Psychiatria Danubina, 2015; Vol. 27, No. 2, pp 198-200 *Case report*

LOW-DOSE CLOZAPINE THERAPY FOR A BIPOLAR PATIENT WITH ABNORMAL LEVELS OF THYROID FUNCTION AND ANTI-THYROID ANTIBODIES

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INTRODUCTION

The relationship between mood disorders and abnormalities of the endocrine and immune systems have been described (Horning et al. 1998, Kanba et al. 1998). Thyroid abnormalities associated with lithium treatment have been widely reported, including goiter, hypothyroidism, hyperthyroidism, and autoimmune thyroiditis (Kibirige et al. 2013). The presence of anti-thyroid antibody titers in bipolar patients has also been associated with hypothyroidism, particularly in patients undergoing lithium therapy (Chakrabarti 2011). Many studies that investigated whether anti-thyroid peroxidase antibodies are associated with lithium exposure had produced contradictory findings. Kupka et al. (2002) suggested that an increased incidence of anti-thyroid antibodies was found in bipolar patients prior to treatment compared to the general population and is not associated with lithium treatment.

Clozapine has been used in the treatment of bipolar disorder for many years (Chang 2006). So far there are many hypotheses regarding the effect of clozapine in mood disorder. Here we report a bipolar patient receiving long-term treatment. She was initially prescribed lithium treatment but in vain. Two years after taking low-dose clozapine, her manic symptoms resolved and hypothyroidism improved without any detectable antithyroid antibody.

CASE REPORT

A 39-year-old single female was diagnosed of bipolar I disorder since age 27. No abnormality was reported in her developmental history. Neither substance abuse nor systemic disease was noted in her past history. Her first admission to the psychiatric ward was for severe manic symptoms with aggressive behavior occurred when she was 27 years old. At that time, her thyroid function tests were: tetraiodothyronine (T4): 8.3 ug/dl (normal, 4-12 ug/dl); 3,5,3`-triiodothyronine (T3): 161.0 ng/dl (normal, 70-200 ng/dl); and thyroid-stimulating hormone (TSH): 2.1 UIU/ml (normal, 0-6 UIU/ml). No anti-thyroid antibody was detected at that time. Her regimen included lithium 1200 mg/day, haloperidol 10 mg/day, and trihexylphenidyl 4 mg/day.

After five years, she was hospitalized again due to another manic episode. This time, exophthalmos was observed. Endocrinologist was consulted, and thyroid echo and aspiration cytology were arranged. Her thyroid function levels were all within normal limits (Table 1), but positive anti-thyroid antibodies were noted, including anti-microsomal antibody (AMA) (titer: 1:400), anti-thyroglobulin antibody (ATA) (titer 1:1600) and thyrotropin binding inhibitory immunoglobulin (TBII) (3.94%). Thyroid echo revealed both lobes of the thyroid were large with heterogeneity and slightly low echogenicity. Aspiration cytology showed high cellularity of benign follicular cells with some lymphocyte. Grave's disease was diagnosed though no specific treatment was suggested by the endocrinogist.

Four more years passed, and she was admitted again for anothermanic episodes. Her thyroid functions revealed hypothyroidism and higher AMA (1:1600) and ATA (1:6400) titers than before. Because of refractory manic symptoms and hypothyroidism, lithium was stopped and sodium valporate (1200 mg/day), chlorpromazine (600 mg/day), and trihexylphenidyl (2 mg/day) were added with thyroxin supplementation (0.05-0.1 mg/day). She had to be admitted again after six months due to manic symptoms with prominent psychotic features when she was 37 years old. At that time, her thyroid function revealed TSH 5 UIU/l, T3 65 ng/dl, T4 6.05 ug/dl, free T4 1.21 ng/dl, AMA 1:400, and ATA 1:400. Clozapine was initiated to manage her manic symptoms. Her manic symptoms improved within one month (Young Mania Rating Scale score, from 41 to 7) with clozapine monotherapy of 100 mg/day, without mood stabilizers or other medications. After two years of follow-up in the outpatient clinic, her mental status remainedstable and herthyroid functions approached normal limits. Her AMA, ATA and TBII titers becamenegative by the time she was 39 years old (Table 1).

Table 1. Serum levels of thyroid function and anti-thyroid antibodies during the clinical courses

	Free T4 (0.79-2.01 ng/dl)	T4 (4-12 µg/dl)	T3 (70-200 ng/dl)	TSH (0.25-5.5µIU/ml)	AMA titer	ATA titer	Comment
27 year-old	No data	8.30	161	2.10	Negative finding	Negative finding	Baseline data (Before Lithium use)
32 year-old	1.05	4.92	73.3	4.27	1:400	1:1600	Lithium use for five years
36 year-oldt	1.79	10.20	87.7	8.60	1:1600	1:6400	Lithium use for nine years
37 year-old	1.21	6.05	65	50	1:400	1:400	Valporate for two years, thyroxine for six months
39 year-old	1.47	10.40	122	1.58	Negative finding	Negative finding	Clozapine use for two years

T4 – tetraiodothyronine; T3 – triiodothyronine; TSH - thyroid-stimulating hormone; AMA - anti-microsomal antibody; ATA - anti-thyroglobulin antibody

DISCUSSION

Long-term lithium therapy has been associated with a variety of thyroid abnormalities including goiter, hypothyroidism, and less commonly, hyperthyroidism. Additionally, lithium may have an immuostimulant effect, inducing or exacerbating pre-existing autoimmune disease. The demonstration of antithyroid antibodies in patients developing thyroiditis and goiter while on lithium therapy also supports this theory (Chakrabarti 2011). It is not clear whether the role of lithium in the development of autoimmune thyroiditis is accelerating the progression, stimulating antibody formation, or is independent of thyroid autoimmunity. There is no evidence on whether stopping lithium reverses these thyroid abnormalities (McKnight et al. 2012).

No thyroid abnormalities developed until physiologically challenged by ‘‘antithyroid’’ stressors in patients with rapid cycling bipolar disorder (Bauer et al. 1990). Such stressors may include spontaneously occurring thyroid disease or goiterogenic drugs such as lithium. The clinically relevant consequences may occur while the compensatory potential reduced due to multiple risk factors, either environmental or intrinsic (immunogenetic background), especially in the first two years of lithium treatment and in middle-aged women (Bocchetta et al. 2001). In our case, the serum concentration of TSH, AMA, ATA, and TBII were elevated markedly after taking lithium for several years. Grave’s disease was impressed according to the clinical manifestation and laboratory finding. However, antithyroid antibody titer remained positive (1:400) after lithium was discontinued for more than one year and only became negative under clozapine 100mg/day treatment after two years. During that time, she could maintain a stable mood without becoming manic as titers of antithyroid antibodies became negative.

Thyroid abnormalities, not only abnormal thyroid hormones but also euthyroid state with thyroid autoimmunity, are more prevalent in patient with mood disorder than in the general population and treatment responses may be influenced (Giynas et al. 2014). In a community, individuals with thyroid autoimmunity had higher risk of developing at least one diagnosis of mood disorders (Carta et al. 2004).

In addition, the abnormally activated T cell immune system may also play an important role in bipolar disorder (Breunis et al. 2003). Correction of immune abnormality in patients with bipolar disorder is important for the interaction of thyroid abnormalities and affective symptoms in bipolar disorder (Barbero et al. 2014). Immunomodulatory property of clozapine has been discussed before. It was discovered that clozapine modulates the cytokine network (Raaska et al. 2002). The reactive metabolite of clozapine covalently binds to neutrophils (Gardner et al. 1998) and could be responsible for clozapine-induced arganulocytosis , interstitial nephritis (Elias et al. 1999), and myocarditis (Wooltorton 2002). Clozapine treatment did affect in vitro peripheral blood mononuclear cells by suppressing spontaneous and clozapine-induced proliferation and levels of soluble interleukin-2 receptor (Hinze-Selch et al. 1998). Higher serum clozapine level is associated with increased anti-phospholipid antibodies in patients with schizophrenia (Shen et al. 2009). In addition, the dosage of clozapine in this case was merely 100 mg/day, much lower than the 315 mg/day reported in a review of clozapine treatment in bipolar patients (Frye et al. 1998).

In this case, we observe the correlation between change in the levels of thyroid function and the course of disease. Antithyroid antibodies still existed but decreased after withdrawal of lithium with unstable clinical condition. The titer of AMA and ATA approaches to zero after clozapine was prescribed for two years. Positive thyroid-antibody titer disappeared with time is very uncommon. The mechanism of clozapine in mood disorder might involve the normalization of thyroid function and needs to be confirmed in future studies.

CONCLUSIONS

We reported the successful management of a case of bipolar disorder who developed Grave’s disease with low-dose clozapine. The case illustrated the possibility

that changes in thyroid function and anti-thyroid antibodies may be involved in the mechanism of clozapine therapy for refractory bipolar disorder. It is quite uncommon that positive thyroid-antibody titer disappeared over time. Exploring the mechanism related to the effectiveness of clozapine and the role of autoimmunity in bipolar disorder could be an area of future interest.

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