclidine, and trihexyphenidyl. [8,9] These drugs help reduce the involuntary movements caused by RS. However, it is important to note that symptoms often return if the medication is stopped. [14] Research by Durst et al. (2000) showed that switching patients from zuclopenthixol (a typical antipsychotic) to olanzapine (an atypical antipsychotic) effectively managed RS symptoms. The treatment started with a daily dose of 5 mg of olanzapine, which was later increased to 10 mg. This adjustment not only helped control RS symptoms but also improved the patients' psychotic symptoms. In some cases, anticholinergic medications are not effective. For example, when RS is caused by risperidone. switching to a different antipsychotic like quetiapine can help.[40] Altindag and Yanik (2005) found that starting quetiapine at 100 mg per day and gradually increasing the dose to 700 mg over 4 weeks significantly improved RS symptoms.^[41] Tarsy, Baldessarini, and Tarazi (2002) suggest that medications with strong anticholinergic effects, like clozapine and olanzapine, may be the most effective treatment options for managing RS.[42] These drugs not only help control the movement disorder but also address the underlying psychotic symptoms, making them a suitable choice for many patients.

Study limitations

This narrative mini-review is subject to potential selection bias and may not comprehensively capture all relevant studies due to its non-systematic approach.

Moreover, available evidence on Rabbit Syndrome is largely limited to case reports and small series, which restricts the generalizability and strength of the conclusions. As such, insights into pathophysiology and management should be interpreted with caution and revisited as more robust data emerge.

CONCLUSION

RS remains a significant, though rare, extrapyramidal side effect that is mostly linked to the prolonged use of potent neuroleptic drugs. This disorder is characterized by rapid and rhythmic perioral movements around the mouth, distinct from other dyskinesias. It mainly affects women who are middle-aged or older. Despite the advancements in antipsychotic treatments, the use of secondgeneration antipsychotics has resulted in a lower incidence of adverse effects. However, the concern about RS persists, particularly with medications like risperidone. Effective management of RS requires a meticulous equilibrium between decreasing the amount of neuroleptic drugs that cause the condition and administering anticholinergic medicines. Atypical antipsychotics such as olanzapine and quetiapine have demonstrated potential for relieving symptoms. Further study is crucial to better understand the exact processes behind RS and to create specific treatments that reduce its recurrence, while effectively controlling the fundamental psychiatric illnesses for which neuroleptics are prescribed.

Informed consent

This is not required for a narrative review as the study did not include any data primarily collected by the authors.

Declaration of Helsinki

The study was conducted according to the ethical principles of the Helsinki Declaration.

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Not applicable.

Author contributions

FAP, AA, AURG, and PS were involved in the conceptualization, design of the study, and definition of intellectual content. FAP, AA, AURG, and PS were involved in data collection/ acquisition. All authors were involved in data/statistical analysis and interpretation of the data. All authors were involved in the writing and revision of the manuscript for intellectual content. All authors were also involved in the manuscript review and agreed to be accountable for all aspects of the work.

Data availability

Authors are available and are ready to supply the data upon request through the corresponding author.

Ethical policy and Institutional Review Board statement

This is not required for a review article as study did not include any data primarily collected by the authors.

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Conflicts of interest

There are no conflicts of interest.

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