CASE REPORT

Managing psychotic depression and diagnostic uncertainty in liaison psychiatry

Joanne E Davies,¹ Sarah Johnson²

¹Department of Psychiatry, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

²Liaison Psychiatry, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Correspondence to

Dr Sarah Johnson, sarah.johnson4@uhbristol.nhs.uk

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SUMMARY

A middle-aged woman presented with a history of symptoms of depression with psychotic features severely affecting her physical health. Neuroimaging of her brain suggested pathological changes out of keeping with her age, leading to further investigations including genetic testing for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was also considered as a differential diagnosis as an initial serum test for anti-NMDAR autoantibodies was positive. Her symptoms resolved following treatment with electroconvulsive therapy. Despite her initial neuroimaging, her genetic test for CADASIL was negative and her subsequent test for anti-NMDAR autoantibodies was negative, suggesting that the initial test may have been a false positive.

BACKGROUND

Neurological conditions can manifest with psychiatric symptoms and, therefore, it is prudent that an organic aetiology is considered when patients present with psychopathological syndromes.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary cerebral small-vessel disease associated with mutations of the NOTCH3 gene.¹ It can present with migraine, with aura and ischaemic strokes in addition to psychiatric symptoms in up to 70 per cent of cases.² It generally presents with mood disturbance, but psychotic phenomena can also be present.³

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune synaptic disease that can present with neuropsychiatric symptoms including psychosis, seizures and dyskinesias.⁴

We report a case where the initial diagnosis of a major depressive episode with psychotic features was complicated by incidental radiological findings indicative of CADASIL, in addition to a positive autoantibody serum test suggestive of anti-NMDAR encephalitis. The diagnostic uncertainty was compounded by the time delay associated with laboratory test results particular to each diagnosis.

CASE PRESENTATION

A woman in her late forties presented to the emergency department (ED) due to abnormal vaginal bleeding; however, her examination were

unremarkable. She was referred to liaison psychiatry due to her high level of distress. She presented with rapid speech and anxiety but no other significant psychopathology was observed. She was signposted to her general practitioner (GP) for ongoing management of her anxiety.

She represented to the ED 6 weeks later as her mental state had significantly deteriorated. There was evidence of severe self-neglect and she presented as dishevelled and malnourished with a body mass index of 16.7. She was suspicious of the medical staff and presented with depressed mood and delusions of infestation. She expressed delusions of guilt relating to harming her children despite a lack of evidence to corroborate this.

Previously, she had been treated for postnatal depression in her thirties by her GP with antidepressant medication. She also had a history of headaches and had been diagnosed with trigeminal neuralgia. She had no other significant medical or psychiatric history. Of note, her mother was diagnosed with dementia at the age of 66. She disclosed a previous history of alcohol dependence, but denied current use of alcohol or illicit substances. She had an extensive history of smoking tobacco since adolescence.

Following her representation to ED, she required a medical admission due to her grave physical state. Notably, there was no evidence of any neurological deficits on examination throughout her admission.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Following admission, a CT pulmonary angiogram was performed due to acute onset of respiratory compromise. It demonstrated pulmonary emboli (PE) and a pneumothorax with lobar collapse. The PE was likely secondary to recent immobility and dehydration.

Blood tests indicated a brief rise in C reactive protein and white cell count following diagnosis of PE. Other blood tests (including calcium, urea and electrolytes, thyroid stimulating hormone, liver function tests and anticardiolipin) were normal. All tests to rule out an infective cause were negative, including sputum for acid-fast bacilli, urinary legionella/pneumococcal antigens, a respiratory viral screen and blood tests for HIV and syphilis.

An electroencephalogram did not demonstrate any definite abnormality.

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An initial serum test for anti-NMDAR autoantibodies was positive. Anti-voltage gated potassium channel antibody titre was normal.

A CT scan of her brain demonstrated marked patchy subcortical and periventricular low attenuation in both frontal and temporal lobes, abnormal for her age. Possible differentials from this scan included ischaemia, vasculopathy or inflammation.

An MRI scan of her brain demonstrated multiple widespread confluent white-matter hyperintensities in the periventricular and subcortical regions, predominantly in the frontal and temporal lobes bilaterally. The ventricular spaces appeared slightly prominent, suggesting a degree of cerebral atrophy.

This was reviewed at the neuroradiology meeting and CADASIL and Susac's syndrome were suggested as differential diagnoses. CADASIL appeared more likely, given her psychiatric symptoms, history of headaches and family history of early-onset memory loss. Susac's syndrome appeared less likely given her history of grossly normal vision and hearing which are both typically affected in this syndrome.⁵

The diagnosis of CADASIL cannot be made definitively using radiological evidence alone.⁶ Genetic testing was performed and no pathological variants of the NOTCH3 gene were found. Notably, there was a delay of several months between the test being performed and reported.

TREATMENT

She was initially treated for a major depressive episode with psychotic features with an antidepressant (sertraline) and an antipsychotic (olanzapine) while receiving medical treatment for the PE and pneumothorax. Her mental state continued to deteriorate and she became mute and intermittently agitated. Her oral intake was negligible. She was detained under Section 2 of the Mental Health Act 1983 (MHA) and fed via a nasogastric (NG) tube.

It was deemed clinically appropriate to commence electroconvulsive therapy (ECT) as an emergency and lifesaving treatment thereafter (using section 62 of the MHA) due to her grave mental and physical state. Neurology input was sought, given the differential diagnosis of CADASIL and pending genetic test. It was advised that CADASIL is not a contraindication to lifesaving ECT.⁷ ECT was commenced bi-weekly and, weekly thereafter, for a total of ten treatments.

Her mood, volition and insight improved rapidly and she became reactive in affect. Her appetite normalised and NG feeding was discontinued. The differential diagnosis of CADASIL was tentatively discussed with the patient, pending the results of the genetic test. CADASIL is inherited in an autosomal dominant manner and therefore her family were counselled accordingly.⁸

OUTCOME AND FOLLOW-UP

Her physical health stabilised after 1 month in the general hospital. She was transferred to a psychiatric hospital to continue her treatment including ECT, medication optimisation and cognitive behavioural therapy (CBT) with the ward-based clinical psychologist.

Notably, her initial anti-NMDAR autoantibodies serum test was reported as positive around the time she was transferred to the psychiatric hospital. She had already demonstrated a response to ECT at this point. Anti-NMDAR encephalitis is associated with certain neoplasms, particularly ovarian

teratomas.⁹ Her weight loss, possible history of vaginal bleeding and development of PE may have indicated an underlying neoplasm; however, a CT of the abdomen was performed that excluded the presence of an intra-abdominal neoplasm. Moreover, it is unlikely that she would have made a rapid, complete recovery from anti-NMDAR encephalitis with ECT and without the implementation of immunotherapy.¹⁰ A repeat anti-NMDAR autoantibody serum test was subsequently negative.

She was discharged home after a 2-month psychiatric admission with support from the community mental health team. She was prescribed olanzapine and mirtazapine for ongoing pharmacological treatment and was advised to continue a course of CBT in the community but chose not to attend.

The negative genetic test for CADASIL was reported several weeks after her psychiatric admission. This was discussed with the patient and her family during her subsequent outpatient appointments with Psychiatry and Neurology. In view of the results of the genetic test, it was suggested that the changes demonstrated on her MRI could have been related to her heavy use of tobacco.¹¹

At 8 months, post-discharge from hospital, the patient had remained well with no further relapses.

DISCUSSION

Overall, this was a challenging case to manage due to the severity of the patient's physical and mental state and the delayed acquisition of important diagnostic test results.

The National Institute for Health and Care Excellence guideline for the treatment of depression in adults suggests that an antidepressant should be augmented with an antipsychotic for patients presenting with depression with psychotic features.¹² ECT should be considered for treatment of severe depression that is life-threatening or when other treatments have been ineffective.¹² This patient did not improve with appropriate pharmacological management and her negligible oral intake eventually necessitated life-preserving treatment with ECT.

The Royal College of Psychiatrists' ECT handbook recommends that, for cases where it is prescribed to save a life, there are no absolute contraindications to ECT.⁷ A previous, small-case series of four patients has suggested ECT is generally a safe treatment option to consider for patients with severe psychopathological syndromes that could be related to a suspected underlying acute neurological syndrome.¹³ Therefore, it was deemed appropriate to administer ECT despite the pending genetic test.

With regards to depression, a recent meta-analysis has indicated that response rates to ECT are 58%–70%.¹⁴ Moreover, there is further evidence to suggest superior efficacy for ECT when treating depression associated with psychotic features.¹⁵ The patient's rapid response to ECT and subsequent complete recovery supports our initial diagnosis of a major depressive episode with psychotic features.

It was suspected that the initial serum test for anti-NMDAR autoantibodies was a false positive given the overall clinical picture and subsequent negative result. Indeed, it has been demonstrated that the utilisation of a single screening method for anti-NMDAR autoantibodies using serum samples can produce irrelevant, false positive results. It has been suggested that positive serum screening should be validated with other test methods such as use of cerebrospinal fluid.¹⁶

Learning points

- Electroconvulsive therapy can be used as a treatment for depression+/-psychotic symptoms and, when prescribed as a lifesaving treatment, there may be no absolute contraindications to its use. In this case it was administered with careful consideration of differential diagnoses and with multidisciplinary input.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is an autosomal dominant, cerebral small-vessel disease that can present with psychiatric symptoms but cannot be diagnosed using neuroimaging alone and requires genetic testing for errors in the NOTCH3 gene.
- Anti-N-methyl-D-aspartate (NMDA) encephalitis can present with psychiatric symptoms and positive serum anti-NMDA receptor autoantibodies; however, autoantibody screens can yield false positive results. Therefore, it is important to repeat the test if the clinical symptoms and signs do not correlate with the test result and to consider other differentials.

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Contributors Both authors were involved in direct patient care and management. SJ prepared some early draft notes and JD wrote the manuscript using these notes and further examination of patient files. SJ completed a literature search and JD did further literature search for the discussion. Both wrote learning points and edited the final version.

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