CASE REPORT

Schizophrenia-like disorder associated with etanercept treatment

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SUMMARY

A report on the development of a schizophrenia-like disorder after the start of etanercept in a middle-aged woman who had no history of psychiatric illness. Etanercept was discontinued and she was treated with sulpiride for 6 months. There has been no relapse of psychosis since etanercept was discontinued, despite being off sulpiride for 3 months. Unfortunately, subsequent treatment she has had for her rheumatoid arthritis has not afforded the same level of symptom control as etanercept. This report points to the need for more research into the differential impact of reduced-tumor necrosis factor (TNF) α levels in the different regions of the brain. It highlights the need for pharmacovigilance especially in individuals on etanercept and other TNF inhibitors. It also highlights the need to systematically consider differential diagnosis before arriving at a diagnosis of psychiatric illness even in the presence of highly suggestive constellation of symptoms.

BACKGROUND

Etanercept is a soluble receptor fusion protein that binds and inactivates tumour necrosis factor (TNF), a proinflammatory cytokine that is overproduced in the joints of patients with rheumatoid arthritis,[1] and some other autoimmune rheumatological disorders. Although it has been highlighted as a generally well-tolerated treatment for inflammatory diseases, a possibly increased risk for infection, congestive heart failure, malignancies and demyelinating disease has been described.[2] At present, psychosis is not listed as a possible adverse effect by the manufacturers.

This report highlights the case of a middle-aged woman with no psychiatric history with an onset of schizophrenia-like disorder 4 weeks after the start of etanercept.

CASE PRESENTATION

A 54-year-old married mother reported with a history of hypothyroidism for the past 15 years which was controlled with levothyroxine and a 10-year history of rheumatoid arthritis. She had been treated with methotrexate, prednisolone and sulfhasalazine among others in the past. Suboptimal response and allergic reactions led to discontinuation of these at various respective times. She was started on etanercept 25 mg once weekly by her rheumatologist in 2011 and received optimal response. However, 4 weeks later she began having auditory hallucinations with a persecutory content. She subsequently developed systematised delusions of persecution, grandiosity and control. This was associated with a lack of insight. She continued to comply with etanercept and her symptoms worsened until she was admitted in an acute psychiatric health unit 12 months later. This admission followed her presentation to the police station to report a delusional idea that the lives of her family members were in imminent danger.

The patient is a homemaker in a stable family unit who had previously been in high-functioning employment for over 24 years. She had no psychiatric history and no family history of psychosis. Apart from hypothyroidism and rheumatoid arthritis she had no other medical history of note. She also had no history of illicit drug or significant alcohol use.

A confusional state was ruled out on admission. All investigations performed on admission in August 2012 including a CT scan of the brain and other investigations were normal apart from a subclinical hypothyroidism with a thyroid stimulating hormone-level 5.2 mIU/L (n=0.27–4.2 mIU/L) and thyroxine level 11 pmol/L (n=11–25 pmol/L). This was explained by non-compliance with her prescription of levothyroxine for the previous 4 days. In addition, no neuropsychiatric or other symptoms of hypothyroidism were superimposed on her presentation. She was not depressed, anergic or cognitively impaired.

Etanercept was withheld and an antipsychotic drug sulpiride 200 mg twice daily was prescribed resulting in the rapid resolution of her symptoms within 10 days. She was discharged following remission of her symptoms. Her rheumatology team decided not to restart etanercept. This meant that the patient was on etanercept for a total period of 12 months. She was subsequently started on naproxen and paracetamol. Unfortunately, her arthritis is not as well controlled. The patient was maintained on sulpiride 200 mg twice daily for 6 months after which it was discontinued. There has been no relapse in her psychiatric state since her discharge, despite being off sulpiride for the last 3 months.

OUTCOME AND FOLLOW-UP

The patient has been followed up in our outpatient clinic. She was maintained on sulpiride for 6 months after which it was discontinued. There has been no relapse in her psychiatric state since her discharge, despite being off sulpiride for the last 3 months.

DISCUSSION

Schizophrenia is a psychotic disorder with abnormalities in perception, thought, emotions and

behaviour. There is evidence for reduced risk of schizophrenia in individuals with rheumatoid arthritis[3]; which is an autoimmune disease that targets synovial tissues, cartilages and bones; and leads to joint damage and disability.[4]

There is some evidence that inflammatory changes such as activation of microglia and cytokine release have a role in schizophrenia,[5 6] but the evidence is conflicting.[7] TNFα is a proinflammatory cytokine whose level is raised in the joints of patients with rheumatoid arthritis. It has been implicated in excitatory brain injury; and blockage of endogenous TNFα has been shown to be neuroprotective.[8] However, TNFα has also been shown to possess a dual role both in promoting and protecting neurons from death[5] and beneficial neuroprotective effects of TNFα at distinct concentrations at different regions of the brain has been highlighted in animal studies.[5 9]

The way in which a medication like etanercept may lead to a psychotic episode is not clear. It could be that an indiscriminate reduction in endogenous TNFα in the brain of humans may impact adversely on distinct areas of the brain in which a critical level of TNFα is necessary for neuroprotection leading to the emergence of psychosis and other neuropsychiatric adverse effects.

In the patient's case we excluded alcohol and substance misuse. Also, apart from levothyroxine the patient was not on any other medication. In addition, her symptoms occurred against a background of no personal or family history of psychiatric illness. Although the temporal relationship between the onset of etanercept and of schizophrenia-like disease could be coincidental, it seems highly suggestive of a possible causal link considering other aspects of this case. Apart from one dose of etanercept which she missed in the period of 12 months in which she had been on etanercept, she had been fully compliant and the psychotic symptoms persisted. The patient's symptoms also resolved rapidly after stopping etanercept and her functioning has returned to premorbid levels. Although the use of sulpiride could be relevant in inducing remission of the schizophrenia-like disease, subsequent discontinuation of sulpiride has not coincided with a new episode of schizophrenia-like disease.

Our case joins the list of a growing number of cases of pointing to a differential psychiatric impact of etanercept and other cytokine modulators. It adds to previous report of three cases of acute psychosis while on anti-TNFα treatment; in which like our case two of the individuals were in their 50s and on etanercept.[10] Conversely, there has been a report of a resolution of psychotic symptoms in a patient with comorbid Crohn's disease following treatment with infliximab (a monoclonal antibody against TNFα) in combination with quetiapine. The patient remained psychotic-symptom free at the time of that report, but still on a reduced dose of quetiapine.[11] In a further case in which cyclosporine appeared to exacerbate a paranoid schizophrenia, the substitution of etanercept for cyclosporine was linked to clinical improvement.[12]

This report points to the need for more research into the differential impact of a reduced TNFα levels in the regions of the brain. It highlights the need for pharmacovigilance especially in individuals on etanercept and other TNF inhibitors. It also highlights the need to systematically consider differential diagnosis before arriving at a diagnosis of mental illness even in the presence of highly suggestive constellation of symptoms.

Learning points

- This report points to the need for more research in the differential impact of tumor necrosis factor (TNF)-α levels on the different regions of the brain.
- This case highlights the need for pharmacovigilance in individuals on etanercept and other TNF inhibitors particularly for the emergence of adverse symptoms of psychosis.
- It adds to previous report of three cases of acute psychosis while on anti-TNFα treatment; in which like our case two of the individuals were in their 50s and on etanercept.[5]
- It also highlights the need to systematically consider differential diagnosis before arriving at a diagnosis of psychiatricpsychiatric illness even in the presence of highly suggestive constellation of symptoms.

Competing interests None.

Patient consent Obtained.

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