CASE REPORT

Can cycles of chills and fever resolve bipolar disorder mania?

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SUMMARY

Treatment resistance is common in populations of patients with bipolar disorder stressing the need for new therapeutic strategies. Favourable effects of fever on mental disease have been noted throughout history. Today there is increasing evidence that immunological processes are involved in the pathophysiology of mental disorders. We present a case in which a patient with treatment resistant bipolar disorder mania seemingly recovered as a result of recurrent fever. This indicates that artificial fever might become a last resort therapy for treatment resistant mania.

BACKGROUND

Treatment resistance is common in populations of patients with bipolar disorder (BD) both in the depressive and manic phases.¹ Even under optimal maintenance conditions, almost half of patients with symptom remission will have recurrence in 2 years under standard care.² Very few studies have addressed treatment-resistant bipolar mania. Clozapine and electroconvulsive therapy (ECT) have some documented effect.^{3–5} There is an urgent need for new options for treatment for this group of patients.⁶

Fever is a primal host defence that has evolved over millions of years which exerts beneficial responses in combating infections.⁷ Could fever also have positive effects on mental disease? The ancient Greeks believed it to be so. Hippocrates reported favourable effect of fever on epilepsy and Galen described a patient recovering from melancholia after an attack of quartan fever. Indeed Parmendies is known for the saying: “Give me the power to produce fever and I’ll cure all disease.”⁸

However, it was not until the first half of the 20th century that artificial fever therapy saw its heyday. In 1927 Julius Wagner-Jauregg was awarded the Nobel Prize in physiology for his use of malarial inoculations to treat general paresis. Although the vast majority of patients who received artificial fever therapy suffered from neurosyphilis, Wagner-Jauregg proposed that fevers might be helpful in a variety of psychiatric disorders, including mania and melancholia.⁹

CASE PRESENTATION

A 38-year-old woman with BD was involuntarily admitted to department of psychiatry due to acute mania with mood congruent psychotic symptoms.¹⁰ Prior to admission she had been in remission for roughly 1.5 years. She had developed the manic episode in spite of ongoing treatment with two antiepileptic mood-stabilisers (valproate 600 mg×1

and lamotrigine 100 mg×1). Likely to have triggered the episode was sleep deprivation in conjunction with a home exam. At the time of admission she was agitated and delusional with increased psychomotor activity and speech. She scored 37 points on Young Mania Rating Scale¹¹ corresponding to a severe manic episode. In prior manic episodes she had been highly treatment resistant. Lithium, valproate and a number of first-generation and second-generation antipsychotics had been tried both in monotherapy and in combination without adequate effect. She had regularly been treated with ECT at former manic episodes. She denied ECT at the present admittance due to cognitive side effects after prior treatment series.

Initially the dose of valproate was increased to 1200 mg×2. This had no effect on the manic symptoms. It was then decided to start treatment with clozapine, which she had never tried before. Clozapine was administered in increasing doses from 50 to 250 mg over a 7-day period while valproate was reduced to 900 mg×2. A slight sedative-hypnotic effect was noted, otherwise her manic condition persisted. After 10 days on clozapine she suddenly developed fast rising fever, neck stiffness and visual hallucinations. Clozapine and valproate were immediately discontinued and she was admitted to medical ward.

INVESTIGATIONS

At admittance to the department of medicine she was suffering from delirium. She had chills with fever of 39.7°C, a slight tachycardia of 110 and a somewhat elevated blood pressure of 141/92. Apart from this clinical examination was normal. Laboratory findings showed slightly elevated C reactive protein of 65 mg/L otherwise normal values. Chest X-ray was normal. A lumbar puncture was performed showing clear cerebrospinal fluid with normal amounts of protein and glucose, absence of leucocytes and no certain microbes. Eventually all microbiological tests (blood cultures, urine cultures, throat cultures and cerebrospinal fluid cultures) turned out to be negative.

During her 4-day stay in the department of medicine she had at least five episodes with cycles of chills and fever with temperatures ranging from 37° to 40.2°C (figure 1). Her clinical condition varied in correlation with the temperature fluctuations with fatigue and reduced level of consciousness co-occurring with the chills of high fever. After four nights the medical condition stabilised and she was transferred back to psychiatric ward. She is now afebrile.

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Figure 1 Temperature curve.*Days after admittance to department of medicine.

DIFFERENTIAL DIAGNOSIS

There are a number of potential causes for the fever. Viral infection despite negative microbiological cultures is possible. However clozapine-induced fever which is a relatively frequent and benign condition is probably more likely. It usually has a spiking pattern, peaks within the first 2 weeks of treatment, lasts 2.5 days on average and is typically below 40°C. Nonetheless clozapine-induced fever peaking to 41°C is described.¹²

Two feared clozapine-induced conditions are agranulocytosis and neuroleptic malignant syndrome (NMS). The former was immediately ruled out by normal granulocyte count. NMS is a life-threatening neurological disorder caused by dopamine receptor blockade typically consisting of muscle rigidity, hyperthermia, autonomic instability, altered consciousness and elevated plasma creatine phosphokinase.¹³ There are, however, no unanimous diagnostic criteria for NMS which sometimes can make it hard to distinguish between NMS and clozapine side effects.¹⁴ Indeed one current view on clozapine-induced fever regards it as a mild variation of NMS.¹⁵

TREATMENT

During her stay at the department of medicine she was only treated symptomatically with acetaminophen, lorazepam and intravenous Ringer's acetate.

OUTCOME AND FOLLOW-UP

When returning to the department of psychiatry she was without any symptoms of mania. Mood-stabilising medication with valproate and lamotrigine was reintroduced. During the following week she had no symptoms indicating a BD affective episode. The involuntary commitment was no longer warranted. She remained stable for about 2 weeks but was then readmitted with resurgence of manic and depressive symptoms. This mixed episode persisted until she gave her consent and received ECT—a total of 10 series—5 months later. She has since been in remission for 2 years on lamotrigine 200 mg and valproate 600 mg. She is currently without symptoms and working part time.

DISCUSSION

Inflammatory processes may play a crucial part in the pathogenesis and progression of mental disease.¹⁶ Several studies have shown altered level of various cytokines during symptomatic and asymptomatic phases of BD.^{17–20} Some of these cytokines such as TNF- α , IL-1, IL-6 (proinflammatory cytokines) and IL-1RA (anti-inflammatory cytokines) are key agents involved in fever.²¹ We hypothesise that the cycles of chills and fever and/or

inflammatory processes associated with this led to the patient's improvement. Despite the increasing scientific focus on immunology and mental disease there is hardly any published research of recent time on possible effects of fever on affective disorder. One clinical study showed that endotoxin-induced cytokine synthesis and fever transiently improved mood in patients with major depression.²² We have not been able to find any similar reports regarding fever and mania.

There is an urgent need for novel therapeutic strategies targeting BD which do not respond to usual treatment. Our case report could indicate that artificial fever may yet again find its role as a last resort therapy for treatment resistant affective disorder. Further research exploring the pathophysiology of fever and its relation to mania is needed in order for this to become a real treatment alternative.

Learning points

- ▶ There is a need for new therapeutic options targeting treatment resistant bipolar disorder.
- ▶ There is increasing evidence that inflammatory processes are involved in the pathophysiology of bipolar disorder.
- ▶ Fever might be beneficial in combating mania.
- ▶ Therapeutic strategies involving artificial induction of fever and cytokine synthesis might be a future treatment alternative for treatment resistant mania.

Contributors AS and AVE were involved in treating the patient, collected supplementary data, drafted the manuscript and approved the final version of the manuscript.

Competing interests None.

Patient consent Obtained.

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