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CASE REPORT

Delirious mania intractable to treatment

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We present the case of a 68-year-old lady with a background diagnosis of bipolar disorder, who developed significant episodes of intractable delirium during each of her last three inpatient psychiatric admissions, where she was admitted with mania and psychosis. The case demonstrates diagnostic and management difficulties secondary to this delirium. We discuss the probable cause of this delirium and the various management strategies utilised in an effort to ameliorate her condition.

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Key words: Bipolar disorder, delirium, insomnia.

Introduction

We present the case of Ms C.D., a 68-year-old single lady, living independently in sheltered accommodation, with a background diagnosis of bipolar disorder (although a differential diagnosis of schizoaffective disorder has been postulated). She was admitted voluntarily to the acute psychiatric unit owing to developing mania and co-morbid psychotic symptoms, with her predominant symptoms being elated mood, irritability and persecutory delusions. However, during her subsequent inpatient admission, she developed an unexplained delirium, which proved resistant to treatment.

Case history

Ms C.D. presented to the acute psychiatric unit in the company of a family member, as she had become increasingly distressed by delusional beliefs of a persecutory nature. These included believing that one of her neighbours wanted to harm and potentially kill her, and that individuals had been sent by this person to monitor her on a continuous basis. These systematised delusional beliefs were present for ~8 weeks before admission and were associated with increasing levels of distress. She also displayed pressure of speech and insomnia (1–2 hours less sleep than usual), despite treatment with the hypnotic Zolpidem. She reluctantly agreed to a voluntary inpatient admission with her medication regime on admission consisting of Lithium Carbonate 600 mg nocte, Eltroxin 50 mcg mane, Zolpidem 10 mg nocte and Ramipril 2.5 mg mane. Persecutory and referential delusions relating to other individuals became increasingly evident during the initial stages of her inpatient admission, despite the introduction of the anti-psychotic agent Aripiprazole (increasing gradually to 20 mg); however, it was possible for Ms C.D. to be nursed on 'general observations' for the first 18 days of her admission, although her sleep disturbance deteriorated. On the 19th day of her admission, she became disorientated in time and place and required 1:1 nursing in a single room with appropriate non-pharmacological management of delirium for the next 14 weeks.

During this period, she exhibited marked and fluctuating disorientation, significant inattention and slept on average only 1 hour during the course of a night. This was complicated by repeated falls. A urinary tract infection (UTI) was detected ~5 weeks after her admission to hospital; however, treatment and resolution of this was not associated with any alteration in her clinical presentation. Her serum Lithium levels necessitated frequent monitoring, with her plasma level reaching 1.5 mmol/l at one point secondary to dehydration. Her psychosis remained, albeit was less prominent given her disorientation. She received treatment with a variety of psychotropic agents either as monotherapy or in combination, including Zopiclone, Promethazine, Haloperidol, Lorazepam and Olanzapine, none of which ameliorated her sleep disturbance.

Owing to her ongoing symptomatology, second opinions from other psychiatrists, the neurology team and the psychiatry of later life team were attained. No neurological condition was demonstrated and a wide variety of investigations proved normal including computed tomography (CT) and magnetic resonance imaging (MRI) brain scans, and thyroid, renal, liver, lipid, electrolyte, hepatitis B and C, VDRL, HIV, porphyrins, IgG, IgA and IgM profiles. She had negative antibodies to anti-amphiphysin, anti-GAD, anti-NMDA receptors, anti-Ri, anti-Hu, anti-Yo and

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anti-voltage-gated K channels. Serum electrophoresis demonstrated no evidence of monoclonal bands. Electroencephalography demonstrated non-specific mild diffuse slowing suggestive of bilateral dysfunction, but no features suggestive of prion encephalopathy or epileptiform activity were evident (she had suffered a seizure 30 years ago). A renal ultrasound to investigate bilateral pedal oedema revealed a lesion at the lower pole of the right kidney, with a subsequent CT of abdomen finding an exophytic enhancing 3 cm mass consistent with a renal carcinoma. There was no radiological evidence of any metastases within the abdomen or pelvis. A renal cell carcinoma was subsequently diagnosed and a right nephrectomy was performed 2 months after discharge from hospital with no complications noted. She attained no treatment for this carcinoma during her admission to the Department of Psychiatry and there was no obvious association between her delirium and the presence of this carcinoma.

After 14 weeks of her initial admission, she gradually became more orientated, despite no significant alterations in her pharmacotherapy in the previous 4 weeks and her scores on cognitive testing improved significantly. Although at times it was not possible to undertake cognitive testing when she was delirious, an example of her cognitive functioning during this time demonstrated a Mini-Mental State Examination (MMSE) score of 14/30, a Montreal Cognitive Assessment score of 9/30 and an Addenbrooke's Cognitive Examination – Revised score of 29/100, with her scoring no points on any tests for attention. These improvements in orientation and cognitive testing (e.g. 29/30 on MMSE and 5/5 for attention) coincided with a normalisation of her sleep pattern. Persecutory delusions remained evident on discharge, but were less intense in nature and she was less distressed by these beliefs. Her pharmacotherapy on discharge from hospital consisted of Lithium 400 mg nocte, Sodium Valproate Chrono 800 mg nocte, Olanzapine 2.5 mg nocte, Promethazine 75 mg nocte, Zopiclone 7.5 mg nocte, Eltroxin 50 µg mane and Ramipril 2.5 mg mane.

Past psychiatric history

Ms C.D. has a 30-year history of bipolar disorder with 10 previous psychiatric inpatient admissions, including one previous involuntary admission in 2011. She has been treated with a variety of mood stabilisers, antipsychotics and anti-depressants. Her pharmacotherapy regime during her longest period of mood stability (6 years) consisted of Lithium Carbonate 800 mg nocte, Sodium Valproate Chromo 800 mg nocte and Quetiapine 300 mg XR. She had a history of non-adherence to treatment and occasional harmful use of alcohol, which had deleterious effects on her mental state. Since 2009, her three psychiatric admissions, where she was initially presented with psychotic symptoms – namely, referential and persecutory delusions (including the most recent admission) – have been complicated by the emergence of a delirium of unexplained origin.

Both of these admissions displayed a similar presentation to the most recent admission outlined above. During the first of these admissions, she developed disorientation on day 6 of her admission to the acute psychiatric inpatient unit, with a plethora of medical investigations demonstrating negative or normal findings. Her delirium coincided with marked inattention and significant sleep disturbance resistant to treatment with multiple pharmacological agents, including all psychotropic agents described in her recent admission, with trials also of Quetiapine and Zuclopenthixol Acuphase intramuscularly on three occasions owing to severe agitation. She required 1:1 nursing for 14 weeks during this admission. She was discharged from hospital on Lithium Carbonate 400 mg nocte, Sodium Valproate 400 mg TID and Olanzapine 2.5 mg nocte, with no overt evidence of psychosis and no sleep disturbance. Her second admission followed a very similar course and was of 12-week duration. Her delirium was complicated by marked inattention, repeated falls, urinary incontinence and a poor sleep pattern. Similar to the other two described admissions, there appeared to be a relationship between improvement in attention and disorientation and an improvement in her sleep pattern, and despite significant medical input, no organic cause was identified and no psychotropic agents were deemed related to this clinical picture.

Neuropsychological testing (occurring over the course of three assessments) between her two most recent admissions demonstrated some mild executive dysfunction and visuospatial construction impairments, and mild deficits in delayed and immediate memory. She scored within the normal range for attention and language skills. Her pre-morbid IQ was estimated in the low average range. The neuropsychological battery utilised included the Weschler Memory Test-III, the Repeatable Battery for the Assessment of Neuropsychological Status and the Controlled Oral Word Association Test.

She has no history of deliberate self-harm or aggression towards others, no forensic history, no history of psychoactive substance abuse and no family history of psychiatric illness.

Discussion

Delirium is a common occurrence in the acute hospital setting, with reports of a 'point prevalence' of 20% of inpatients experiencing delirium (Ryan *et al*. 2013). This case demonstrates the diagnostic and management

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difficulties secondary to a refractory and prolonged delirium. Diagnostically, Ms C.D. demonstrated evidence of three discrete episodes of marked inattention: disturbance of cognition, hypoactivity and insomnia with emotional disturbance, consistent with a diagnosis of delirium (International Classification of Disease (ICD)-10, 1994). This diagnosis is supported by its rapid onset in each instance and electroencephalography findings of general diffuse slowing. No clear organic cause for her delirium was identified on any occasion, despite a large array of medical investigations. The renal cell carcinoma identified on the third admission had not metastasised and her condition ameliorated despite its presence, and consequently, we believe it was not associated or causative for her delirium.

On each admission, Ms C.D. displayed several symptoms of mania including insomnia, irritability, pressure of speech, grandiosity and persecutory delusions, and consequently after her third such presentation, a diagnosis of delirious mania was deemed most probable. Fink (1999) defined 'delirious mania' as a rapid onset syndrome resulting in delirium, psychosis and mania. The six criteria for delirious mania outlined by Bond (1980) consisted of (1) acute onset, (2) the presence of hypomania or mania, (3) development of signs and symptoms of delirium, (4) a past history of mania or depression, (5) a family history of affective disorder and (6) response to treatment for mania. Ms C.D. fulfils the first four of these criteria; however, she has no known family history of affective disorders. Her treatment response whilst present was slow. Affective symptoms, although present were not particularly prominent in this case. However, this is consistent with a previous report where a diagnosis of delirious mania was given to an individual with a rapid onset of disorientation, fluctuating sensorium, altered level of consciousness and severe cognitive dysfunction in the absence of frank manic symptoms or a medical condition (Maldeniya & Vasudev, 2013).

It is possible that several factors contributed to her repeated episodes of delirium, including mania, environmental change and insomnia; and multi-factorial models in relation to the aetiology of delirium are well validated (Inouye & Charpentier, 1996). Indeed, the development of delirium may be viewed as being dependent on inter-relationships between susceptible patients with multiple predisposing factors and exposure to precipitating factors (Inouye *et al*. 2014). However, we believe that the principal reason for C.D.'s delirium was mania, as her medications were not significantly altered before admission, she only became delirious after almost 3 weeks in a different environment (the acute psychiatric inpatient unit) and her UTI developed 3 weeks after she became delirious, and resolution of same was not associated with an amelioration in her delirium. Furthermore, although a change in environment was a possible precipitating factor in the emergence of delirium, it is worth noting that during a subsequent almost 3-week admission to a surgical ward for a nephrectomy, there was no evidence of delirium, despite having the additional risk factor of major surgery. Consequently, this increases the likelihood that her three recent episodes of delirium were secondary to mania. In addition, C.D. demonstrated no evidence of any form of dementia such as Lewy body or vascular dementia. When not delirious, she functions well in relation to activities of daily living, performs reasonably well on cognitive assessment (commensurate to her IQ), has no disturbance of gait or history of falls and has never experienced any perceptual abnormalities. Furthermore, she has had no detectable changes on CT or MRI brain scans, indicative of dementia. MRI brain scanning has included diffusion-weighted imaging and MRI with gadolinium and fluid-attenuated inversion recovery studies. Her MMSE scores are consistently 29 or 30 on the MMSE after an episode of delirium. Unfortunately, we were unable to arrange positron emission tomography scanning during her recent hospital admissions. She has a history of mild systolic hypertension for which she is prescribed low-dose Ramipril, which (to our knowledge) she is adherent with and her blood pressure has been well controlled over the last 10 years.

Sleep disturbance is common in patients with delirium and has been suggested as an aetiological risk factor (Inouye, 2006; Watson *et al*. 2012; Inouye *et al*. 2014), albeit a potentially modifiable risk factor. The National Institute for Clinical Excellence (NICE) guidelines for the prevention of delirium recommend the promotion of good sleep patterns (NICE, 2010; Watson *et al*. 2012). Insomnia predated the onset of delirium for C.D.; however, the most likely cause for her sleep disturbance was mania, with both her mania and subsequently her insomnia contributing to the ensuing delirium. Multiple investigations and medical opinions were undertaken on each admission owing to the unexplained nature of C.D.'s delirium. Consequent to this, a renal cell carcinoma was diagnosed during the third admission; however, it could reasonably be argued that she was over-investigated to ascertain a cause for her delirium.

Conclusion

This case report highlights the diagnostic and management difficulties presented by a delirium of unknown origin. The probable cause of this condition was delirious mania, despite the patient not displaying very prominent manic symptoms. A greater awareness of the possibility of delirious mania, particularly in

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elderly individuals, may enable clinician's to diagnose this condition earlier and perhaps modify the level of investigations undertaken for individuals with this presentation.

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Conflicts of Interest

The authors declare no conflict of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this case report was not required by their local REC.

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