Severe lithium-induced primary hypothyroidism

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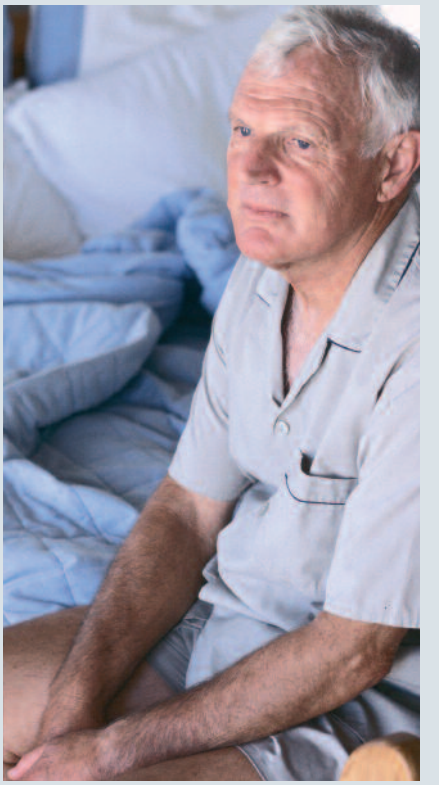

This acute presentation in general practice section is about the immediate management and investigation of an acute presentation in general practice. It is inspired by, but is not based on, a real patient situation.

John is a 65-year-old man who has well-controlled bipolar disorder and lives alone. He has been on lithium 250 mg, one tablet every morning and two every night, for many years. He is an ex-smoker and ex-drinker. Unfortunately, he lost his mother nine months ago, and five months ago he had a serious viral illness and this was the last time you saw him. His mood then seemed flat and he had gained weight. You arranged for him to see his psychiatrist urgently. He attended this appointment, but he has now not had his routine lithium level taken for almost eight months. John also takes thyroxine 150 µg/day (for lithium-induced primary hypothyroidism), simvastatin 40 mg/day, candesartan 8 mg/day (for essential hypertension) and the psychiatrist has commenced him on quetiapine 50 mg every night for depression. He last had low normal lithium levels and was euthyroid on his last blood test eight months ago.

The psychiatrist's secretary phones you to say that John has recently missed a follow-up appointment. What do you do next?
Answer: You telephone John and ask him how he is. You could explain that you haven't seen him recently and that you think his blood tests are due and his prescriptions might be due for renewal. You might tell him that you would also like to see him because you are concerned about how he is feeling after such a bad few months.

John seems flat and distant on the telephone and doesn't say much. You arrange, with his permission, for transport via his close friend to take him to see you and set aside an urgent appointment.

What are your most pressing concerns?
Answer: You are concerned that John has developed severe depression and could even be suicidal. You are also concerned that he may not have been taking his psychiatric and thyroid medications (in particular) and that he may have taken up drinking and smoking again. He is at risk of dehydration, malnutrition and untreated infections. Another important concern would be that, if John is very hypothyroid, he may develop heart failure. These problems are all even more concerning because he lives alone.

John comes in to see you. He has psychomotor retardation, makes poor eye contact and has gained a lot of weight (approximately 20 kg you think). He says he is not drinking or smoking again and is hesitant when he says on questioning that he is not suicidal. You suspect he has developed hypothyroidism from ceasing his thyroxine (and probably his other medications too) due to apathy from worsening depression.

What symptoms related to his thyroid might John complain of and what signs might you find on examination? (One should bear in mind that many of these symptoms are not obvious in mild-to-moderate hypothyroidism.)
Answer: If John were markedly hypothyroid he might complain of constipation, feeling cold, sluggish and tired, having dry skin and brittle hair, and easy weight gain. He may develop impotence (from impaired testosterone synthesis). If the hypothyroidism were very severe, he might have poor concentration and trouble thinking quickly, he might be sleeping more, his ring could be tight from finger swelling and food might not taste of much. He might have muscle cramps (note, women develop heavier periods).

On physical examination you might find John is overweight and has a deep, croaky voice, coarsened facial skin, puffy lips, loss of outer eyebrow hair, dry sparser lank head hair, dry and pale skin, and puffy fingers and toes. He might also have bradycardia, gynaecomastia, lower body temperature and sluggish reflexes. In chronic lithium-induced hypothyroidism, the thyroid is usually normal or there is a small, smooth goitre. Small nodules may be present.

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John has signs of hypothyroidism, appears to have psychomotor retardation and seems very depressed. What investigations should be considered?

Answer: John should have full thyroid function testing (thyroid-stimulating hormone [TSH], free thyroxine [T_4], free triiodothyronine [T_3]), and his lithium level should be measured. Thyroid antibodies are not present in people with lithium-induced primary hypothyroidism but should be measured to exclude coexistent autoimmune thyroid disease. Severe hypothyroidism is a cause of macrocytic anaemia (the anaemia due to impaired erythropoietin synthesis, impaired iron and folate absorption) so a full blood count, iron studies and measurement of red cell folate (representing folate stores as opposed to a serum folate, which only shows what John ate recently) and vitamin B_{12} (as part of the anaemia and psychiatric screen) levels should be carried out. Measurement of urea, electrolytes and creatinine levels should also be carried out and may show lowered sodium and a reduced glomerular filtration rate. Liver function tests and corrected serum calcium and fasting blood glucose levels should be requested. John should have an ECG as a baseline and this might show a low voltage bradycardia.

A fasting cholesterol is not immediately important nor accurate because John may not have been eating normally or taking his medication, so this test is best carried out when he has recovered and is euthyroid. Lipid levels are higher in people with untreated hypothyroidism. Serum prolactin is typically mildly elevated in people with severe hypothyroidism and this knowledge is not going to change the management. Testosterone level is often decreased and this knowledge is also not going to change the management. Its measurement should be reconsidered if the patient is still impotent when he is euthyroid.

The results show a TSH level of 100 IU/L (upper limit: 3.5 IU/L), a free T_4 level of 6.1 pmol/L (normal range: 12.0–22.0 pmol/L) and a free T_3 level of 2.1 pmol/L (normal range: 2.6–6.0 pmol/L). John has a macrocytic anaemia with a haemoglobin level of 105 g/L (normal level more than 125 g/L for men). He has normal red cell folate and vitamin B_{12} levels (it takes a year or so for normal hepatic stores of these two vitamins to be used up resulting in deficiency, if there is no other cause for deficiency other than dietary inadequacy alone). He has normal liver function tests and an estimated glomerular filtration rate of 53 mL/min/1.73 m² (low normal is 55 mL/min/1.73 m²). His calcium level is normal and his fasting blood glucose level is 5.0 mmol/L. His ECG is normal, apart from being of low voltage and showing a bradycardia of 55 beats per minute, regular.

How would you now manage John?

Answer: You admit John urgently to a psychiatric unit under the psychiatrist who knows him. An endocrinologist should be consulted and John would normally be recommenced on 50 µg thyroxine initially (a low dose, so as not to precipitate rapidly raised metabolic demands that could result in angina). The thyroxine should be increased by 25 to 50 µg every three weeks until he is again taking 150 µg/day (50 µg would be used if John had no known history of ischaemic heart disease and no symptoms of this develop during treatment). During this time his thyroid function should be monitored every four weeks (more frequently is not needed because there is a lag time for the level to reach a steady state due to the long half-life of thyroxine). His bipolar depression should be stabilised as an inpatient.

What is lithium-induced hypothyroidism?

Answer: This is hypothyroidism due to lithium therapy that is usually reversible but may be permanent, especially if there is coexistent autoimmune thyroiditis. It usually occurs within the first six to 18 months of lithium therapy and is more common in women and those with a genetic tendency to autoimmune thyroid disease. Typically, there is a normal thyroid or a small, smooth goitre. The cause of lithium-induced hypothyroidism is inhibition of thyroid hormone synthesis and secretion, inducing primary hypothyroidism. Lithium is more toxic in the abnormal gland (for example, with pre-existing autoimmune thyroid disease).

The development of lithium-induced hypothyroidism is not a contraindication to the use of lithium, but thyroxine replacement is indicated. Care is required with ongoing thyroxine replacement in patients taking lithium to maintain euthyroid status.

Outcome: John is discharged eight weeks later with both endocrinology and psychiatric follow up scheduled in the next month (and hopefully, a copy of the discharge summary sent to you, the GP). If he remains euthyroid on thyroxine and stable psychiatrically, he may then return to six-monthly thyroid function testing. It would be strongly advisable for him to see you (plus other psychiatric allied health professionals if this is necessary) every one to two weeks in the first few months after discharge to ensure he is stable and coping. **ET**