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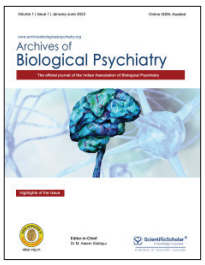

Case Report *Psychiatry*

Low-dose amisulpride causing extrapyramidal symptoms in Hashimoto's thyroiditis patient: A case report

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ABSTRACT

Amisulpride, an atypical antipsychotic, is characterized by a lower likelihood of causing extrapyramidal side effects and greater effectiveness in managing negative symptoms compared to traditional neuroleptics. A rare instance of extrapyramidal symptoms (EPSs) observed at a low dose of amisulpride in a patient treated for schizophrenia, who was later diagnosed with Hashimoto's thyroiditis (HT), is highlighted in this case report. The patient was initially maintained well on amisulpride, but compliance issues arose. When we restarted amisulpride on an inpatient basis at Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, we observed the re-emergence of EPSs. These symptoms resolved after discontinuing amisulpride and adding promethazine, trihexyphenidyl, and propranolol within 2 days. This case suggests the need for further research into amisulpride's side effects, particularly in patients with HT and the Indian population.

Keywords: Amisulpride, Atypical antipsychotic, Extrapyramidal symptoms, Hashimoto's thyroiditis, Titubation

INTRODUCTION

Antipsychotics are well-established in the treatment of schizophrenia; however, their use is associated with potential adverse effects, including drug-induced movement disorders such as extrapyramidal symptoms (EPS).[1] Careful assessment and monitoring of these side effects are essential to optimize treatment outcomes and minimize the risk of misdiagnosing EPS as worsening psychotic symptoms.

While antipsychotics play a crucial role in managing schizophrenia, drug-induced movement disorders can significantly impact cognitive function and social rehabilitation. EPS is frequently mistaken for symptoms of psychotic illness. For example, bradykinesia and facial masking may be misinterpreted as blunted affect and motor retardation, whereas akathisia can resemble agitation, anxiety, or insomnia. Similarly, dystonias and dyskinesias are often confused with schizophrenic mannerisms and motor disturbances.[2]

Amisulpride, an atypical antipsychotic, is distinguished by its high selectivity for dopamine D2-like receptors (Ki = 2.8 nmol/L for D2 and Ki = 3.2 nmol/L for D3), binding with significantly higher affinity to these receptors than to any other receptor subtype.[3] Unlike many other atypical antipsychotics, amisulpride does not exhibit significant binding to 5-HT2A receptors, as confirmed by positron emission tomography studies. Its efficacy in treating schizophrenia has

been demonstrated in clinical trials, with a side-effect profile reported to be comparable to that of placebo.[4]

Due to its receptor selectivity, amisulpride is considered particularly suitable for investigating whether effective antipsychotic treatment with minimal EPS can be achieved through selective action at limbic and cortical dopamine D2/D3 receptors.[5,6] It acts presynaptically in the frontal cortex, potentially enhancing dopaminergic transmission, and postsynaptically in the limbic system, possibly reducing excessive dopaminergic activity. This dual mechanism is thought to contribute to its efficacy in alleviating both positive and negative symptoms of schizophrenia.[7] In addition, amisulpride has been identified as a potent 5-HT7 receptor antagonist, suggesting a unique antidepressant action distinct from other antipsychotics.[8]

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disorder, characterized by chronic thyroid inflammation that can lead to hypothyroidism in 20–30% of affected individuals.[9] Thyroid dysfunction has been implicated in various neuropsychiatric conditions, and the interplay between thyroid autoimmunity and antipsychotic treatment warrants further investigation.

This case report highlights an uncommon presentation of EPS induced by low-dose amisulpride in a patient with schizophrenia and comorbid HT. Given amisulpride's generally favorable EPS profile, this case underscores the need for further research into its side effects, particularly in patients with thyroid dysfunction and within the Indian population.

CASE REPORT

A 37-year-old female with a known history of catatonic schizophrenia (symptoms of catatonia and suspiciousness and total duration of illness is 1.5 years with no thyroid abnormality) had been well-maintained (no residual symptoms with no history of EPS associated with amisulpride) on amisulpride 200 mg from December 2023 to April 2024 but discontinued her medication for 3 months due to non-compliance due to financial issue. She was brought to Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, by her husband in August 2024 with chief complaints of crying spells, maintaining a fixed position for long periods, not following commands, exhibiting a blank stare, not eating food, and poor self-care for 3–4 days. On psychiatric examination, her Bush-Francis Catatonia Rating Scale (BFCRS) score was 22/69, leading to a diagnosis of catatonia. After treating catatonia with lorazepam over 2 days of inpatient care (BFCRS score reduced to 0 and also maintained at 0 in subsequent days), then amisulpride was restarted at 50 mg once daily and gradually titrated up to 200 mg/day in the next 7 days (25–50 mg increment/2 days). Three days after starting amisulpride 200 mg/day, tremors in her hand and head nodding (Titubation) were observed, which worsened with tongue protrusion. The abnormal involuntary movement scale (AIMS)[10] scale was used to assess these symptoms, and the score was 14 (from items 1 to 7). We discontinued amisulpride and initiated injection of promethazine, tablet trihexyphenidyl, and propranolol, which led to an improvement in the symptoms within 2 days, and the score of AIMS reduced to 2.

Routine investigations revealed elevated serum thyroid-stimulating hormone with normal T3 and T4 levels. Further investigations showed raised anti-thyroid peroxidase antibodies, confirming HT. Levothyroxine 25 μg was initiated. Clinically, there were no signs and symptoms of hypothyroidism present.

Physical examination

After 3 days of starting amisulpride, the patient's temperature, pulse, and blood pressure were normal. The patient was fully conscious and oriented to time, place, and person. Neck stiffness and myoclonus were not present. The abdomen, respiratory, and cardiovascular systems were normal. Central nervous system (CNS) examination showed bilateral pupil normal reactive to light, all cranial nerves were normal, deep tendon reflexes biceps, triceps, supinator, and knee reflexes were normally present, sensory and cortical function were intact, no signs of meningeal irritation, and Romberg test was negative; however, on stretching his arms, rhythmic, 7–8 Hz hand tremor was noted bilaterally upper extremities which were resting tremors and moderate in severity and she has titubation which was increasing on protrusion of tongue.

DISCUSSION

Amisulpride is a substituted benzamide with high selectivity for D2/D3 receptors. Its atypical profile is attributed to its preferential action in limbic structures rather than the striatum, reducing EPS risk. However, at low doses, significant D2 receptor blockade in the striatum may still occur, potentially leading to EPS.[3] This raises the question of whether HT may predispose individuals to increased EPS susceptibility with amisulpride.

Recent studies suggest that HT, an autoimmune disorder affecting the thyroid gland, has potential implications for neurodegenerative conditions, including Parkinson's disease.[11] Hashimoto's encephalitis, an autoimmune manifestation of HT, has been associated with movement disorders, cognitive impairments, and neuroinflammation.[12] Studies using 123I-ioflupane single-photon emission computed tomography imaging have shown that treatment of Hashimoto's encephalitis improves dopamine transporter

binding, highlighting the role of thyroid-related autoimmunity in dopaminergic dysfunction.[13]

Autoimmune mechanisms in HT may contribute to neuroinflammation and an increased risk of EPS. Proinflammatory cytokines such as interleukin-1, interleukin-2, interleukin-6, and tumor necrosis factor, along with autoreactive antibodies, have been implicated in the pathogenesis of Parkinsonian features in HT patients.[14] Furthermore, a nationwide epidemiological study from Sweden demonstrated a higher prevalence of Parkinson's disease in individuals with HT.[15] Given that movement disorders are common in CNS autoimmune conditions, it is plausible that HT may predispose patients to EPS when treated with dopamine-blocking agents like amisulpride.

Potential explanations for EPS with low-dose amisulpride:

- At low doses, amisulpride significantly blocks postsynaptic D2 receptors in the striatum while minimally affecting the mesolimbic pathway (Schoemaker *et al*., 1997).[3]
- The relationship between HT and increased EPS susceptibility requires further investigation.

A study by Mandal *et al*.[16] reported three cases of extrapyramidal side effects occurring at low doses of amisulpride, including Parkinsonian symptoms, akathisia, and acute dystonia. Similar to our case, their findings suggest that EPS can emerge at doses lower than previously considered risk-inducing (>400 mg/day). However, unlike our patients, these cases did not have underlying thyroid dysfunction. This suggests that HT may be an additional risk factor, potentially enhancing susceptibility to EPS through mechanisms such as neuroinflammation and altered dopamine regulation.

CONCLUSION

This case report highlights the occurrence of EPS at low doses of amisulpride in a patient with HT. While amisulpride is considered to have a lower risk of EPS, our observations suggest that underlying thyroid dysfunction may enhance susceptibility.

- This observation contradicts findings from Western studies reporting a lower incidence of EPS with Amisulpride.
- Clinicians should be aware of the potential for EPS, even at low doses, particularly in patients with autoimmune thyroid disorders.
- Further research is required to explore the association between HT and antipsychotic-induced EPS, particularly in the Indian population.

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