# Interferon-alpha induced 'tertiary mania'

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## INTRODUCTION

Interferon-alpha (IFN-A) is an increasingly popular treatment for various clinical conditions. It has been independently associated with autoimmune hypothyroidism and psychiatric syndromes. The case reported is of a 32-year-old woman who developed acute mania with psychotic symptoms during treatment with IFN-A for essential thrombocythaemia. Features of this case that warrant discussion include the complex aetiology and the need for awareness of such serious potential complications of IFN-A therapy.

## DISCUSSION

IFN-A is one of the interferons, a group of proteins with antiviral, antiproliferative and immunomodulatory effects. IFN-A has been used in recent years to treat an ever wider range of conditions including benign and malignant haematological disorders, chronic hepatitis and breast cancer. Because of its broad activity, IFN-A has a significant adverse effect profile (Kingsley, 1999). Most adverse effects are self-limiting and restricted to the period of therapy. However, some have longer lasting implications.

One such adverse effect is the development of autoimmune thyroid disease, which has been shown in one study by Gisslinger et al (1992) to occur in more than 20% of chronic IFN-A patients. Many patients with this complication have been found to have developed positive thyroid autoantibodies, especially thyroid microsome antibody (Gisslinger et al, 1992; Watanabe et al, 1994), although up to half of patients may have previously tested negative for such autoantibodies before IFN-A treatment (Baudin et al, 1993).

It is important to note that the development of autoimmune thyroid disease as an adverse effect of IFN-A may be a reversible phenomenon, all patients in one study by Baudin et al (1993) demonstrating normal thyroid function within 2 years of stopping therapy.

The concept of 'secondary mania' was established by Krauthammer and Klerman (1978) and many antecedent organic causes have since been reported.

Hypothyroidism presenting with psychiatric symptoms was first documented in 1888, although Asher only wrote the classical description of 'myxoedematous madness' in 1949. IFN-A has also been directly associated with the development of psychiatric syndromes. These usually occur approximately 1–3 months after commencing IFN-A therapy and may present as secondary affective disorders or organic states (Renault et al, 1987).

The presentation of the patient described, with grandiosity, irritability, distractability and poor concentration, persecutory delusions, pressure of speech and flight of ideas, met the *International Classification of Disorders* (ICD-10) diagnostic criteria for mania with psychotic symptoms (World Health Organization, 1992). However, it remained necessary to establish whether this was a primary manic episode, a secondary psychiatric adverse effect of IFN-A or the tertiary result of IFN-A-induced autoimmune hypothyroidism.

In view of the profound nature of the hypothyroidism and its presumed

## CASE REPORT

A 32-year-old woman with no previous history of psychiatric illness was admitted to an acute psychiatric unit, having been behaving increasingly bizarrely over the previous week. She had persecutory delusions and grandiosity, but admitted to a 2-week history of low mood. Her sleep was disturbed and she had not slept at all on the night before admission. At admission she fluctuated between elation and aggression. Her speech was pressured and she demonstrated flight of ideas as well as poor attention and marked distractability.

She had been treated for the previous 4 years with recombinant interferon-alpha by subcutaneous injection for essential thrombocythaemia, her dose having been gradually reduced to 3 megaunits twice-weekly at the time of admission. Physical examination on admission revealed no abnormalities. However, routine biochemical investigation revealed her to be profoundly hypothyroid, with a free thyroxine of 1 pmol/litre (10–26) and a thyroid-stimulating hormone of >84 mU/litre (0.5–6.5). Further investigation revealed a raised thyroid microsome antibody at 6400 units (<400). Her platelet count was $435 \times 10^9$/litre, revealing her essential thrombocythaemia to be well controlled. All other investigations, including electrocardiogram, lipids, creatinine kinase and lactate dehydrogenase, were normal.

The patient required restraint and sedation. Her mental state improved rapidly over the following few days on oral haloperidol 5 mg three times daily. On discovery of her hypothyroidism, she denied a history of any classical physical symptoms. She was commenced on thyroxine 50 μg daily and her interferon-alpha discontinued. Her haloperidol was reduced and then discontinued at 1 month post-discharge. She has since remained well during the subsequent 12 months.

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short duration before the onset of the psychiatric syndrome, as the patient had not yet developed recognized physical symptoms of myxoedema, there appeared to be a strong temporal relationship between the psychiatric syndrome and the hypothyroid state. In addition, the patient had been using IFN-A uneventfully for many months and had no previous psychiatric history. It would therefore seem likely that this woman developed a tertiary mania as a result of IFN-A-induced acute autoimmune hypothyroidism.

## CONCLUSIONS

This case illustrates the necessity always to consider an organic diagnosis to account for any acute psychiatric presentation. In addition, the value of routine thyroid function testing in acute psychiatric admissions is borne out here.

Regarding the use of IFN-A therapy, clinicians considering this should be aware of the potential adverse effects. Thyroid function and autoantibody status should be established before commencing therapy and then monitored regularly during treatment. The manufacturers also recommend that in patients with a history of psychiatric illness, especially those with a history of suicidal ideation, IFN-A should only be used with cautious monitoring of the patient's mental state. HM


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