

# Iatrogenic myxoedema madness following radioactive iodine ablation for Graves' disease, with a concurrent diagnosis of primary hyperaldosteronism

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## Summary

Myxoedema madness was first described as a consequence of severe hypothyroidism in 1949. Most cases were secondary to long-standing untreated primary hypothyroidism. We present the first reported case of iatrogenic myxoedema madness following radioactive iodine ablation for Graves' disease, with a second concurrent diagnosis of primary hyperaldosteronism. A 29-year-old woman presented with severe hypothyroidism, a 1-week history of psychotic behaviour and paranoid delusions 3 months after treatment with radioactive iodine ablation for Graves' disease. Her psychiatric symptoms abated with levothyroxine replacement. She was concurrently found to be hypertensive and hypokalemic. Primary hyperaldosteronism from bilateral adrenal hyperplasia was diagnosed. This case report serves as a reminder that myxoedema madness can be a complication of acute hypothyroidism following radioactive iodine ablation of Graves' disease and that primary hyperaldosteronism may be associated with autoimmune hyperthyroidism.

## Learning points:

- Psychosis (myxoedema madness) can present as a neuropsychiatric manifestation of acute hypothyroidism following radioactive iodine ablation of Graves' disease.
- Primary hyperaldosteronism may be caused by idiopathic bilateral adrenal hyperplasia even in the presence of an adrenal adenoma seen on imaging.
- Adrenal vein sampling is a useful tool for differentiating between a unilateral aldosterone-producing adenoma, which is managed surgically, and an idiopathic bilateral adrenal hyperplasia, which is managed medically.
- The management of autoimmune hyperthyroidism, iatrogenic hypothyroidism and primary hyperaldosteronism from bilateral idiopathic adrenal hyperplasia in patients planning pregnancy includes delaying pregnancy 6 months following radioactive iodine treatment and until patient is euthyroid for 3 months, using amiloride as opposed to spironolactone, controlling blood pressure with agents safe in pregnancy such as nifedipine and avoiding  $\beta$  blockers.
- Autoimmune hyperthyroidism and primary hyperaldosteronism rarely coexist; any underlying mechanism associating the two is still unclear.

## Background

Neuropsychiatric manifestations of hypothyroidism include various mood disorders, ranging more commonly from mild depression to a rarer state of agitation or psychosis. ‘Myxoedema madness’ is a rare and paradoxical reaction when patients with severe hypothyroidism exhibit psychosis. Asher initially described it in 1949 (1), and the majority of case reports since feature patients with chronic untreated Hashimoto’s thyroiditis.

To our knowledge, this is the second reported case of iatrogenic myxoedema madness following radioactive iodine ablation of Graves’ disease, but it is the first time this phenomenon has been reported in conjunction with a diagnosis of primary hyperaldosteronism attributable to bilateral adrenal hyperplasia. This case report once again emphasizes how fluctuations in thyroid hormone levels following radioactive iodine ablation (iatrogenic hypothyroidism) can lead to acute psychosis and resolve with levothyroxine (L-T<sub>4</sub>) supplementation.

Moreover, there is a paucity of reports detailing an association between primary hyperaldosteronism and Graves’ disease, which this case illustrates. It is unclear if this association is incidental, as it falls outside of traditional multiple endocrine neoplasia or polyglandular autoimmune syndrome associations.

## Case presentation

A 29-year-old woman was diagnosed with Graves’ disease in July 2014. She had no history of other endocrinopathies or mental health issues. Her mother had Hashimoto’s thyroiditis but her family history was otherwise negative.

Her initial presentation was with a 1-month history of palpitations, 8 kg weight loss over 2 weeks and a systolic blood pressure of 200 mmHg. Her investigation showed overt hyperthyroidism (c.f. Table 1 for thyroid function test values) and a thyroid uptake scan showing diffusely increased uptake (41% at 24 h, normal range 10–25%), consistent with Graves’ disease. She was prescribed propranolol 20 mg by mouth (p.o.) three times a day (tid) and methimazole 5 mg p.o. twice a day (bid). Methimazole was stopped 1 week prior to radioactive iodine ablation in early August 2014, when she received 370 MBq of <sup>131</sup>I. Two months later, she was still mildly hyperthyroid with systolic BPs ranging from 150 to 175 on home readings. Propranolol was switched to metoprolol SR 100 mg p.o. every day and nifedipine XL 30 mg p.o. every day (die).

One month later she presented to the emergency room with a blood pressure of 167/109, a heart rate of 157

**Table 1** Thyroid function tests.

Date	TSH (mIU/l) (0.40–4.40)	Free T <sub>4</sub> (pmol/l) (8–18)	Free T <sub>3</sub> (pmol/l) (3.5–6.5)
July 23, 2014	0.03	21.1	6.8
August 4, 2014	0.05	12.5	5.4
October 8, 2014	0.30	14.4	3.8
November 1, 2014	> 100	< 1.90	2.46
November 11, 2014	> 100	6.30	
December 17, 2014	18.15	12.10	
January 5, 2015	28.90	11.10	
March 4, 2015	5.79	16.20	
April 9, 2015	3.80	14.90	
May 15, 2015	2.93	17.60	

and a 1-week history of anxiety and paranoid ideations. She was newly distrustful of everyone around her and extremely jealous. Psychotic behaviours were witnessed in the emergency room. For example, she was throwing money on the floor to keep nurses away, spitting her pills in the sink and blessing every part of her body that the physicians had touched with a large handheld wooden cross. She had no illusions or hallucinations. Bloodwork on arrival also revealed hypokalemia at 2.4 mmol/l with other electrolytes within normal range.

## Investigation

Regarding the investigation of her thyroid disorder, on presentation to the emergency room, her bloodwork confirmed overt hypothyroidism. She was diagnosed with acute psychosis secondary to a general medical condition. A computed tomography (CT) scan and a magnetic resonance imaging (MRI) of the head were normal.

Regarding her hypertension and hypokalemia, serum renin, aldosterone levels and a random cortisol were requested; they returned later as renin 1.46 ng/l per s and aldosterone 1140 pmol/l for an aldosterone/renin ratio of 780 (pmol/l)/(ng/l per s), cortisol 376 nmol/l. At the first follow-up visit, a 24-h urine collection for metanephrines and catecholamines and a contrast-enhanced abdominal CT scan were ordered. The 24-h urine collection was within normal range and the abdominal CT showed a 5 mm left adrenal gland nodule compatible with an adenoma.

To confirm the diagnosis of primary hyperaldosteronism, a saline loading test was done; 2 l of i.v. normal saline were infused over 4 h. The aldosterone level was 755 pmol/l pre-loading and 599 pmol/l post-loading. The results of bilateral adrenal vein sampling under adrenocorticotrophic hormone (ACTH) stimulation (50 µg/h) are shown in Table 2.

**Table 2** Adrenal vein sampling results: March 23, 2015.

Test	Result
Cortisol IVC	304 nmol/l
Cortisol LAV	6928 nmol/l
Cortisol RAV	7803 nmol/l
Selectivity index (cortisol RAV/IVC)	25.66 (SI > 3.0 denotes successful catheterization under ACTH stimulation)
Selectivity index (cortisol LAV/IVC)	22.78
Aldosterone IVC	2277 pmol/l
Aldosterone LAV	336 851 pmol/l
Aldosterone RAV	550 752 pmol/l
LAV aldosterone/cortisol ratio	48.62 nmol/l per pmol per l
RAV aldosterone/cortisol ratio	70.58 nmol/l per pmol per l
RAV/LAV A/C ratio (lateralization index)	1.45:1 (4:1 is diagnostic for lateralization)

IVC, inferior vena cava; LAV, left adrenal vein; RAV, right adrenal vein; SI, selectivity index.

According to current guidelines (2) these results, with a ratio of both adrenal veins' aldosterone/cortisol ratios, do not meet criteria for lateralization of aldosterone hypersecretion (which should be greater than 4:1 under cosyntropin stimulation). Our patient was thus diagnosed with primary hyperaldosteronism from bilateral adrenal hyperplasia, despite the CT finding of adenoma.

## Treatment

She was hospitalised for 2 days in early November 2014, prescribed a load of 200 µg p.o. L-T<sub>4</sub>, followed by 50 µg p.o. die. Despite her young age and absence of cardiovascular co-morbidities, the consultant endocrinologist chose this regimen empirically. Given her psychotic state and known anxiety while thyrotoxic, a replacement strategy of a lower initial L-T<sub>4</sub> dose with gradual uptitration was chosen. The rationale for that decision was that several case reports have described the precipitation of psychosis or mania by L-T<sub>4</sub> replacement in hypothyroid patients (3, 4). Moreover, she received risperidone for several days as an inpatient. The initial hypokalemia was treated with i.v. potassium chloride infusion in the emergency room and monitored on the ward and as an outpatient.

After the diagnosis of bilateral idiopathic adrenal hyperplasia was confirmed as an outpatient, medical treatment, which was preferable to surgical treatment in this case, was instituted with amiloride, which is safer in pregnancy (pregnancy category B) as opposed to the traditional mineralocorticoid antagonist spironolactone (pregnancy category C). She remained on nifedipine XL

30 mg p.o. die for hypertension management and metoprolol SR was discontinued.

## Outcome and follow-up

She was seen as an outpatient 1 week after discharge. The paranoid ideations and psychotic behaviours resolved with L-T<sub>4</sub> supplementation alone and no antipsychotic medication. At the time, her free thyroxine (fT<sub>4</sub>) was still low, so her L-T<sub>4</sub> dose was increased to 75 µg p.o. die. Her thyroid-stimulating hormone (TSH)-receptor antibody titre was elevated at 72.80 IU/l (normal 0–1.75). One month later, she was seen again as an outpatient: her thyroid function tests were normalizing. In follow-up 2 months later, as the TSH had increased slightly, the L-T<sub>4</sub> dose was increased to 100 µg p.o. die. After 5 months of L-T<sub>4</sub> supplementation, the patient was euthyroid and normotensive.

As the patient was planning a pregnancy, she was advised to use contraception until at least 6 months after radioactive iodine treatment and until TSH levels were at target (TSH < 2.5 for the first trimester of pregnancy) for at least 3 months, in line with current guidelines (5). Our patient was referred to an obstetrical medicine clinic in November 2014 for joint follow-up and pregnancy planning.

## Discussion

In summary, our patient developed acute psychosis due to severe hypothyroidism following radioactive ablation for Graves' disease and was concurrently diagnosed with primary hyperaldosteronism secondary to bilateral adrenal hyperplasia explaining her hypertension and hypokalemia.

A Medline search from 1949 to the present using the terms 'hypothyroidism', 'radioactive iodine', 'myxoedema madness' and 'acute psychosis' found only one case report suggesting a relationship between acute hypothyroidism following radioactive iodine ablation in a patient with Graves' disease and psychosis (6). This case was very similar to ours. The authors described a 26-year-old woman diagnosed with Graves' disease who received 533 MBq of <sup>131</sup>I. Three months after treatment she was admitted to the psychiatry ward with acute psychosis. She was started on L-T<sub>4</sub> 100 µg die, lorazepam 2 mg die and risperidone 1 mg bid with reduction in psychomotor agitation, paranoid ideations and thought disorder. At 6 months of follow-up, she was biochemically euthyroid and was maintained on L-T<sub>4</sub> 100 µg die. This case resembled ours in several aspects.

The patients were of similar age and were female and the psychiatric symptoms were similar. The timing of psychosis following radioactive iodine treatment for Graves' disease was also similar. In both cases, L-T<sub>4</sub> supplementation was associated with improvement in psychotic ideations and paranoia within 2–3 days of administration, likely too short a time to see any changes with risperidone.

Another contributing factor to our patient's psychiatric symptoms, along with acute hypothyroidism, may be severe hypokalemia. A retrospective study by Lam *et al.* (7) demonstrated that hypokalemia had a 27.7% prevalence in hospitalized psychotic patients and may be intrinsically linked to agitation and the use of antipsychotics. Similarly, Hatta *et al.* (8) found a significant correlation between serum potassium concentration and the level of symptoms of acute agitation in schizophrenic men admitted to a psychiatric emergency.

A Medline search since 1960 using the terms 'primary hyperaldosteronism', 'bilateral adrenal hyperplasia', 'hyperthyroidism', 'thyrotoxicosis', 'Graves' disease' and 'myxoedema' was performed. Two case reports with a title suggesting an association between primary hyperaldosteronism and Graves' disease were found (9, 10), but no abstract was available. Graves' disease and primary hyperaldosteronism may coexist incidentally; however, any underlying mechanism associating the two remains unclear. Regarding the association between myxoedema from primary hypothyroidism and hyperaldosteronism, we found two case reports (11, 12) written in foreign languages from the 1970s detailing cases of myxoedema coma combined with hyperaldosteronism. However, the full articles were not accessible, so information on the cases is limited.

In conclusion, the association of primary hyperaldosteronism from bilateral idiopathic adrenal hyperplasia and iatrogenic hypothyroidism following radioactive iodine ablation of Graves' disease is extremely rare: our case report describes it for the first time.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

#### Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

#### Patient consent

The patient provided written consent.

#### Author contribution statement

All authors were involved in the diagnosis and clinical management of this patient. V Larouche gathered all clinical data, was the primary author and followed the patient in the General Internal Medicine Clinic at the Royal Victoria Hospital of the McGill University Health Centre. L Snell and D V Morris reviewed and commented on the manuscript. L Snell was the supervising attending staff in General Internal Medicine Clinic. D V Morris was the endocrinologist on consultation service who initially saw the patient when she presented to emergency room in November 2014.

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Received in final form 11 August 2015

Accepted 2 September 2015