Hypofrontality With Positive Anti-NMDA Receptor Antibodies

To the Editor: Anti-NMDA receptor antibodies have been implicated in cases of acute encephalitis presenting with psychiatric symptoms. We present, with the patient's consent, a likely case of anti-NMDA receptor encephalitis manifesting with insidious frontal lobe dysfunction.

Case Report

A 35-year-old man was admitted to an acute psychiatric ward following concerns from his family about worsening self-neglect and bizarre behavior. In the weeks prior to admission, he had barricaded himself in his flat, refused to allow anyone to visit, and was spending most of his days sitting in the kitchen with the television continually switched on. Shortly after admission he was detained under Section 2 of the Mental Health Act.

The history, taken from his mother and sister, suggested an insidious onset of personality changes and functional decline over a 4-year period, beginning with occasional short-term memory loss and disorientation in time. He was reported to have returned from work early, slept for a few hours, and on waking in the evening, got dressed and returned to his workplace. As a result, he was unable to keep his job. There were also changes in the patient's eating behavior, including bingeing on food until he vomited, putting whole packets of chewing gum in his mouth, and drinking excessive volumes of hot tea. He stopped eating regular meals and lost significant weight. His personality is reported to have changed from being gentle and good-humored to short-tempered and suspicious. Other bizarre behavior included wandering the streets at night wearing sunglasses, sleeping in the kitchen, and emptying the contents of his mother's cupboards into plastic bags.

There is a family history of mental illness. His sister has a diagnosis of emotionally unstable personality disorder, and his grandmother and his brother suffered from depression. The personal history was unremarkable.

His behavior was on the ward extremely disorganized. On several occasions, he urinated in inappropriate places and became verbally aggressive when told not to. He gorged himself with food until he vomited, and walked around with vomit in his beard. He had marked anterograde amnesia, and had to be reminded of the location of his room several times a day. He slept in unusual places, including the laundry room. There was no evidence of hallucinations, delusions, or mood disorder. His speech was monotonous and hesitant, and his affect was flat. There was marked apathy, and he required prompting with all activities of daily living. Physical examination was unremarkable, except for mildly increased tone distally in both upper limbs.

Neurocognitive tests revealed significant deficits. He scored 69/100 on the Addenbrooke's Cognitive Examination (ACE-R). There was marked perseveration with verbal fluency tests. A National Adult Reading Test revealed a predicted IQ of 114. However, on the Weschler Adult Intelligence Scale, he scored an IQ of 80 with weaknesses in both verbal and performance scales. Hayling and Brixton tests revealed significantly impaired executive function. Blood tests were all negative, including caeruloplasmin, HIV, and syphilis serology. Cerebrospinal fluid analysis revealed mildly raised polymorphs, but was otherwise unremarkable. A CT head scan was reported normal, whereas an MRI revealed nonspecific volume loss and white-matter hyperintensities.

Based on the insidious onset of social withdrawal, behavioral change, incongruous affect, and impairment in executive function in the absence of positive psychotic symptoms, a provisional diagnosis of simple schizophrenia was considered. Olanzapine was commenced at 20 mg a day, and a reduction in disinhibited behavior, hyperorality, and irritability was achieved. However, his cognitive function continued to decline, and his performance on a repeat ACE-R revealed a score of 48/100. His diagnosis was reviewed, and, given the progressive nature of the cognitive decline, frontotemporal dementia was considered.

He was referred to a neurology ward for further investigations. A battery of blood tests was performed, which revealed a positive result for anti-NMDA receptor antibodies. Assuming a diagnosis of anti-NMDA receptor antibody encephalitis, he received plasma exchange therapy and corticosteroids. Antipsychotic medication was stopped without any deterioration in his mental state. Some improvement in cognitive function and behavior was noted after the plasma exchange. His ACE-R score increased to 75/100, and his family reported some improvement in his memory. He continued to require assistance with activities of daily living, but there

were no further reports of the disinhibited behavior that he had presented with early in his admission. He was discharged to the care of his mother.

No further improvement on his ACE-R score was measured after a second course of plasma exchange. However, 6-month follow-up revealed significant improvements in function, including increased spontaneity of behavior, greater care with personal hygiene, and the ability to prepare meals unaided. He continued to display negative symptoms of poverty of speech and blunted affect, but his condition remained stable without any further deterioration.

Discussion

Our patient's presentation with insidious behavioral changes, social withdrawal, incongruous affect, and impaired executive function indicates frontal lobe dysfunction. The cause of this was a matter of debate for some time. Both simple schizophrenia and frontotemporal dementia can manifest in this manner, and our patient's presentation fulfilled the criteria for both diagnoses.[1,2] Furthermore, data from neuroimaging and neuropsychological tests are often not specific enough to distinguish these two conditions.[3] There were some features not suggestive of simple schizophrenia, including the adult onset, good premorbid functioning, and the improvement in mental state despite discontinuation of antipsychotic medication.[4] There were also features not suggestive of frontotemporal dementia, including the absence of a family history, and the measured improvement of cognitive function after plasma exchange.[5]

NMDA-receptor hypofunction has been implicated in the pathophysiology of the negative symptoms of schizophrenia.[6] However, we are not aware of any specific association with anti-NMDA receptor antibodies. Reported cases of anti-NMDA receptor encephalitis typically describe an acute onset with fever, seizures, dyskinesias, and autonomic lability, features that were absent in our patient.[7] To the best of our knowledge, presentations with chronic and insidious frontal lobe dysfunction have not been reported.

It is possible that the presence of anti-NMDA receptor antibodies in this case was an incidental finding unrelated to our patient's symptoms. To our knowledge, the prevalence of these antibodies in the general population is not clear. However, the clinical improvement after treatment with plasma exchange and corticosteroids, despite discontinuation of antipsychotic medication, suggests an immune-mediated pathology. If this is so, then this case reveals a previously unreported possible presentation of anti-NMDA receptor encephalitis.

Further studies are warranted to determine the prevalence of these antibodies in the population, and to establish whether there is any association with simple schizophrenia or frontotemporal dementia-like presentations. If such an association is found, anti-NMDA receptor encephalitis would be an important and potentially treatable differential diagnosis to consider in cases of insidious frontal lobe dysfunction.

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Dr. Hane Maung, M.B. BChir
Dr. Gaetano Dell'Erba, M.D.
Cambridgeshire and Peterborough NHS Foundation Trust, Huntingdon Acute Care Service, Hinchingbrooke Hospital, Huntingdon, United Kingdom PE29 6NT
Correspondence: Dr Gaetano Dell'Erba; e-mail: hane.maung@cpft.nhs.uk

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