CASE REPORT

Severe depression masquerading as Creutzfeldt-Jakob disease

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SUMMARY

We report a case of melancholic depression with catatonic features presenting as a rapidly progressive organic brain syndrome, initially thought to be probable Creutzfeldt-Jakob disease. The case highlights the fundamental importance of thorough exclusion of treatable pathology masquerading as an irreversible syndrome.

BACKGROUND

A premorbidly high-functioning and cognitively intact 80-year-old woman was transferred to our institution from a peripheral centre for further assessment after a 6-week history of rapid deterioration in functional state, of unclear cause. She had initially been admitted to hospital with a presumed mild respiratory tract infection; however, developed progressive hypophonia, bradykinesia and tremor over 2 weeks. There was also a history of mild hypophonia and increasing anxiety over the preceding several months. There was no previously reported history of anosmia. She became anorexic and began to lose weight, was unable to mobilise, required staff assistance to transfer from bed to chair and was doubly incontinent. Her medical history was of hypertension, reflux oesophagitis and a distant rectal carcinoma (completely excised). Psychiatric history was significant for unipolar non-melancholic depressive episodes with mixed anxiety features with initial onset in the postpartum period, though this information only became available later in the course of admission. These episodes had been treated effectively with tricyclic antidepressant monotherapy. The patient had been established on sertraline in the weeks prior to admission. She had no known exposure to agents associated with parkinsonism.

CASE PRESENTATION

On arrival at our institution she was virtually mute, with bilateral bradykinesia and upper limb tremor. Motoric negativism, posturing, generalised hyperreflexia and prominent frontal release signs were noted, as was the absence of myoclonus. Cognition and mental state were difficult to assess due to intermittent mutism and whispering hypophonia, though she appeared oriented in her interactions. Over the following 2 weeks she had further physical and functional decline, as well as increasing perseveration, agitation and hypervigilance. She appeared distressed with an anxious, restricted affect and a manner that was seemingly nihilistic,

often gesturing for people to leave her alone. Her thought content was not further discernible. She did not appear to be actively responding to internal stimuli.

INVESTIGATIONS

Extensive bloodwork including thyroid function and antibodies, B₁₂, folate, antineuronal and antisynaptic neuronal antibodies (including anti N-methyl-D-aspartate (NMDA), glutamic acid decarboxylase (GAD) and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antibodies), viral serology, autoimmune and vasculitic screens were all normal. Two MRI showed only minor white matter disease with no other abnormalities (figure 1). Serial EEGs showed profound generalised slowing (5–6 Hz θ and 2–3 Hz δ range) with no organised posterior rhythm, but no epileptiform or periodic complexes (figure 2). Cerebrospinal fluid (CSF) analysis was abnormal showing a positive 14–3–3 protein, though oligoclonal bands were absent and all other indices were normal. CSF τ analysis was not available.

DIFFERENTIAL DIAGNOSIS

After structural and infective processes and toxic-metabolic encephalopathy were largely excluded by urgent brain MRI, CSF analysis and blood tests the main differential diagnoses were autoimmune encephalitis and CJD, prior to the consideration of major depression.

TREATMENT

The patient was trialled on levodopa given the parkinsonian features, with limited response. Gastrointestinal symptoms and hypotension limited dose escalation. After a month of further (though slower) decline in our hospital, the possibility of palliation was considered in light of the likely diagnosis of an irreversible organic brain syndrome, specifically probable CJD on the basis of clinical features and CSF 14–3–3 positivity. However, during this period she was also referred to the neuropsychiatry team given her agitation and history of previous depression and anxiety.

Aspects of the patient's presentation at neuropsychiatric review were considered compatible with the syndrome of catatonia. These included marked negativism, intermittent mutism, posturing and manneristic gesturing. Her clinical presentation with marked agitation and anxiety, particularly in the context of her positive history of affective disorder, and the lack of convincing evidence for a

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Figure 1 (A and B) Axial fluid-attenuated inversion recovery MRI showing mild periventricular white matter hyperintensity. (C) Axial diffusion-weighted MRI which did not identify any abnormalities.

Figure 2 (A) Awake EEG in longitudinal bipolar montage showing diffuse admixed θ and δ range slowing. (B) Repeat EEG 2 months later, following electroconvulsive therapy, with normalisation of previous slowing.

rapidly progressive dementia syndrome (since formal assessment of cognitive function was very challenging) argued for diagnostic consideration of melancholic depression with an atypical presentation. Antidepressant therapy was switched from sertraline to nortriptyline in view of past treatment with tricyclic antidepressants, but on this occasion without benefit.

Following discussion with her family, it was elected to trial electroconvulsive therapy (ECT), given the gravity of pursuing palliative management in light of certain features atypical for CJD. These atypical features included slower than expected decline in our hospital, essentially normal MRI, lack of periodic complexes on EEG and the previously described features suggestive of catatonia. A course of ECT was initiated at ultrabrief pulse width, the choice of pulse width reflecting concern about the patient's possibly impaired cognitive status. The patient had a remarkable response to ECT with improvement in physical functioning noted as early as the first treatment session. She completed an 8-week course of ECT with a total of 10 treatments, and the frequency of these was gradually tapered. Clinical progress with disappearance of frontal signs and the emergence of a more stable, euthymic mental state was accompanied by normalisation of her EEG, allowing for her eventual return to independent community living. A repeat CSF 14–3–3 performed 6 weeks after the initial analysis (both tested at the National Reference Laboratory) was negative.

OUTCOME AND FOLLOW-UP

At outpatient review, 3 months and 9 months postdischarge, the patient had maintained clinical improvements in mood and functioning. She was euthymic, though mildly anxious about her health, considered consistent with her premorbid personality. Interestingly, while there was also a major improvement in her parkinsonian features, subtle extrapyramidal signs remained at follow-up assessment, with facial masking, left-sided resting tremor, rigidity and bradykinesia and substantial symptomatic response to levodopa and a diagnosis of Parkinson's disease was made, based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.¹

DISCUSSION

This case demonstrates that primary psychiatric disorders can masquerade as major neurological disease. It also highlights the importance of a thorough evaluation for all potentially reversible causes of a progressive organic brain syndrome and the role of empirical treatment. We are confident that melancholic depression with catatonic features was the main diagnosis in this case, particularly given the patient's history and clinical presentation, supported further by her dramatic response to ECT. The extrapyramidal features at follow-up suggest that subtle pre-existing Parkinson's disease may have contributed to the motor features and may have even contributed to the onset of depression.

According to the revised diagnostic criteria of Zerr *et al*² our case would have been classified as 'possible' CJD on clinical grounds, with the positive 14–3–3 elevating this to 'probable'. This highlights the danger of over-reliance on surrogate markers such as the 14–3–3 for premortem diagnostic confirmation, if the gold standard investigation of brain biopsy is not conducted. It has been postulated that in CJD there is release of 14–3–3 into the CSF as a consequence of neuronal cell death and lysis,³ but it is recognised as an imperfect disease marker. Sensitivity and specificity of 14–3–3 for CJD ranging from 53% to 96% and 50% to 96%, respectively, have been reported^{4–7} (estimated at 85–90% each by the Australian National Reference Laboratory where our specimens were analysed), with variations depending

on the clinical context in which the result is obtained.⁸ While the positive predictive value has been suggested to be as high as 95%,⁹ elevated 14–3–3 has been noted in various central nervous system diseases, particularly acute major stroke or severe viral encephalitis with marked neuronal loss,⁷ but also in pathologically confirmed neurodegenerative disorders including Alzheimer's disease and frontotemporal dementia.¹⁰ In a 10-year longitudinal multicentre study⁸ of 14–3–3 specificity in a large cohort of patients, Stoek and colleagues estimated that 4.3% of more than 10 000 referrals for CSF 14–3–3 testing had a differential diagnosis of a psychiatric disorder, and thus emphasised the importance of a thorough clinical evaluation.

Psychiatric manifestations of the prion disease CJD are well documented, particularly in variant disease, but there is little, if any, documentation in the literature of the reverse situation with psychiatric disease mimicking CJD. It is well known that variant CJD often presents with psychiatric or behavioural symptoms; however, there is also more recent evidence for similar manifestations in sporadic CJD (sCJD),¹¹ typically later in the disease course but possibly even at initial presentation. A recent review of first presenting symptom in a US sCJD cohort¹² found that behavioural or psychiatric manifestations were the first symptom in 20% (most commonly agitation/irritability in 36% or depression in 16%). In addition, there have been reports of CJD (sporadic and variant)^{13–15} presenting with progressive akinetic mutism and demonstrating pyramidal and extrapyramidal signs and non-specific EEG and MRI findings until late, with positive 14–3–3 in CSF, thus bearing close resemblance to our case. These cases provide potential plausibility for an initial diagnosis of probable CJD in a case such as ours.

The diffuse slowing seen on EEG in our case is atypical for depression, though more regional changes, albeit inconsistent and non-specific, have been commented on and debated in the literature.^{16–17} Diffuse slowing was a feature which argued for major neurological disease in our patient. However, the characteristic periodic sharp wave complexes of CJD¹⁸ and typical MRI findings such as striatal and/or cortical T2 hyperintensity or increased diffusion restriction¹⁹ were notably absent. Such typical EEG and MRI findings certainly increase the likelihood of CJD, but are not seen in all cases particularly early in the disease. Their absence by no means excludes CJD, but should encourage an aggressive search for potentially treatable CJD mimics.

Differential diagnoses for rapidly progressive organic brain syndromes suggestive of CJD²⁰ will be influenced by the constellation of clinical findings at presentation. It is critically important to consider potentially reversible conditions including toxic or metabolic encephalopathies, autoimmune disease, infection and malignancy (including paraneoplastic syndromes). A prospective 12-year epidemiological study from the German CJD surveillance centre²¹ identified that a third of non-CJD cases were due to potentially reversible disorders. A retrospective series from the US National Prion Diseases Pathology Surveillance Centre²² identified 71 of 304 (23%) prion-negative autopsy cases which had a potentially treatable diagnosis.

Of particular note is the importance of considering autoimmune encephalitis (such as anti-NMDA encephalitis) in cases presenting with rapidly progressive cognitive, motor and psychiatric features. It is well known that these disorders may present initially with psychiatric features including anxiety, depression and/or catatonia²³ and indeed may even respond clinically to electroconvulsive therapy.²⁴ Against this differential in our case was the patient's atypical age, absence of usual motor features such as seizures and dyskinesias, unremarkable MRI and CSF analysis and ultimately negative autoantibodies.

This case emphasises that severe depression is another eminently treatable and reversible disorder that can masquerade as CJD. We believe that this may be an under-recognised phenomenon and encourage close collaboration between neurology and psychiatry units when other investigations are not absolutely diagnostic for CJD and there are any clinical features suggesting depression or other psychiatric disease.

Learning points

- ▶ Primary psychiatric disorders can masquerade as major neurological disorders. Rigorous evaluation of all potentially reversible aetiologies for progressive organic brain syndromes is recommended, including consideration of psychiatric phenomenon.
- ▶ Over-reliance on surrogate biomarkers is cautioned against. Interpretation of results within the broader clinical context is required, as this informs the sensitivity and specificity of a positive result.
- ▶ In suspected irreversible brain syndromes where viable treatment is available for plausible differential diagnoses, a trial of empirical treatment should arguably be pursued, rather than foreclosure on palliative management.
- ▶ Close collaboration between neurology and psychiatry units is critical in similar clinical contexts.

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Competing interests None.

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