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Paliperidone Induced Hypothyroidism: A Case Report

By Mohammed A. Mohammed, Abdullah Almarzogi, Anas Ibn Auf

ABSTRACT *~ The relationship between antipsychotic medications and thyroid dysfunction has been highlighted in various studies and case reports, particularly concerning subclinical hypothyroidism. This report presents the case of a 31-year-old male patient diagnosed with schizophrenia who received short-term treatment with paliperidone. Routine follow-up assessments revealed significant changes in thyroid function, including marked elevation in thyroid-stimulating hormone (TSH) levels and a slight decrease in free thyroxine (FT4) levels. These alterations were associated with ongoing paliperidone use, suggesting a potential link to hypothyroidism. The findings underscore the importance of continuous thyroid function monitoring in patients prescribed paliperidone to identify potential side effects and ensure comprehensive management of both psychiatric and endocrine health. This case emphasizes the need for increased awareness among healthcare providers regarding the endocrine effects of antipsychotic medications, particularly second-generation agents like paliperidone, to facilitate early detection and timely intervention, ultimately improving patient outcomes.* Psychopharmacology Bulletin. *2025;55(2):104–109.*

Introduction

Mental disorders such as schizophrenia are often associated with a range of metabolic and endocrine disturbances, which can be exacerbated by the medications used in their treatment.[1,2] One recognized but relatively uncommon side effect of antipsychotic therapy is drug-induced hypothyroidism, particularly with second-generation antipsychotics.[3] These medications, including olanzapine, quetiapine, and risperidone, have been shown to affect thyroid function, potentially leading to subclinical or overt hypothyroidism in some patients.[4–6]

Paliperidone, the active metabolite of risperidone, shares many of the same receptor-binding properties and pharmacological actions. Despite the well-documented side effects of paliperidone, including hyperprolactinemia and metabolic disturbances, its impact on thyroid function has not been widely reported.[7] In this case report, we present a patient who developed thyroid

Mohammed, Almarzogi, Erada and mental health complex, Taif, Saudi Arabia. Auf, Erada and mental health complex, Taif, Saudi Arabia; Department of Psychiatry, Eastern Sudan College for Medical Sciences and Technology, Port Sudan, Sudan.

To whom correspondence should be addressed: Anas Ibn Auf, Erada and mental health complex, Taif, Saudi Arabia; Department of Psychiatry, Eastern Sudan College for Medical Sciences and Technology, Port Sudan, Sudan. E-mail: anasibnauf@hotmail.com

dysfunction following paliperidone use, an association that has not been thoroughly documented in the literature. This underscores the potential for paliperidone, like other second-generation antipsychotics, to disrupt thyroid regulation, highlighting the importance of routine thyroid function monitoring in patients undergoing treatment with this drug.

Case Presentation

A 31-year-old male with a 10-year history of schizophrenia had been stable for several years on aripiprazole, attending regular follow-ups at an outpatient clinic. However, he recently began experiencing psychological distress due to psychosocial stressors and expressed dissatisfaction with aripiprazole. After a comprehensive review of his physical health and lab investigations (Table 1), aripiprazole was replaced with paliperidone.

TABLE 1

Lab Results Before Prescribing Paliperidone At The Outpatient Clinic

TEST NAME	RESULT	COMMENT	NORMAL RANGE	UNIT
TSH3	1.81	NORMAL	[0.27–4.2]	u IU/ml
FT3	4.77	NORMAL	[3.1–6.8]	pmol/L
FT4 FREE THYROXINE	17.81	NORMAL	[12–22]	pmol/L
Serum Prolactin	33.39	LOW	[86–324]	mu/L
WBC	8.48	NORMAL	[3.5–10]	$X10^3$/uL
NEU	4.82	NORMAL	[1.63–6.96]	$X10^3$/uL
LYM	2.74	NORMAL	[1.09–2.99]	$X10^3$/uL
MONO	0.711	NORMAL	[0.24–0.79]	$X10^3$/uL
EOS	0.154	NORMAL	[0.03–0.44]	$X10^3$/uL
BASO COUNT	0.063	NORMAL	[0–0.08]	$X10^3$/uL
RBC	5.39	NORMAL	[3.5–6.5]	$X10^6$/uL
HGB	15.8	NORMAL	[12–18]	g/dl
HCT	47.7	NORMAL	[35–52]	%
MCV	88.4	NORMAL	[84–96]	FL
MCH	29.3	NORMAL	[28–34]	pg
MCHC	33.2	NORMAL	[32–36]	g/dl
PLT	280	NORMAL	[150–450]	$X10^3$/uL
BUN	2.6	NORMAL	[2.7–8.1]	mmol/L
CREA	79	NORMAL	[44–106]	umol/l
CHOL	4.29	NORMAL	[0–5.2]	mmol/L
TRIG	1.5	NORMAL	[0.1–1.7]	mmol/L
HDL	98	NORMAL	[0.9–1.55]	mmol/L
ALP	105	NORMAL	[35–129]	U/L
ALT	61.4	HIGH	[5–41]	U/L
ALB	42.3	NORMAL	[35–50]	g/L
AST	35	NORMAL	[5–40]	U/L
BILIRUBIN DIRECT	2.9	NORMAL	[0.1–3.4]	umol/l
BILIRUBIN TOTAL	5.8	NORMAL	[0.1–21]	umol/l
GGT	37	NORMAL	[5–61]	U/L

Over the next two months, the patient showed some improvement but continued to exhibit persistent psychotic symptoms. As a result, his paliperidone dose was increased to the maximum allowable limit, i.e. 12 mg per day, and he was subsequently switched to the long-acting injectable formulation due to concerns about treatment adherence. Despite these interventions, the patient was brought to the emergency room by his family due to increasing irritability, aggression, and self-directed talking. He had no history of substance use and was a non-smoker.

On mental status examination, the patient appeared agitated and provided some irrelevant answers. His mood was irritable, and he exhibited delusions of persecution, reference, and infidelity. He also reported suicidal ideation. Although he denied experiencing auditory hallucinations, his behavior was suggestive of a hallucinatory state. Insight and judgment were both impaired. Consequently, the patient was admitted to the hospital for further management.

On physical examination, the patient's vital signs were stable, and no abnormalities were detected. Laboratory investigations was done on admission and revealed subclinical hypothyroidism, with an elevated thyroid-stimulating hormone (TSH) level of 7.11 uIU/mL and a slightly decreased free thyroxine (FT4) level of 11.88 pmol/L. Prolactin was mildly elevated at 374.2 mU/L (Table 2). Once the results were obtained upon admission and considering the insufficient control of his psychiatric symptoms, paliperidone was discontinued, and aripiprazole was promptly reintroduced based on its prior efficacy in this patient.

During his hospital stay, the patient responded well to aripiprazole at dosage of 30 mg per day, with a gradual improvement in his psychotic features. Interestingly, one month after his admission and the discontinuation of paliperidone, his thyroid function normalized (TSH = 1.21 uIU/mL, FT3 = 5.63 pmol/L).

Discussion

Antipsychotics, particularly second-generation (atypical) antipsychotics, are widely used in the treatment of schizophrenia and other psychotic disorders. Although they are associated with fewer motor side effects compared to first-generation antipsychotics, they still pose certain risks, including metabolic and endocrine dysfunctions, which can affect the thyroid. The thyroid gland plays a crucial role in regulating metabolism, and its dysfunction, particularly hypothyroidism, can significantly impact a patient's mental and physical health, potentially complicating the management of psychiatric disorders.[3]

The patient described here developed subclinical hypothyroidism, characterized by elevated thyroid-stimulating hormone (TSH) and

TABLE 2

Lab Results On Hospital Admission After Receiving Paliperidone For 3 Months

TEST NAME	RESULT	COMMENT	NORMAL RANGE	UNIT
TSH3	7.11	HIGH	[0.27–4.2]	u IU/ml
FT3	4.22	NORMAL	[3.1–6.8]	pmol/L
FT4 FREE THYROXINE	11.88	LOW	[12–22]	pmol/L
Serum Prolactin	374.2	HIGH	[86–324]	mu/L
WBC	5.91	NORMAL	[3.5–10]	$X10^3$/uL
NEU	4.07	NORMAL	[1.63–6.96]	$X10^3$/uL
LYM	1.37	NORMAL	[1.09–2.99]	$X10^3$/uL
MONO	0.377	NORMAL	[0.24–0.79]	$X10^3$/uL
EOS	0.049	NORMAL	[0.03–0.44]	$X10^3$/uL
BASO COUNT	0.045	NORMAL	[0–0.08]	$X10^3$/uL
RBC	5.58	NORMAL	[3.5–6.5]	$X10^6$/uL
HGB	16	NORMAL	[12–18]	g/dl
HCT	47	NORMAL	[35–52]	%
MCV	84.2	NORMAL	[84–96]	FL
MCH	28.7	NORMAL	[28–34]	pg
MCHC	34	NORMAL	[32–36]	g/dl
PLT	194	NORMAL	[150–450]	$X10^3$/uL
BUN	4.8	NORMAL	[2.7–8.1]	mmol/L
CREA	87	NORMAL	[44–106]	umol/l
CHOL	4.54	NORMAL	[0–5.2]	mmol/L
TRIG	0.93	NORMAL	[0.1–1.7]	mmol/L
HDL	1.2	NORMAL	[.9–1.55]	mmol/L
ALP	100	NORMAL	[35–129]	U/L
ALT	33.4	NORMAL	[5–41]	U/L
ALB	41.9	NORMAL	[35–50]	g/L
AST	25.4	NORMAL	[5–40]	U/L
BILIRUBIN DIRECT	3	NORMAL	[0.1–3.4]	umol/l
BILIRUBIN TOTAL	9.7	NORMAL	[0.1–21]	umol/l
GGT	29	NORMAL	[5–61]	U/L

slightly decreased free thyroxine (FT4) levels, during treatment with paliperidone. Subclinical hypothyroidism is typically asymptomatic but can progress to overt hypothyroidism, especially in individuals with underlying thyroid vulnerabilities.[7] The patient's thyroid function normalized after discontinuing paliperidone, suggesting that this drug was a contributing factor to his thyroid dysfunction.

Paliperidone, the active metabolite of risperidone, is a second-generation antipsychotic that shares many of the same receptor-binding properties as its parent drug. Although hyperprolactinemia is a well-established side effect of risperidone and paliperidone due to dopamine D2 receptor blockade in the tuberoinfundibular pathway, thyroid abnormalities are less commonly reported.[1] However, emerging evidence suggests that antipsychotics like paliperidone can affect

the hypothalamic-pituitary-thyroid (HPT) axis, potentially leading to elevated TSH levels and subclinical hypothyroidism.[8]

Several studies and case reports have explored the relationship between antipsychotics and thyroid dysfunction, particularly subclinical hypothyroidism. A 2003 case report documented a patient who developed subclinical hypothyroidism while being treated with risperidone. The patient's TSH levels normalized after discontinuation of the drug, indicating a direct link between risperidone and thyroid dysfunction.[9] Another case noted that risperidone caused overt hypothyroidism, which required thyroid hormone replacement.[4] Although primarily associated with metabolic syndrome, olanzapine has also been linked to thyroid dysfunction. In one study, olanzapine was associated with a small but significant increase in TSH levels in some patients, although this effect was less pronounced than with risperidone or paliperidone.[8] Quetiapine, generally considered to have a lower risk of endocrine side effects, has also been reported to increase TSH levels with long-term use. One study suggested that quetiapine might induce thyroid dysfunction in a subset of patients, though more research is needed.[3] Regarding paliperidone, very few cases have been reported with paliperidone but its similarity to risperidone suggests a comparable risk of thyroid dysfunction. In a clinical study, mild but significant elevations in TSH were observed in patients taking paliperidone compared to those on other antipsychotics.[8]

The thyroid abnormalities seen with antipsychotic use, particularly second-generation agents, may arise from several mechanisms; one of them is Dopamine Receptor Blockade. Dopamine inhibits the secretion of TSH from the anterior pituitary gland. Antipsychotics, particularly those with strong D2 antagonism like risperidone and paliperidone, may reduce the inhibitory effects of dopamine on TSH release, leading to elevated TSH and, in some cases, hypothyroidism.[1]

Another mechanism that may contribute to thyroid abnormalities is Serotonin Pathway Alteration. Second-generation antipsychotics also affect serotonin receptors, particularly 5-HT2A, which are involved in regulating the HPT axis. Alterations in serotonin levels may also contribute to thyroid dysfunction.[4] Hyperprolactinemia, a common side effect of many antipsychotics, has also been associated with thyroid dysfunction. Elevated prolactin levels can affect the release of gonadotropins, which in turn may influence thyroid hormone regulation.[1]

Given the potential for thyroid dysfunction, particularly subclinical hypothyroidism, in patients taking antipsychotics including paliperidone, regular monitoring of thyroid function is essential. Baseline assessments of TSH and FT4 should be performed before initiating antipsychotic therapy, followed by periodic monitoring, especially in patients receiving

drugs like risperidone or paliperidone, which have been associated with thyroid abnormalities.[7] If thyroid dysfunction is detected, discontinuation of the offending agent or switching to an antipsychotic with a lower risk profile (such as aripiprazole) should be considered, particularly if thyroid function does not improve spontaneously.

Conclusion

This case highlights the potential for paliperidone to induce subclinical hypothyroidism, a rare but clinically significant side effect of antipsychotic therapy. While the exact mechanisms remain under investigation, evidence suggests that alterations in dopamine and serotonin pathways, as well as hyperprolactinemia, may play a role. Clinicians should be aware of this risk and monitor thyroid function in patients receiving antipsychotics, particularly second-generation agents like paliperidone and risperidone, to prevent long-term complications and optimize both psychiatric and physical health outcomes. It is recommended to conduct longitudinal studies to further assess the impact of paliperidone on thyroid function over time, particularly in diverse populations. ✤

References

1. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs*. 2004;64(20):2291–2314.
2. Misiak B, Stańczykiewicz B, Wiśniewski M, Bartoli F, Carra G, Cavaleri D, et al. Thyroid hormones in persons with schizophrenia: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;111:110402.
3. Kelly DL, Conley RR. Thyroid function in clinical trials with second-generation antipsychotics. *Schizophr Res*. 2006;83(2–3):201–2.
4. Haupt DW, Newcomer JW. Hyperprolactinemia with atypical antipsychotics: biology and management. *Harv Rev Psychiatry*. 2001;9(3):163–172.
5. Shaddel F, Lockstone M. Thyroid dysfunction in Down's syndrome secondary to risperidone. *Prog Neurol Psychiatry*. 2022;26(4):19–21.
6. Kumar YS, Garla VV. Subclinical Hypothyroidism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
7. Shoja Shafti S, Shahveisi B. Subclinical hypothyroidism in schizophrenic patients receiving atypical antipsychotics. *Ther Adv Psychopharmacol*. 2010;3(4):221–9.
8. Hagg S, Spigset O, Mjörndal T. Effect of antipsychotic drugs on thyroid function in patients with schizophrenia. *Neuropsychopharmacology*. 2001;24(3):354–363.
9. Yolken RH, Torrey EF. Infectious agents and schizophrenia: a developmental perspective. *Schizophr Bull*. 2008;34(6):1074–80.