CASE REPORT

Acute psychosis in a pregnant patient with Graves' hyperthyroidism and anti-NMDA receptor encephalitis

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SUMMARY

A previously healthy 36-year-old woman presented with visual hallucinations and acute psychosis manifested predominantly as hypersexuality. Laboratory testing demonstrated elevated free thyroxine levels, suppressed thyroid-stimulating hormone levels and presence of thyroid-stimulating immunoglobulin and *thyroid peroxidase (TPO) antibodies* consistent with Graves' disease. Despite achieving biochemical euthyroidism, she remained profoundly hypersexual. She did not respond to additional treatment with antipsychotics and corticosteroids, prompting further evaluation. Cerebrospinal fluid analysis detected pleocytosis, elevated IgG, and presence of antibodies against anti-N-methyl-D-aspartate receptor (NMDAR), glutamic acid decarboxylase 65 and TPO. These results suggested a diagnosis of anti-NMDAR encephalitis. Prior to initiation of immunomodulator therapy, she was discovered to be pregnant with date of conception around the time of her original presentation. She received plasmapheresis with resolution of psychosis and decrease in free thyroxine levels. Graves' disease remitted during the remainder of the pregnancy but relapsed 5 months post partum. She has not had further neuropsychiatric symptoms.

BACKGROUND

Thyroid function tests are routinely obtained from patients who present to the emergency room with psychiatric symptoms to rule out a thyroid-mediated cause. Indeed, psychiatric symptoms are frequently seen in the early presentation of Graves' hyperthyroidism, with the most common symptoms being irritability and anxiety, as well as insomnia and anorexia.[1 2] Frank psychosis and mania have been less commonly reported with Graves' hyperthyroidism and their occurrences are thought by some to typically occur in patients with a pre-existing psychiatric diagnosis.[3] Patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis may present with psychiatric symptoms, predominantly as mood and thought pattern disturbances.[4] While Graves' hyperthyroidism should be considered in the differential diagnosis of psychosis, if symptoms persist despite normalisation of thyroid hormone levels, another cause should be investigated. We report such a case of acute psychosis exhibited as hypersexual behaviour in a patient found with concomitant autoimmune Graves' hyperthyroidism and anti-NMDAR encephalitis.

CASE PRESENTATION

A previously healthy 36-year-old Hispanic woman presented with a 4-day history of bizarre behaviour, visual hallucinations, hypersexuality, and pressured and disorganised speech in the setting of a 50 pound weight loss over 6 months. Family history was notable for a sister with hyperthyroidism. On examination, the patient was tachycardic, tremulous and had a diffusely enlarged thyroid.

INVESTIGATIONS

Laboratory investigations were notable for serum free T4 level of 3.53 ng/dL (reference range 0.76–1.46 ng/dL), serum thyroid-stimulating hormone level <0.01 mIU/L (reference range 0.36–3.74 μIU/mL), serum free T3 level of 10.38 pg/mL (reference range 2.18–3.98 pg/mL), elevated serum thyroid-stimulating immunoglobulin level 609%, elevated serum thyroid peroxidase antibody level (TPO-Ab) 585 IU/mL (reference range 0–34 IU/mL), and a negative urine pregnancy test. She was started on methimazole (30 mg/day) with normalisation of thyroid hormone levels, but her psychosis and hypersexuality persisted, suggesting that other causes of her psychiatric symptoms should be explored. On further evaluation, a brain MRI showed no acute intracranial process. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (white cell count 44 per mm^3, 95% lymphocytes), presence of TPO-Ab (653 IU/mL, no reference range available) and elevated IgG level 5.7 mg/dL (reference range 0.00–3.40 mg/dL). West Nile and herpes simplex virus, and ACE testing in the CSF were negative. EEG was normal.

As she remained psychotic, treatment for possible inflammatory versus Hashimoto's encephalitis was initiated. She received 3 days of oral methylprednisolone, then 7 days of intravenous methylprednisolone followed by a 1-month high-dose prednisone taper. Despite normalisation of her thyroid hormone levels (free T4 1.07 ng/dL, total T3 63 (reference range 60–181 ng/dL), total T4 9.9 (reference range4.7–13.3 μg/dL)) and treatment with corticosteroids as well as several mood stabilisers, she remained hypersexual.

Four weeks into her hospitalisation, results from CSF sent to an outside send-out laboratory returned positive (1:5 titre) for anti-NMDAR antibodies and anti-glutamic acid decarboxylase 65 (GAD-65) antibodies. Anti-GAD antibodies were also detected in serum. Serum anti-NMDAR antibodies were negative. CT of the chest, abdomen

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and pelvis did not detect a primary neoplasm. Pursuit of treatment with rituximab for anti-NMDAR encephalitis was halted when a repeat pregnancy test was positive. Ultrasound confirmed a viable fetus at 6 weeks gestation. All teratogenic medications were discontinued.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses considered were: hyperthyroidism-induced psychosis, Hashimoto's encephalopathy and other encephalitis (infection, autoimmune, etc). CSF pleocytosis and elevated proteins were supportive of autoimmune or infectious encephalitis. Infectious encephalitis was excluded by testing as stated above. Psychosis and altered mentation persisted after normalisation of thyroid hormone levels and there was no response to steroids as expected in Hashimoto's encephalopathy.

TREATMENT

The patient received seven rounds of plasmapheresis for anti-NMDAR encephalitis with a corresponding improvement of her psychosis and hypersexuality. The serum free T4 level decreased below normal range while receiving plasmapheresis and she was started on low-dose levothyroxine, which she continued taking until her second trimester when she remained euthyroid without hormone replacement.

OUTCOME AND FOLLOW-UP

The patient gave birth to a healthy full-term baby boy. At about 5 months post partum she became hyperthyroid, secondary to recurrence of Graves' disease. Thyroid function tests normalised with methimazole and definitive treatment with radioactive iodine ablation is on hold until she is no longer breast feeding. To date, no psychiatric symptoms have recurred other than mild subjective memory impairment.

DISCUSSION

We present a unique case of acute psychosis and hypersexuality in a patient with concomitant Graves' hyperthyroidism and anti-NMDAR encephalitis. While hyperthyroidism rarely can be a precipitant of acute psychosis, it usually occurs in those with pre-existing psychiatric disorders.[3] Classic neuropsychiatric manifestations of hyperthyroidism include agitation, depression, anxiety and irritability. Hashimoto's encephalitis generally presents as altered sensorium, myoclonus and seizures, and a hallmark feature is responsiveness to steroid treatment. In contrast, anti-NMDAR encephalitis is autoimmune encephalitis associated with IgG antibodies against the NR1 subunit of the NMDAR. A female predominance exists and typical presentation includes psychiatric symptoms, seizures, dyskinesia, decreased consciousness and sometimes respiratory or autonomic instability.[5] The majority of cases are paraneoplastic, especially associated with ovarian teratomas.[6] Current recommendation for treatment includes steroids, intravenous immunoglobulin, plasmapheresis and immunomodulators such as rituximab and cyclophosphamide as well as tumour removal if a paraneoplastic process is involved.[7] While the majority of patients respond to immunotherapy, some may have permanent neurological deficits or die. Others may also relapse after recovery.[6]

Our patient's presentation is unique in several aspects. First, while isolated psychiatric episodes are a rare presentation of anti-NMDAR encephalitis and hyperthyroidism, there are no prior reports of hypersexuality as the predominant presentation. Second, she presented with two active autoimmune diseases. While patients with Graves' disease have increased risk of other coexisting autoimmune conditions such as rheumatoid arthritis, Hashimoto's hypothyroidism and coeliac disease, there is currently no known definitive association with anti-NMDAR encephalitis.[8] There is only one other case report of an individual who presented with concomitant Graves' disease and anti-NMDAR encephalitis, although ours is the first reported case of both autoimmune disorders in pregnancy.[9] Also interesting is that our patient did not have an ovarian tumour, which is found in the majority of individuals with anti-NMDAR encephalitis.

Our patient responded well to plasmapheresis and had an uneventful pregnancy with good outcome. Post partum, her Graves' disease relapsed but the encephalitis remains in remission. There is a single case report of anti-NMDAR encephalitis in pregnancy with a good pregnancy outcome, but in that case, the patient did relapse post partum suggesting that it may mimic other autoimmune disorders that remit in pregnancy and relapse post partum.[10]

The presence of anti-GAD-65 antibodies in this patient's CSF is also interesting. CSF antibodies against the 65-kd GAD isoform are detected in autoimmune neurological diseases such as stiff person syndrome, myasthenia gravis and Lambert-Eaton syndrome. Presence of serum GAD-65 antibodies predispose to certain autoimmune diseases such as type 1 diabetes, autoimmune thyroid disease, pernicious anaemia and Addison's disease—our patient has autoimmune thyroid disease.[11 12]

The history of our patient's hyperthyroidism treatment is also worth noting. She became euthyroid with methimazole and her thyroxine levels decreased further when she underwent plasmapheresis despite being off antithyroid medications. Plasmapheresis has been used as a temporary measure to decrease thyroid hormone levels in patients who cannot tolerate traditional therapy.[13 14]

Learning points

- Although hyperthyroidism is associated with neuropsychiatric symptoms, persistence of symptoms despite normalisation of thyroid levels should prompt further evaluation for another cause.
- Anti-N-methyl-D-aspartate receptor and Graves' disease are both autoimmune disorders that may have a shared mechanism of pathophysiology, as suggested by our case. As in some other autoimmune diseases, the disease may remit in pregnancy and relapse post partum.
- This case also highlights the management of multiple autoimmune disorders in pregnancy.

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