high urinary nitrates, white blood cell count, and bacteria levels. Hemoglobin, hematocrit, liver function tests, and thyroid-stimulating hormone were all normal. Brain magnetic resonance imaging revealed aged-appropriate changes.

Miss X was treated with ciprofloxacin for a urinary tract infection, and started on quetiapine, haloperidol, donepezil, and memantine to manage the behavioral change. She was sent home, where she persisted in being restless, talkative, and requiring little sleep. Miss X then saw a psychiatrist, who admitted her to a psychiatric unit. All previous medications were discontinued, and lithium was initiated with excellent response.

**DISCUSSION**

Keeping Miss X’s age in mind, it was imperative to exclude delirium and dementia. It was reasonable to assume that the combination of urinary tract infection and uremia may have led to delirium, but at no point in her history was fluctuation in mental status, the central feature of delirium, observed. She also persisted in exhibiting altered behavior in spite of appropriate medical management during her first admission. With regard to dementia, Miss X never displayed genuine cognitive impairment in her history or examination. Furthermore, behavioral manifestations tend to occur in the latter stages, when memory derangement is patent and functionally limiting.

Miss X’s symptoms were characteristic of mania. Very late-onset (aged ≥ 65) mania is generally due to an underlying medical disorder, frequently neurological (e.g., tumors, stroke, injury). Triggering organic conditions broadly include toxic, metabolic, and infectious entities. Likewise implicated are drugs, such as dopamine agonists, corticosteroids, antidepressants, thyroid supplements, benzodiazepines, and antihistamines. Miss X was chronically taking alprazolam, which has been reported to induce mania, but the authors believe this to be an unlikely culprit because all cases described were much younger, and manic symptoms occurred within 3 weeks of treatment.

After Miss X was ascertained to be free of any precipitating medical conditions, it was concluded that she was suffering from bipolar I disorder. There is a paucity of evidence on the incidence of primary bipolar disorder after the age of 90, although a profound decline is generally anticipated. Although both forms of mania (manic symptoms due to underlying medical factors and primary mania from a bipolar affective disorder) respond to drugs such as lithium, anticonvulsants, and antipsychotics, correcting the inciting condition is the management priority in secondary mania. Foremost in the care of patients with altered behavior is to distinguish between an organic etiology and a primary psychiatric malady. With older age comes a longer list of differential diagnosis, which makes the task of establishing the right diagnosis more challenging. Nonetheless, this case emphasizes that when faced with an older adult presenting with mania, the clinician must exclude an underlying condition before heading down the psychiatric path.

**REFERENCES**


**ACKNOWLEDGMENTS**

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Sponsor’s Role: None.

**COGNITIVE IMPROVEMENT WITH INTRATHecal ADMINISTRATION OF INFlixIMAB IN A WOMAN WITH ALZHEIMER’S DISEASE**

To the Editor: Alzheimer’s disease (AD) is the most common cause of dementia in older adults and is characterized clinically by cognitive decline and pathologically by the formation of amyloid β-peptide (Aβ) and neurofibrillary tangles in the brain. There have been no effective drugs than can modify the process of AD. Here, a case of AD with severe cognitive impairment in which treatment with intrathecal injection of infliximab was associated with rapid clinical improvement of cognition in addition to modulation of the concentration of Aβ1-42/p-tau in cerebrospinal fluid (CSF) and peripheral blood is presented.

A 57-year-old Han Chinese woman was admitted to the hospital. Four years before, she had had difficulty recalling something that happened a few minutes ago, finding her way home in a familiar environment, and using electrical equipment. Donepezil was given, but was discontinued after 6 months because of cost. Progressively, she lost the ability to perform almost all activities of daily living. General physical examination was unremarkable. The 12 cranial nerve, motor and cerebellar, and sensory examinations were normal. She had difficulty recalling personal information and the name of physician after 90 seconds despite repetitive introductions throughout the examination. She scored 4 points on the Mini-Mental State Examination (MMSE). On the Montreal Cognitive Assessment (MoCA), she could not copy a cube, and she drew
only a line in the clock-drawing test. She recognized only “camel” of the three animals. After three trials to register five words, she retrieved nothing even with categorical or multiple choice cueing 180 seconds later. She could repeat no more than three continuous arabic numbers. When asked to list all the animals she could in 60 seconds, she listed nothing. She could repeat a single word but not a complete sentence. She could not perform simple calculations or serial sevens. She was not oriented to the calendar date, day of the week, year, city, or place. Abstract concepts could not be expressed. Hence, she scored 1 point. Magnetic resonance imaging showed bilateral mild hippocampal atrophy. Before treatment, concentrations of Aβ₁₋₄₂, Aβ₁₋₄₀, and p-tau in the CSF were 278.17, 13.82, and 29.54 pg/mL, respectively. Other laboratory examination before treatment was unremarkable. According to the revised National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association criteria (2007), the diagnosis of probable AD was definite.

After her hospitalization, the patient’s medications included donepezil 5 mg/d, nicergoline 30 mg/d and huperzine A 100 μg three times per day. After obtaining written informed consent from her husband, infliximab (Remicade, Cilag AG, Schaffhausen, Switzerland) (50 mg in 5 mL of sterile water) was administered for 10 minutes by intrathecal injection when lumbar puncture was performed. One week later, a second treatment was given. At the same time, CSF and peripheral blood were stored at −80°C for enzyme-linked immunosorbent assay (ELISA).

Half an hour after dosing, she scored 4 on the MOCA. She could recognize all three animals. It took three trials for the patient to register five words, and 180 seconds later she could retrieve one without any cueing, one with categorical cueing, and one with multiple choice cueing. She could repeat five continuous arabic numbers but not six or more.

Two hours later, she scored 9 on the MOCA. She was now oriented to year, month, and place and could correctly name the city as Nanjing. She could tell us her son’s name and where he was. Throughout testing, she appeared at times to be inappropriately euphoric. The improvement lasted for six months after treatment, her cognition returned to the level before infliximab.

The results of ELISA showed that infliximab administration increased the concentration of Aβ₁₋₄₂ and p-tau but not Aβ₁₋₄₀ in the CSF and blood 7 days after the treatment (Table 1).

### Table 1. Concentration of Amyloid β-Peptide (Aβ₁₋₄₀, Aβ₁₋₄₂, and P-Tau in Cerebrospinal Fluid (CSF) and Blood Before and After Treatment with Infliximab

<table>
<thead>
<tr>
<th>Aβ₁₋₄₀ Concentration</th>
<th>Before Infliximab</th>
<th>One Week After Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ₁₋₄₀ in CSF, pg/mL</td>
<td>13.82</td>
<td>13.84</td>
</tr>
<tr>
<td>Aβ₁₋₄₀ in blood, pg/mL</td>
<td>59.99</td>
<td>59.82</td>
</tr>
<tr>
<td>Aβ₁₋₄₂ in CSF, pg/mL</td>
<td>278.17</td>
<td>298.37</td>
</tr>
<tr>
<td>Aβ₁₋₄₂ in blood, pg/mL</td>
<td>379.15</td>
<td>388.87</td>
</tr>
<tr>
<td>p-tau (p181) in CSF, pg/mL</td>
<td>29.54</td>
<td>40.77</td>
</tr>
<tr>
<td>p-tau (p181) in blood, pg/mL</td>
<td>38.73</td>
<td>110.74</td>
</tr>
</tbody>
</table>

**DISCUSSION**

There have been several reports that anti-tumor necrosis factor alpha (TNFα) agents may affect amyloidosis in inflammatory disease, such as rheumatoid arthritis and familial Mediterranean fever. Rapid cognitive improvement after perispinal etanercept administration had been reported. This may be the first report to suggest an effect on Aβ/p-tau in a person with AD by anti-TNF. Similar results were obtained in animals. A previous study indicated that intracerebroventricular administration of infliximab reduced amyloid plaques and tau phosphorylation in APP/PS1 mice.

The case report suggests the pivotal role of TNF-α and the interaction between TNF and amyloid in the pathogenesis of AD. The efficiency and safety of infliximab need to be researched further in large sample trials or randomized control trials. The current results suggest that intrathecal infliximab offers a superior alternative therapeutic approach for AD and potentially for other neurodegenerative disorders in which TNF-α is involved in the pathogenesis, such as Parkinson’s disease and amyotrophic lateral sclerosis.

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**Author Contributions:** JQS, BRW, WWJ, JC, YWZ, and LLZ performed the case study. JQS, YDZ, and JX wrote the letter (corresponding authors).

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### REFERENCES


RESEARCH STUDIES

WHEN HOSPITAL PATIENTS FALL: PRELIMINARY DATA FROM FERRARA, ITALY

To the Editor: Falls are a common, serious problem in older adults. One-third of people aged 65 and older fall at least once a year, and the risk increases with age.1 Moreover, falls represent a social and economic burden; in the United States, more than 2.6 million older adults experience a fall-related injury, and health costs exceed $19 billion.2 Acute diseases do not occur randomly over time but exhibit circadian variations. In particular, myocardial infarction, stroke, and aortic diseases occur more often in the morning.3–7 Although anecdotal evidence and clinical experience suggest a nocturnal preference for falls events, chronobiological studies are not available. This study was aimed to verify whether hospital falls occur randomly throughout the day or exhibit a rhythmic pattern.

RESULTS

During 2009, 371 consecutive falls were recorded (mean age 73.8 ± 17.6, 55.8% men). A circadian variation was

Figure 1. Chronobiological analysis of circadian distribution of in-hospital patients’ falls: total events (Azienda Unità Sanitaria Locale, Ferrara, Italy, 2009).