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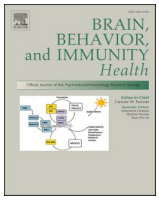

Complexities of cooccurrence of catatonia and autoimmune thyroiditis in bipolar disorder: A case series and selective review

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ABSTRACT

In recent years the neurobiological underpinnings of catatonia have been an emerging area of interest. Catatonia is frequently encountered in mood disorders, neurological disorders and systemic illnesses. Furthermore, the manifestation of catatonia in autoimmune disorders such as NMDA receptor antibody encephalitis and thyroiditis reinforces its neuropsychiatric nature. Irrespective of cause benzodiazepines and electroconvulsive therapy remain the standard treatments for catatonia, although a proportion fail to respond to the same. This report describes three women with pre-existing bipolar disorder presenting in catatonia. Interestingly in all three, while benzodiazepines and electroconvulsive therapy failed, a dramatic resolution of catatonia with corticosteroids was noted following the detection of Hashimoto's thyroiditis. Hashimoto's encephalopathy presenting as catatonia has been reported, but our patients' profile differed in having had an a priory diagnosis of bipolar disorder. Given that both catatonia and thyroid dysfunction are frequently encountered in bipolar disorder, Hashimoto's encephalopathy as a potential cause for this concurrent manifestation in bipolar disorder may be overlooked. Therefore, it is essential to suspect Hashimoto's encephalopathy when catatonia manifests in bipolar disorder. A timely evaluation would be prudent as they may fail to respond to standard treatments for catatonia but respond remarkably to corticosteroids, saving much time and angst. Recent evidence implicates immune system dysfunction, with neuroinflammation and peripheral immune dysregulation contributing to the pathophysiology of bipolar disorder as well as catatonia. Findings from this study reaffirm the role of immune system dysfunction common to the etiopathogenesis of all these disorders, highlighting the complex interplay between catatonia, thyroiditis and bipolar disorder.

1. Background

Catatonia was described by Karl Ludwig Kahlbaum in 1874 as a complex neuropsychiatric condition with a cyclical and progressive course. In his original description of 26 cases, 11 had neurological signs and a significant proportion suffered concomitant neurological conditions including neurosyphilis, tuberculosis and epilepsy (Berrios, 1996). However, Emil Kraepelin subsumed catatonia under dementia praecox, relegating it to a schizophrenia subtype that potentially limited a further understanding of catatonia as a discrete entity. Over the late 20th century, catatonia has been noted across mood disorders, neurological and medical conditions. The widely accepted nosological status of catatonia at present is similar to that originally proposed by Kahlbaum. Catatonia is akin to psychiatric/medical disorders as general paralysis of the insane is to syphilitic illnesses, presenting as a distinct syndrome or a manifestation of the underlying disease.

Catatonia has been reported (Fink et al., 2010; Rasmussen et al., 2016) in up to 28% of bipolar disorder patients and 20% of persons with depressive disorders (Starkstein et al., 1996; Taylor and Fink, 2003). Around 30–40% of those with catatonia have underlying medical or neurological conditions (Carroll et al., 1994; Huang et al., 1999), such as metabolic disorders, parkinsonism, systemic and CNS infections and autoimmune diseases (Daniels, 2009; Espinola-Nadurille et al., 2019; Fink et al., 2010; Rasmussen et al., 2016).

Interestingly, irrespective of aetiology, benzodiazepines and electroconvulsive therapy have demonstrated effectiveness in the treatment of catatonia (Pelzer et al., 2018).

Over the preceding three decades, insights from genetics,

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multimodal imaging and immunochemistry have provided clues to the neurobiological underpinnings of catatonia. Both, endocrinal and immune system dysfunction have been linked to the pathophysiology of catatonia. The endocrine system influences neuronal development and synaptic plasticity, while immune-mediated processes modulate neuronal functioning and integrity. Altered glial cell functioning leads to development of aberrant neuronal networks, with immune-mediated mechanisms involving excitotoxicity and oxidative stress contributing to degenerative processes (Garcia-Segura et al., 1996; Rogers et al., 2019; Giotakos, 2019; Rege and Hodgkinson, 2013).

The association of mood disorders, including bipolar disorder, and thyroid dysfunction is well established (Bauer et al., 2008; Whybrow et al., 1969). Nonetheless, recent findings allude to inflammation and immune system dysregulation contributing to the pathophysiology of bipolar disorder (Barbosa et al., 2014; Bauer et al., 2008; Modabbernia et al., 2013; Rege and Hodgkinson, 2013; Rosenblat and McIntyre, 2016, 2017). Thyroid autoantibodies have been detected in bipolar disorder despite the absence of clinical or biochemical features suggestive of thyroiditis (Leyhe and Müssig, 2014). Additonal observations of thyroperoxidase autoantibodies (Anti-TPO) unrelated to lithium exposure in 28% bipolar disorder patients (Kupka et al., 2002) are indicative of peripheral immune system dysregulation. Conversely, a spectrum of psychiatric symptoms have been noted in autoimmune thyroiditis (Menon et al., 2017). Thyroid hormone alterations also influence treatment response and outcomes in mood disorders, further highlighting the intricacies of the relationship between thyroid dysfunction, mood disorder and immune system alterations (García-Alberca et al., 2010; Placidi et al., 1998). Findings of thyroid autoantibodies in catatonia associated with thyroid disease, irrespective of hyperthyroid, hypothyroid or euthyroid states, add further to this complexity (Rogers et al., 2019).

Hashimoto's thyroiditis is an autoimmune thyroid disorder characterised by the development of auto antibodies targeting thyroid peroxidase (Anti-TPO), thyroglobulin (Anti-Tg) or thyroid-stimulating hormone-receptors (TRAbs). The disease pathogenesis is attributed to a complex interplay of various genetic and environmental factors (Chistiakov, 2005). Hashimoto's encephalopathy, also termed Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), was first described by Lord Brain (Brain, 1966). It is a neuroendocrine complication of Hashimoto's thyroiditis (Ferracci et al., 2004). Elevated pro-inflammatory cytokines in autoimmune conditions are proposed to influence alterations in neuronal networks, leading to the development of psychiatric manifestations such as mood disorders (Benros et al., 2013; Felger and Lotrich, 2013).

An association between autoimmune thyroiditis and catatonia has been reported previously (Bharadwaj et al., 2012; Endres et al., 2017; Grebenciucova, 2014; Karthik et al., 2017; Lalanne et al., 2016; Ransing et al., 2016; Shree et al., 2020). However, the observed overlap of immune system dysregulation across catatonia, autoimmune disorders and bipolar disorder does not appear to have been described till date. Here we describe three such patients with bipolar disorder who presented in catatonia with autoimmune thyroiditis, highlighting the complex interplay between catatonia, autoimmune thyroiditis and bipolar disorder.

1.1. Case 1

A 22-year old female presented with a 2 month history of pervasive sadness, anhedonia, ideas of guilt, suicidal ideations followed by 5 days of mutism, staring, posturing, immobility, rigidity and withdrawal. She had two past mood episodes, the first being a depressive episode about 15 months prior to the current episode, the other a manic episode 2 months prior to the onset of the current episode. Thyroid function tests were normal during the first episode. However, hypothyroidism was detected 9 months before the current episode, and she was started on Levothyroxine 50 mcg. The Bush Francis Catatonia Rating Scale (BFCRS) score was 14. Her liver function tests, serum creatinine, blood urea, serum electrolytes (sodium, potassium, chloride, calcium, phosphorous), haemogram, thyroid function tests (T3, T4, TSH) were normal in the current episode. Following a failed trial with 6 mg lorazepam for catatonia, bifrontal electroconvulsive therapy (ECT) on alternate days was commenced at 1.5 times the threshold stimulus. Since there was only a partial improvement in catatonic symptoms following 7 ECT sessions, additional investigations were ordered, that revealed elevated Anti-TPO, Anti-Tg antibodies at 390 IU/ml and 2089 IU/ml, respectively. Ultrasonography of the thyroid revealed nodules in both lobes, and FNAC conformed colloid goitre. EEG revealed triphasic waves in frontotemporal leads. MRI of the brain, CSF analysis, ANA profile, and antibodies for autoimmune encephalitis revealed no abnormalities. She was clinically diagnosed as bipolar disorder and autoimmune thyroiditis with Hashimoto's encephalopathy in catatonia. Intravenous methylprednisolone 1 gm daily for 3 days was initiated followed by oral prednisolone 40 mg daily in consultation with the neurologist. Her catatonic symptoms dramatically improved and the BFCRS score reduced to 1 over one week.

1.2. Case 2

A 47-year-old woman, in her perimenopausal period, presented with a history of bipolar disorder of 15 years duration, having experienced 3 manic and 5 depressive episodes. She had no mood episodes during pregnancy or postpartum. Catatonic features were noted in each of her depressive episodes. Hypothyroidism was diagnosed 2 years after the onset of bipolar disorder and treated with thyroxine supplementation. She was also diagnosed with systemic hypertension at the age of 46. Her current presentation of 3 months duration was characterised by withdrawn behaviour, posturing, staring, withdrawal and reduced sleep. On examination, she had automatic obedience, mitgehen, and tachycardia. The total score on BFCRS was 18. Her hemogram and biochemical parameters (liver, renal function, serum electrolytes) were normal. MRI Brain revealed mild cerebral and cerebellar atrophy, and EEG showed no abnormality. CSF cytology and biochemistry was unremarkable.

Autoimmune encephalitis workup, ANA profile, and Wilsons disease workup was negative. Though her current T3, T4, TSH were within normal limits, anti-TPO antibody titres were elevated (414 IU/ml). She was diagnosed with bipolar disorder - catatonia, autoimmune thyroiditis, and systemic hypertension. Following a failed trial of lorazepam 14 mg, Bifrontal ECTs were initiated on alternate days at 1.5 times the threshold stimulus. However, no additional improvement in her catatonic symptoms occurred despite 8 ECT sessions, with BFCRS scores remaining unchanged at 13. In consultation with an immunologist, she was initiated on intravenous methylprednisolone 1 gm daily for 7 days for the elevated anti-TPO levels and subsequently with oral prednisolone up to 30 mg/day. Her catatonic symptoms subsided completely, reflected by a BFCRS score of 0 and the patient returned to her premorbid self. Oral prednisolone was tapered after 2 weeks.

1.3. Case-3

A 50-year-old woman presented with a 15-year illness, having experienced 5 manic and 5 depressive episodes. She had good interepisodic recovery and no exacerbations were noted during pregnancy or postpartum period. Her medical history was significant for hypothyroidism, diagnosed 3 years following the onset of her bipolar disorder. She had undergone a hysterectomy 3 years prior to current presentation. Hypothyroidism was reported in her mother, sister and daughter. The current episode was characterised by mutism, lack of concern about her surroundings, posturing, staring, withdrawal, hiccups and poor self-care. The family also reported weight gain. On examination she had additional catatonic features, namely waxy flexibility and automatic obedience. The BFCRS score was 13. Biochemical parameters (liver, renal function tests, serum electrolytes, fasting glucose) were

within normal limits. However, the thyroid profile was abnormal, with elevated TSH levels (34.93 uIU/ml), low T3 (66.17 ng/dl) and T4 (5.9 μg/dl). Her anti-TPO antibody levels were greater than 1300 IU/L. EEG study was normal. Catatonic symptoms did not improve with 8 mg of lorazepam with the BFCRS score remaining unchanged. She was hence commenced on bifrontal ECTs on alternate days, at 1.5 times the threshold stimulus. A partial improvement was noted following 6 ECT sessions and BFCRS scores reduced to 7. On treatment with oral prednisolone 20 mg/day, improvement was noted in her catatonic symptoms and the BFCRS scores reduced to 0.

2. Discussion

All the three cases of catatonia with bipolar disorder described above, demonstrated an inadequate response to standard treatments for catatonia but responded dramatically to corticosteroids administered for concurrent autoimmune thyroiditis. The response to corticosteroids is also supportive of a diagnosis of Hashimoto's Encephalopathy in these three cases. It may be argued that relatively lower doses of lorazepam as well as fewer ECT sessions were administered. However there reamins a lack of consensus on what constitutes an adequate lorazepam regimen (cumulative daily dose, frequency, duration of treatment, extent of response) or adequate ECT regimen (sessions, electrode placement, seizure threshold, frequency of trials) to deem catatonia as refractory (or non-responsive to standard treatment). Furthermore, the lack of a standardized treatment protocol for catatonia pose challenges to its effective clinical management (Daniels, 2009; Hatta et al., 2007; Rasmussen et al., 2016). However in the cases described, evaluation and treatment strategies adopted for catatonia were consistent with current treatment approaches. These included assessments for identification of underlying causes, and administering adequate trials of lorazepam and ECT (Girish and Gill, 2003; Rasmussen et al., 2016). Additionally, none of the patients received any antipsychotic medication during the acute catatonic state.

Presentations of Hashimoto encephalopathy are diverse and polymorphic. Common neurological manifestations are tremors (80%), transient aphasia (80%), myoclonus (65%), gait ataxia (65%), seizures (60%) and sleep abnormalities (55%) (Castillo et al., 2006), while neuropsychiatric manifestations include acute psychosis (26.1%), depressive disorders (23.9%), bipolar disorder (15.2%), dementia (10.9%), acute encephalopathy and schizophrenia (2.2%) (Menon et al., 2017). A large proportion is initially misdiagnosed as viral encephalitis, Creutzfeldt-Jakob disease or degenerative dementia (Castillo et al., 2006). The diagnosis of Hashimoto encephalopathy is based on the clinical triad of (1) neuropsychiatric symptoms, often affecting more than one area of the central nervous system; (2) the detection of antimicrosomal or antithyroglobulin antibodies in serum; and (3) the elimination of other potential etiologies. A clinical response to corticosteroid therapy is also supportive of the diagnosis (Chaigne et al., 2013; Chong et al., 2003; Kothbauer-Margreiter et al., 1996).

Nevertheless, Hashimoto's Encephalopathy presenting as catatonia is rare, though a few cases have been described in the literature (Bharadwaj et al., 2012; Endres et al., 2017; Grebenciucova, 2014; Karthik et al., 2017; Lalanne et al., 2016; Ransing et al., 2016; Shree et al., 2020). Whilst these cases were initially diagnosed with NMDA encephalitis, dementia, seizures, postpartum psychosis and Grave's disease, our patients differed significantly given they had a long-standing diagnosis of bipolar disorder (15 years in case 3 and 15 months in case 1). Catatonic features are reported in 50% of bipolar disorder patients and hence presumed to be an expected illness manifestation, as occurred with our patients, with one having experienced multiple catatonic episodes and other two having presented with their first episode of catatonia (Sienaert et al., 2013).

Age and sex are considered two important factors that influence the incidence of thyroid autoimmunity. Middle-aged women, in particular, are known to demonstrate the highest prevalence rates of autoimmune thyroid disease (Bocchetta et al., 2016). Furthermore, development of autoimmune thyroid dysfunction during pregnancy has been associated with peripartum onset of depression and postpartum psychosis (Dama et al., 2016; Bergink et al., 2011; Richard et al., 2018). Concurrently, a study from India reported catatonia in 20% of postpartum psychosis patients admitted to a mother-baby unit (Nahar et al., 2017). The established association of post-partum disorders with bipolar disorders, and above findings of significant proportion presenting with catatonia suggest the potential association of immune dysfunction with the pathophysiology of these disorders. A more recent study highlighted female preponderance of catatonia in bipolar disorder as well as a higher age of illness onset among non-responders of catatonia in bipolar disorder (Medda et al., 2015). An Indian study had reported that idiopathic catatonia accounted for nearly 45% of catatonia cases with greater frequencies observed among females. (Benegal et al., 1993). Our cases were all women, consistent with these observations.

Electrophysiological studies, neuroimaging, and cerebrospinal fluid analysis findings can often be inconclusive. Features such as changes in presentation, and inadequate or failed response to standard treatments must raise clinical suspicion and prompt screening for antithyroid antibodies in such cases.

The cerebrospinal fluid analysis may show raised proteins, however, may be normal in a proportion. Our cases had normal levels of CSF protein (Henchey et al., 1995; Menon et al., 2017). All three cases did not have any specific abnormality in their MRI, similar to previous studies that indicate MRI findings are often unremarkable in majority of patients with Hashimoto's encephalopathy (Tamagno et al., 2010; Zhou et al., 2017). However, a recent study reported that two-thirds of biploar disorder patients with catatonia had abnormal cerebral CT and/or MRI findings, although these were largely non-specific (Medda et al., 2015).

One of our patients had an abnormal EEG recording with triphasic waves in the frontotemporal leads, but the other two did not show any EEG abnormalities. EEG is often normal in catatonia (Rasmussen et al., 2016), and EEG findings in Hashimoto's encephalopathy are known to vary during the course of the illness (Henchey et al., 1995), with no detectable abnormalities in up to 20% of patients (Menon et al., 2017). A background slowing in frontotemporal leads with intermittent sharp wave discharges, frontal intermittent rhythmic delta activity, prominent triphasic waves or focal slowing may be present.

Thyroid function tests in Hashimoto's encephalopathy/thyroiditis may range from hypothyroidism (20%), subclinical hypothyroidism (35%), euthyroid (30%) to hyperthyroidism (7%) (Marshall and Doyle, 2006). Similarly, findings that range from hypothyroidism to hyperthyroidism have been observed in both bipolar disorder and catatonia (Chakrabarti, 2011; Iskandar et al., 2014). Symptoms may develop even when patients are euthyroid, making it imperative for clinicians to have a high degree of suspicion. Notably, two of our patients had normal thyroid function tests possibly attributable to levothyroxine supplementation prescribed, while one had uncontrolled hypothyroidism.

Autoimmune thyroiditis is characterised by increased levels of autoantibodies including Anti-TPO, previously named anti-microsomal antibodies, Anti-Tg and TRAbs (Mijajlovic et al., 2010). The findings of thyroid autoantibodies in patients with bipolar disorder despite the absence of clinical or biochemical features suggestive of thyroiditis poses diagnostic challenges, as was noted in our cases.

Despite being the mainstay of treatment, the response to steroid treatment can be variable in Hashimoto's encephalopathy. Previous findings suggest only up to 50% of patients respond to steroid therapy alone, and few remain resistant to treatment(Ferracci et al., 2004; Mijajlovic et al., 2010). Such patients may warrant plasma exchange, intravenous immunoglobulin or immunosuppressant drugs.

Initially Hashimoto's thyroiditis was presumed to have no other systemic clinical manifestations until Becker et al.'s observation of 153 patients with serum antithyroid antibody. He found that upto 25% had concurrent serious medical conditions including myasthenia gravis, haemolytic anaemia, Addison's disease, scleroderma, systemic lupus,

inflammatory bowel disease, glomerulonephritis, rheumatoid arthritis and hepatic cirrhosis (BECKER, 1965), indicative of widespread immune dysregulation. However, in our patients, we did not detect any features of concurrent autoimmune conditions. The etiopathogenesis of Hashimoto's encephalopathy continues to remain obscure. One of the reasons might be its low prevalence, added to the polymorphic and diverse clinical profile (Tamagno et al., 2006). The neuropsychiatric manifestations are thought to result from mechanisms such as vasculitis, cerebral hypoperfusion, autoantibodies against brain-thyroid antigens and encephalomyelitis associated demyelination (Watemberg et al., 2006). The presence of underlying immune dysregulation raises a question of whether catatonia could be a phenotype of autoimmune thyroiditis in bipolar disorder, that warrants testing and monitoring of thyroid antibodies (Morrens et al., 2019). Interestingly, autoimmune disorders such as N-methyl-D-aspartate receptor (NMDAR) encephalitis can lead to a full range of catatonic presentations and has been thought to result from adaptive immune responses to extracellular antigens (Rogers et al., 2019).

The three patients had been diagnosed with thyroid dysfunction soon after the onset of bipolar disorder but had not been evaluated for autoimmune thyroiditis. Increasingly the role of immune dysfunction and oxidative stress has been implicated in the pathogenesis of catatonia and bipolar disorder (Balmus et al., 2016; Morrens et al., 2020; Valvassori et al., 2018). Immune markers such as an increase in monocyte count in catatonia have been noted to be associated with poor response to treatment with lorazepam, and also been suggested as a proxy marker for underlying aberrant microglial activation (Rao et al., 2011; Schmitz et al., 2009). Observations of immune system dysregulation in the pathogenesis of bipolar disorder, catatonia and thyroiditis (Rege and Hodgkinson, 2013; Rogers et al., 2019) and co-occurrence of bipolar disorder, catatonia and thyroid dysfunction suggests a strong interplay between these conditions. The critical determinant in our cases was catatonia, that reinforces our hypothesis of catatonia being a potential clinical phenotype of autoimmune thyroiditis in bipolar disorder.

Previous studies have implicated thyroid dysfunction and antithyroid antibodies in rapid cycling and refractory bipolar disorder (Cowdry et al., 1983; Gan et al., 2019; Gyulai et al., 2003). Bocchetta et al. have even proposed an entity of 'Hashimoto's mood disorders' with a diverse array of presentations ranging from classical treatment responsive mood disorders to treatment-refractory mood disorders to evolving dementias (Bocchetta et al., 2016). However, the causal role and direction of the association between bipolar disorder and circulating thyroid antibodies remain ambiguous. Several genome wide association studies (GWAS) have detected an association of immunity linked genes with the risk for severe mental illness, including bipolar disorder (Liu et al., 2020; Sigitova et al., 2017). In the patients that we have described, it was difficult to ascertain whether the thyroid autoimmunity was present prior to the onset of bipolar illness, as it was specifically tested for in the context of treatment-refractory catatonia. As mentioned previously, testing for thyroid hormones alone may not be conclusive of underlying immune dysfunction either in autoimmune thyroiditis, bipolar disorder or catatonia (Chakrabarti, 2011; Iskandar et al., 2014; Marshall and Doyle, 2006). Hence, it becomes relevant to test for thyroid autoimmunity in bipolar disorders with a catatonic presentation.

3. Conclusion

A plethora of neuropsychiatric symptoms are known to be associated with thyroid autoimmunity and are often misdiagnosed or underdiagnosed. As demonstrated in our cases, despite thyroid disease having been recognized early and treated, it is essential to suspect Hashimoto's encephalopathy in refractory catatonia. This is more so in those suffering from bipolar disorder, given that these patients often respond remarkably to a course of corticosteroids after failing to respond to standard treatments. Thus, it may be prudent to routinely consider evaluation for thyroid autoimmunity in bipolar disorder presenting with catatonia. Future studies should systematically examine the role of immune dysregulation and inflammation, contributing to the pathophysiology of thyroid disease and its relationship to bipolar disorder and catatonia.

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Declaration of competing interest

None.

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