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CASE REPORT

A case of mood disorder with severe side effects of antidepressants in association with resistance to thyroid hormone beta with a THRB mutation

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Abstract

Background: Although resistance to thyroid hormone beta (RTHβ) is associated with attention-deficit/hyperactivity disorder, there are few reports of other concomitant mood disorders in individuals with RTHβ.

Case presentation: A 67-year-old woman who had been previously diagnosed with RTHβ (Refetoff syndrome) came to our department as a depressed patient. She was hospitalized twice for depression and treated with antidepressants both times. Paroxetine (37.5 mg/day) treatment during the first hospitalization did not cause any side effects, but treatment with mirtazapine (15 mg/day) and venlafaxine (150 mg/day) during the second hospitalization caused clonus and disturbance of consciousness, and these adverse effects resulted in a prolonged period of hospitalization. Finally, the patient's symptoms were controlled with quetiapine (75 mg/day).

Conclusion: Poor tolerability to antidepressants was observed, which may be related to thyroid hormone intolerance. Low doses of quetiapine may contribute to improvements in depression.

KEYWORDS
antidepressants, depression, Refetoff syndrome, RTHβ, side effects

1 | INTRODUCTION

Psychiatric disorders are highly integrated with thyroid disorders; T3 is closely related to depression and anxiety because of its ability to regulate serotonin and noradrenaline.[1] It is also known that psychiatric symptoms often persist after thyroid function is normalized by treatment.[1] In addition, previous studies have shown that bipolar disorder is closely related to thyroid dysfunction. Psychiatric medications can affect thyroid function to a greater or lesser extent, and thyroid hormone (TH) levels can also affect the effectiveness of medications,[2] while thyroid autoimmunity has been suggested to be an independent risk factor for mood disorders.[3]

Thyroid hormone resistance (RTH) is a clinical syndrome defined by decreased sensitivity to TH, commonly caused by mutations in the thyroid hormone receptor beta (RTHβ) gene, and referred to as RTH beta or Refetoff syndrome.[4] The exact incidence of RTHβ is unknown because RTHβ is rarely detected by routine thyroid-stimulating hormone (TSH)-based newborn screening programs, but

the incidence of RTHβ was estimated to be one case per 40000 live births.[5] The two most common clinical features of RTHβ are goiter and palpitations.[5]

Although attention-deficit/hyperactivity disorder (ADHD) is known as a psychiatric symptom associated with RTHβ,[4] there are few reports of concomitant mood disorders. In this study, we report a patient with RTHβ, i.e., Refetoff syndrome, and a mood disorder with extremely poor tolerance of specific antidepressants.

2 | CASE PRESENTATION

We encountered a 67-year-old woman who had previously been diagnosed with RTHβ (Refetoff syndrome) and came to our department as a depressed patient with depressed mood, decreased interest and pleasure, decreased appetite, and hypochondria. Thirteen years ago, her eldest son and daughter were diagnosed with schizophrenia, which made her worry about the future of her children, and insomnia began to appear. After that, she gradually developed palpitations, respiratory distress, and tremors in her arms and legs, and she visited a local doctor, who suspected depression and prescribed antidepressants, because nausea was experienced as a side effect, she immediately stopped taking the antidepressants. She was hospitalized for a short period of time for further investigation about palpitations, although no abnormalities were identified. Six years ago, she was transferred to the Department of Endocrinology and Metabolism at our hospital for a thorough examination because she was suspected to have inappropriate TSH secretion syndrome at another hospital. She was diagnosed with the TRβ gene abnormality RTHβ (Refetoff syndrome). Genetic testing showed that she was heterozygous for R383H in the RTHβ gene by direct sequencing. Her son did not have any thyroid dysfunction or genetic abnormalities. Palpitations frequently occurred, and the dose of atenolol, a beta-blocker, was adjusted to 50 mg/day, then palpitations disappeared. A year ago, because she had palpitations, insomnia, and numbness in her hands and feet again, accompanied by depressed mood, decreased interest and pleasure, decreased appetite, and hypochondria, she was referred to our department. She was diagnosed with suspected depression due to TH insensitivity and was admitted to our department on the same day because her anxiety and irritability were marked, and her depressive symptoms worsened. The clinical course of this case is shown in Figure 1. The Hamilton Rating Scale for Depression (HAM-D) score at the time of admission was 25 points. Her height was 148.4 cm, weight was 52.5 kg, blood pressure was 139/90 mmHg, electrocardiogram (ECG) showed sinus rhythm, and heart rate was 48 beats per minute. Liver function, renal function, and blood count were normal: BUN, 17.0 mg/dL; Glu, 105 mg/dL; HbA1c, 5.8%; FT3, 4.14 pg/mL (normal range 2.13–4.07); FT4, 1.6 ng/mL (normal range 0.95–1.74); TSH, 1.544 μIU/mL (normal range 0.61–4.23); and TRAb, 0.50 IU/L or less (normal range 1.30 or less). The dosage of the beta-blocker atenolol was reduced from 50 mg/day to 25 mg/day because of bradycardia on ECG examination. Regarding mood symptoms, the risk of drug-related side effects was considered based on the patient's medical history, and the patient was switched to paroxetine CR tablets, which were slowly titrated up to 37.5 mg/day, with no worsening of psychiatric symptoms. The patient's symptoms stabilized, and she was discharged home after 1 month. The HAM-D score at the time of admission was 2 points. Immediately after discharge from the hospital, the patient had been calm, but 3 months later, she had started to wake up in the middle of the night to cook and became more active late at night. The dosage of the paroxetine CR tablets was tapered down to 12.5 mg/day due to concerns about activation. Then, the midnight activity temporarily decreased, but after 5 months, the midnight hyperactivity started to increase again, and at the same time, anxiety and agitation were observed. Twelve months later, she was admitted to our department. Her HAM-D score was 23 points at admission. Her blood pressure was 164/106 mmHg, ECG showed sinus rhythm, and heart rate was 48 beats per minute. Liver function, renal function, and blood count were normal: BUN, 20.2 mg/

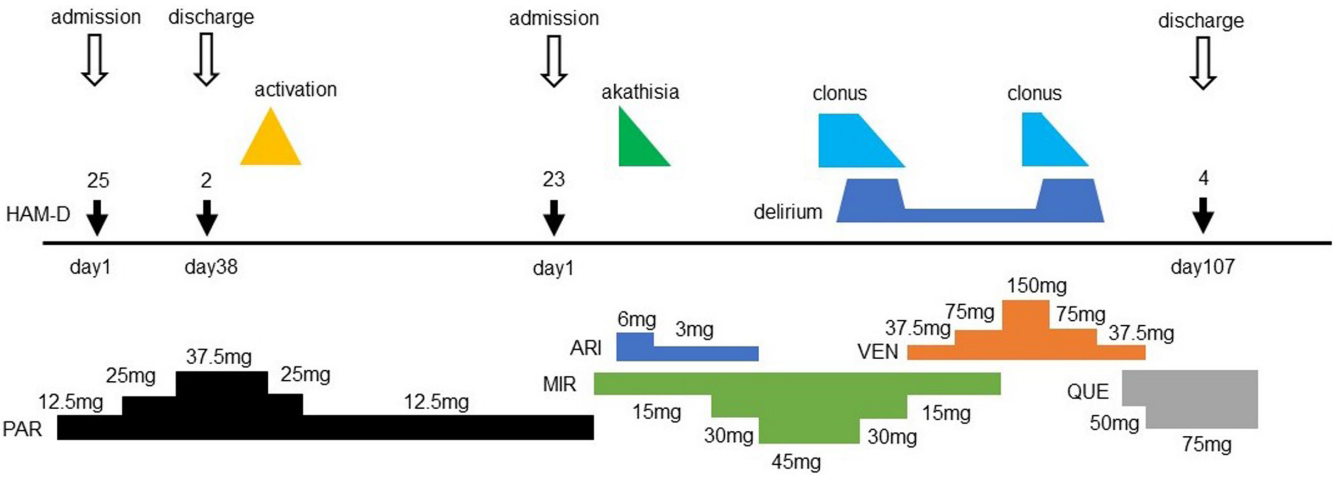

FIGURE 1 Clinical course of this patients including HAM-D score, medication, and adverse clinical symptoms

dL; Glu, 134 mg/dL; HbA1c, 6.1%; FT3, 4.35 pg/mL; FT4, 1.6 ng/mL; TSH, 1.793 μIU/mL; and TRAb, less than 0.50 IU/L. After admission, the patient was prescribed paroxetine CR (12.5 mg) in the outpatient clinic until the 7th sick day. At the treatment policy decision meeting, it was decided that the current condition was to be considered depressive mood disorder, and that the patient should be treated with antidepressant medication. Mirtazapine was started at 15 mg/day. Aripiprazole (6 mg/day) was additionally given, but the patient also had a strong feeling of discomfort in the legs, and anxiety and agitation. These symptoms were determined to be aripiprazole-induced akathisia, and aripiprazole was discontinued. When the dose of mirtazapine was increased to 30 mg/day, mild sustained clonus and rigidity of the upper and lower limbs and disturbance of consciousness were observed, and the patient was judged to have delirium. Therefore, the medication for the patient was changed from mirtazapine to venlafaxine on the 34th day of hospitalization. However, when the dose of venlafaxine was increased to 150 mg/day, strong clonus of the upper and lower limbs and disturbance of consciousness were observed again, and the medication was changed from venlafaxine to quetiapine (50 mg/day). The dosage was increased to 75 mg/day quetiapine, and the mental symptoms gradually stabilized. The patient was discharged home on the 108th day of hospitalization. The HAM-D score at this time was 4 points.

3 | DISCUSSION

This is the first report of a mood disorder patient with RTHβ who had severe side effects of antidepressants. The characteristic feature in this case was that the patient repeatedly developed serotonin syndrome-like symptoms[6] when antidepressants involving serotonin and noradrenaline were administered. On the other hand, the pathogenesis of the clouding of consciousness and clonus is caused by the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine and serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine, but not by the selective serotonin reuptake inhibitor (SSRI) paroxetine during the first admission to our hospital is unknown. Although the details of these phenomena are unknown, they may be related to the pathology of thyroid hormone refractoriness. Finally, depression was improved with quetiapine. Quetiapine has been reported to show efficacy in bipolar depression and has been included in several guidelines.[7–10] Although this patient did not have an obvious manic state, there may have been the pathophysiology of latent bipolar disorder.

The patient had palpitations and irritability associated with tachycardia and depressive symptoms that interfered with daily life, which was judged to be moderate. The most common mental disorders associated with thyroid hormone resistance are ADHD and mental retardation,[4] but in this case, depressive symptoms were present. The possibility that thyroid hormone resistance affects thyroid function and causes depressive symptoms cannot be completely ruled out and led to this diagnosis. Serum-free T4 levels were within the reference range in the present case, although serum-free T4 levels were reportedly elevated in most previous cases of RTHβ.[4] The high serum-free T4 level may have masked the onset of depression, which is the reason for the few reports of mood disorders. The serum-free T4 level in the present case may have resulted in low thyroid function and concomitant depression.

Although treatment of the underlying psychiatric condition may improve psychiatric symptoms in patients with underlying psychiatric disorders, symptomatic treatment of thyroid hormone refractoriness is currently the only treatment available and is difficult to fundamentally treat. Goiter, hyperactivity, and mental "fogginess" are clinical features that can be addressed with appropriate administration of liothyronine (T3) (L-T3) without the side effects of excess TH.[4]

The mildness of mood fluctuations in bipolar disorder (BD) patients seems to correlate with the TSH response to TSH-releasing hormone (TRH) stimulation. Increasing severity of mood symptoms appears to be associated with a decreased TSH response.[11] Thus, changes in thyroid function may cause fluctuations in BD patients. There are two case reports.[4,12] In the case of a 26-year-old man, he was attempted to target depressive symptoms without antidepressant pharmacotherapy, and his mood symptoms gradually improved.[4] A 39-year-old woman with a severe chronic mood disorder refractory to antidepressant therapy who had been previously treated with electroconvulsive therapy showed marked improvement after self-prescribing high-dose L-T3.[12] Therefore, high doses of T3 may contribute to improvements in depression with RTHβ.

ADHD has been reported in 48–83% of individuals with RTHβ and is treated with conventional medications. In the absence of such medications, treatment with L-T3 was found to be effective in reducing impulsivity in 5 of 8 and hyperactivity in 4 of 7 people with both RTHβ and ADHD but not in those with ADHD alone.[13] Bidaily administration of L-T3 was also effective in improving insomnia and hyperactivity in infants with a severe RTHβ phenotype who could not tolerate daily levothyroxine (L-T4) administration.[14]

4 | CONCLUSION

We identified a patient with mood disorder based on thyroid hormone refractoriness. Although the number of reports is small, it is believed that some patients are misdiagnosed and treated. Poor tolerability to antidepressants was observed, which may be related to thyroid hormone intolerance. Low doses of quetiapine may contribute to improvements in depression with RTHβ. It is hoped that the accumulation of case reports of depressive symptoms associated with thyroid hormone intolerance will lead to a better understanding of this disease.

AUTHORS' CONTRIBUTIONS

HKS, RM, and CH were involved in the clinical investigations. NYF wrote the manuscript. HKS, NYF, and KS were involved in the literature review. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

Kazutaka Shimoda has received research support from Novartis Pharma K.K., Dainippon Sumitomo Pharma Co., Astellas Pharma Inc., Meiji Seika Pharma Co., Ltd., Eisai Co., Ltd., Pfizer Inc., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Co., and Takeda Pharmaceutical Co., Ltd., and honoraria from Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Janssen Pharmaceutical K.K., Shionogi & Co., Ltd., Dainippon Sumitomo Pharma Co., Daiichi Sankyo Co., and Pfizer Inc. The funders did not have any role in data collection or in the study design, analysis, decision to publish, or preparation of the manuscript. The remaining authors declare that they have no competing interests to report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as details of the case cannot be disclosed in accordance with the Personal Information Protection Law.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The ethics committee of the School of Medicine at Dokkyo Medical University determined that there was no need to review this case.

INFORMED CONSENT

Written informed consent was obtained from the parent for the publication of this case report.

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