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Thyrotoxicosis and Lithium

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Summary. Two cases are presented in which treatment with lithium was complicated by thyrotoxicosis. The underlying physiological mechanisms are discussed.

Lithium suppresses thyroid function, so the early stages of thyrotoxicosis may be clinically undetectable. The symptoms and signs of thyrotoxicosis may be confused with the side effects of lithium, and if lithium is withdrawn severe rebound thyrotoxicity may occur. Furthermore, some of the side effects of lithium may be aggravated by thyrotoxicity.

These cases provide further evidence of the importance of routine screening of thyroid function before starting treatment with lithium.

Lithium is known to cause goitre (Schou *et al.*, 1968) and clinical hypothyroidism (Crowe *et al.*, 1973). In laboratory studies it has been shown to block the stimulating effect of TSH and inhibit I^{131} uptake in the early stages (Lazarus and Bennie, 1972), to impair coupling of iodotyrosines (Berens *et al.*, 1970) and to interfere with release of hormone from the gland (Williams *et al.*, 1971). Temple *et al.* (1972) and Lazarus *et al.* (1972) have advocated its use in the treatment of thyrotoxicosis, although others argue that it is too toxic a drug to be routinely used for this purpose (Hall and Evered, 1974). Estimates of the incidence of clinically significant complications vary. Schou *et al.* (1968) for example, reported goitre in only 12 of 330 patients treated with lithium, and none of these was myxoedematous, though two patients had an abnormally low PBI. Villeneuve *et al.* (1973) reported hypothyroidism in 14·7 per cent of their 149 cases. Most estimates lie between these two, but studies using special techniques show a much higher incidence of abnormalities. For example, Fieve and Platman (1968), using radioactive scanning, found abnormalities in the thyroid gland in 10 of a series of 19 patients treated with lithium (together with various other drugs). Several studies have shown that the mean PBI is significantly lower and the mean 24-hour I^{131} uptake significantly higher in groups of patients taking lithium compared with normal control groups (Rogers and Whybrow, 1971; Hullin *et al.*, 1972; Cooper and Simpson, 1969; Sedvall *et al.*, 1968). Complications may develop both in patients with previously abnormal glands and in those who have no demonstrative abnormality of the thyroid gland (Crowe *et al.*, 1973), but who may be vulnerable because of a dyshormonogenesis.

In this paper two patients are described who developed thyrotoxicosis while being maintained on lithium. These cases raise questions about the relation between affective illness and thyroid function, the modification of thyrotoxic symptoms by lithium and the manifestations of of the side effects of lithium in the thyrotoxic state.

Case Reports

Case 1

A 64-year-old woman was admitted to hospital in a state of mania in April 1970. Her previous history and subsequent progress are summarized in Table I. She had a ten-year history of manic-depressive psychosis and before 1960 had for many years been subject to frequent severe fluctuations of mood for which no treatment had been sought. She had been admitted to other hospitals for the treatment of depression in 1960, 1961, 1962, 1964 and 1965. On each occasion her depression had been slow to respond

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TABLE I

Year	Hospital admission	Mental state	Other observations	Treatment
1960		Depressed two months Manic one month	First episode of treatment	Maintained almost continuously on tricyclic anti-depressants
1961		Ditto		
1962		Ditto		
1964		Ditto		
1965		Ditto	Never well for more than one week	
1969		Manic three weeks Depressed at discharge		
1970		Ditto		Lithium started
1971	January	Hypomanic		January 1970
	March	Depressed		
		First remission		Continued taking lithium
	November	Mood fluctuating	Weight gain due to fluid retention Goitre	
			P.B.I. 10·3	Lithium stopped
1972	February	Manic	Floridly thyrotoxic	
	March	Mood fluctuating		Single dose I^{131} Carbimazole Lithium started
			Euthyroid	Lithium and Carbimazole stopped
1973	January	Manic	Thyrotoxic	Carbimazole
	March	Depressed		Lithium started
	May		Fluid retention Hypokalaemia ?Hyperaldosteronism	Lithium stopped
	June		Euthyroid	Carbimazole stopped
		Second remission		No medication
1975	February	Remains well		No medication

to various kinds of anti-depressant medication; after delays of several weeks she had been given ECT, and this was always followed by a period of hypomania lasting three to four weeks. She was first admitted to hospital in acute mania in 1969.

During this ten-year period she was described as 'never mentally normal for more than a week'. Her mood fluctuated, being predominantly depressed for periods of three to eight weeks followed by euphoria for a few days. For most of this time she was maintained on tricyclic antidepressants. At times she would become severely retarded or anxious and agitated or would manifest marked obsessional features and feelings of guilt.

Her mother had been chronically unstable and had several episodes of in-patient treatment for depression. There was no other relevant family history.

In view of the long history of disabling illness, treatment was started immediately with lithium in the form of slow-release lithium carbonate (Priadel) 1,200 mg. daily. Within three weeks of starting this she became depressed, and severe fluctuations in mood continued to occur until February 1971; at that date she became stable and she remained well on Priadel 1,200 mg. until November 1971. This was her first remission in ten years.

She then suddenly gained 14 lb. in weight, this being due to fluid retention—possibly secondary to cardiac failure, and lithium was stopped as a precaution. A small goitre was noted at the time, but clinically she was euthyroid. Her PBI was 10·3 μg. per 100 ml. but the significance of this was obscured by a history of high consumption of iodine-containing cough medicine in the week before the test.

After lithium was stopped her weight rapidly returned to the pre-treatment level and continued to fall. Lithium was recommenced for a fortnight, but

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during this time a marked tremor of the fingers developed, and as this was thought to be a side effect of lithium the drug was again withdrawn. She then rapidly became agitated and suspicious and early in February 1972 had to be readmitted to hospital. She was anxious and tense with fine finger tremor, tachycardia and marked lid retraction. By the end of February she was floridly thyrotoxic. The PBI was 13·9 and I^{131} uptake, serum thyroxine iodine, T3 resin uptake and free thyroxine factor were all raised. The test for thyroid antibodies was positive at a dilution of 1 in 10.

In March 1972, she was treated with radio-active iodine and thereafter maintained on carbimazole 5 mg. twice daily. She was again treated with lithium, and she remained fairly well until she relapsed into mania in January 1973 and stopped taking the prescribed medication. She soon became severely depressed, and on re-admission in March she was again thyrotoxic (PBI 11·1). When treated as before with carbimazole 5 mg. b.d. and Priadel 1,200 mg. each day she rapidly became euthyroid, with a blood concentration of lithium within the recognized therapeutic range (0·6–1·5 m.mol./l.). However, her mental state did not improve, and after six weeks she became anorexic, confused and somnolent. Initially this was attributed to an exacerbation of the depressive illness, but ataxia and nausea rapidly followed and the concentration of blood lithium was found to have risen to 2·4 m.mol./l. Renal function was not grossly impaired, so the rise in blood level was assumed to be due either to low dietary intake of sodium or to release of lithium from the tissues. The symptoms of lithium intoxication subsided rapidly when treatment with lithium was stopped, and her mental state became normal without further medication.

After four weeks treatment with lithium was recommenced. During this period the PBI had risen from 3·7 to 8·2. The anti-thyroglobulin titre was 1 : 25 and the anti-microsomal test was positive. Free thyroxine was 54 (normal 40–110), resin uptake ratio 0·9 (normal 0·8–1·2) and free thyroxine index 5·3 (4–14). On lithium she became euthyroid but fluid retention recurred and lithium was therefore again withdrawn at the end of May. In mid-June carbimazole was also stopped and she remained euthyroid.

No attempt was made to re-institute treatment with lithium. She has remained euthyroid and her mental state has been normal apart from slight irritability for eighteen months without medication.

Case 2

A 21-year-old man, one of triplets all of whom have manic-depressive psychosis, had been reasonably well on lithium since 1969. In February 1974 he stopped taking this because he felt tired and mentally dull and suspected that his symptoms were side effects of lithium. In July 1974 he was admitted to hospital for treatment of thyrotoxicosis. He had lost weight and become nervous, increasingly tired and depressed. As a result, before his admission he had decided to take his lithium again (serum lithium was 0·8 m.mol./l.). He was hyperactive, with a moderate tremor and a regular pulse rate of 120. There was a firm, diffuse goitre. PBI was 16·0 μg./100 ml., serum T3 uptake 89 per cent (thyopac) and free thyroxine index 18·0. Thyroid auto-antibodies were not detected.

He was treated with carbimazole 15 mg. four times daily initially, reducing to 5 mg. thrice daily, and lithium 500 mg. thrice daily. He rapidly became clinically euthyroid and in three months gained 2 stones in weight.

He was re-admitted to hospital in a state of mania in December, having stopped taking all medication, but he rapidly recovered when lithium and carbimizole were recommenced.

Discussion

These cases demonstrate the difficulties and importance of distinguishing between the signs of affective illness, of lithium toxicity and of abnormal thyroid function. Such diagnostic difficulties are now well recognized in cases of hypothyroidism but not in thyrotoxicosis, and the mechanism of action of lithium in the thyrotoxic patient is therefore of interest.

The onset of thyrotoxicosis during treatment with lithium is in itself a little surprising. Both patients were mentally well on lithium, indicating that it had a stabilizing effect on their affective responses. Since stress may precipitate thyrotoxicosis (for discussion see Hadden and McDevitt, 1974) lithium might be expected to protect against the onset of this illness. The rapid development of florid thyrotoxicosis in the first patient when lithium was withdrawn could to some extent have been associated with the removal of such protection.

The nature of the relationship between the remission of the long-standing affective illness and the treatment of the intercurrent episode of thyrotoxicosis in the first patient is not clear. The persistence of mental symptoms which had

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been attributed to thyrotoxicity after the gland had been treated is well documented (Carpelan, 1957), but in this case the reverse effect was observed. The patient's affective illness had been believed to be the consequence of genetic predisposition and a previously vulnerable personality, but although she was not clinically thyrotoxic before 1972 her mental instability could conceivably have also been associated with a chronic instability of the thyroid gland predisposing to thyrotoxicosis. A study of some 300 manic-depressive patients has shown that fluctuating thyroiditis is clinically undetected in about 10 per cent of these patients. Although this incidence of thyroiditis is no higher than in a normal population, the marked and rapid changes in antibody titres are of interest (Crane and Rosser, to be published). Throughout her illness, until the remission in February 1971, this patient was frequently prescribed imipramine and amitriptyline. Tricyclic drugs can suppress the release of thyroid hormones (Fieve and Platman, 1968; Whybrow *et al.*, 1972), and such an effect could have concealed some instability in thyroid function.

Lithium could have complicated the diagnosis of thyrotoxicosis in both these patients in various ways.

Firstly, it could have delayed the development of the disease by suppressing the release of hormone from the thyroid gland. Lithium has such an effect on the normal gland, but it is much more marked on the toxic gland, even after treatment with radioactive iodine (Spaulding *et al.*, 1972). The effects are observed clinically with slow-release preparations as well as with ordinary lithium carbonate (Crammer *et al.*, 1974), and the rapid rise in PBI observed in this patient on the three occasions when lithium was stopped suggests that such a mechanism was operating.

Secondly, the apparent extent of this suppression could have been accentuated by a post-lithium, toxic rebound. In the normal gland, a decrease in iodide concentration occurs when lithium treatment starts, followed in a few months by reversion to normal (Lazarus and Bennie, 1972). Probably the initial defect in iodide trapping is overcome by a compensating stimulation of the gland mediated by a rise in TSH secretion. Temple *et al.* (1972), arguing on the basis of the analogy between the escape of the response of the toxic gland to iodine and to lithium, suggest that the accumulation of more hormone in the goitrous gland results in a rise in the rate of release of total hormone, despite a decrease in the fractional rate of secretion. On withdrawal of lithium, therefore, a transient rebound thyrotoxicity might be predicted, due to the response of the goitrous gland to the raised level of TSH. Temple *et al.* showed that after cessation of treatment with lithium the response of the rates of iodine release and hormone disappearance ranged from 'no recovery' to rates which did exceed pre-lithium levels. There is some evidence that such a rebound accentuated the apparent thyrotoxicity in the first patient described here, since the PBI fell gradually in the month following the final withdrawal of lithium from 8·2 μg/100 ml to 6·6 μg/100 ml.

Thirdly, it is also possible that lithium 'damped down' some of the manifestations of thyrotoxicosis. Adrenergic blockers, including combined α and β blockers and also β blockers alone, have been shown to suppress many of the symptoms and signs of thyrotoxicosis, including anxiety, nervousness, neuromuscular weakness, fatigue, tachycardia, hyperactive tendon reflexes and impaired glucose tolerance (Review, Granville-Grossman, 1971). Lithium may increase the uptake of nor-adrenaline at nerve endings, thus decreasing the amount available to adrenergic receptors (Colburn *et al.*, 1967). Lithium could possibly therefore suppress the symptoms of thyrotoxicosis by having either a general anti-excitatory effect or a specific β-blocking action.

Fourthly, some of the symptoms and signs of thyrotoxicosis could have been attributable to the side effects of lithium. The second patient believed that his fatigue, which was probably due to the onset of thyrotoxicosis, was caused by the lithium, and presumably stopping lithium merely aggravated the situation. In the first patient, the goitre and tremor were initially considered to be due to lithium, although it is said that the tremors are distinguishable. Furthermore, the true weight loss from thyrotoxicosis was concealed by fluid retention

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resulting in an apparent gain in weight. This fluid retention appeared to be a side effect of lithium, perhaps mediated by an effect on the kidneys, but subsequently there was peripheral circulatory failure with prominent oedema, probably as a consequence of the action of lithium on thyroxine-sensitized tissues. The occurrence of this particular complication, which proved intractable and recurrent, highlights the importance for clinical practice of the effects of lithium in thyrotoxic patients. The diagnosis and management of this patient could have been simplified had thyroid function been screened before starting treatment with lithium and had the significance of the first raised PBI been investigated before an attempt was made to re-institute lithium treatment.

Conclusion

These case histories illustrate the importance of screening thyroid function before starting maintenance treatment with lithium, as recommended by Crowe *et al.* (1973), and of remaining alert to the possible development of abnormalities during treatment. The likelihood of hypothyroidism is now well recognized, but the special problems arising in the diagnosis and management of thyrotoxicosis in the patient taking lithium are not widely discussed. The possible severity of some of the side effects of lithium on thyroxine-sensitized tissues, the risk of transiently increased toxicity when lithium is stopped, and the possibility of the early symptoms of thyrotoxicosis provoking the patient to stop taking medication, are reasons why it is particularly important not to miss the diagnosis of early thyrotoxicosis. The diagnosis is complicated by the similarities between some of the signs of lithium side effects and of thyrotoxicosis, by the suppression of hypersecretion of thyroid hormones by lithium, and possibly by the suppression by lithium of some of the peripheral manifestations of thyrotoxicosis.

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