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Unusual presentation of more common disease/injury

What works for delirious catatonic mania?

Kamini Vasudev,[1] Heinz Grunze[2]

[1] Department of Rehabilitation Psychiatry, NTW Trust, Morpeth, UK
[2] Division of Psychiatry, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

Correspondence to Kamini Vasudev, kaminivasudev@hotmail.com

Summary

Delirious mania is an under recognised clinical syndrome and little evidence is available to clarify its clinical characteristics and treatment. We analyse a case of delirious mania that was a challenge to treat. It shows the importance of recognising catatonia as a symptom of delirious mania. Electroconvulsive therapy (ECT) and mood stabilisers (lithium and valproate combination) proved to be effective treatments in our case, but a variety of factors contributed to a delay in treatment response.

BACKGROUND

Delirious mania is an under recognised clinical syndrome and relatively sparse literature is available describing its clinical characteristics and treatment.[1 2] A recent report[3] describes the clinical features and treatment response in 16 cases of delirious mania and concludes that the definitive treatment for this condition is electroconvulsive therapy (ECT). Detweiler *et al*, 2009 emphasise the importance of distinguishing delirious mania from excited catatonia.[4] They describe non-malignant and malignant phases of delirious mania on the basis of increasing severity of symptoms and catatonic features. The latter is worsened by antipsychotics and requires treatment with benzodiazepines and/or ECT.

We report a case of bipolar disorder presenting with delirium and mania that was a challenge to treat. The patient spent 2 years on an acute psychiatric ward requiring repeated transfers to psychiatric intensive care unit (PICU). She received a course of ECT early in admission which did not seem to help. She was then tried on a variety of medications followed by another course of ECT to which she responded successfully. We analysed this case to examine the factors complicating the treatment. The dates mentioned are arbitrary and have been used to reflect the chronology of events and time frame.

CASE PRESENTATION

A 46-year-old woman with history of bipolar affective disorder was admitted with a mixed affective episode. With respect to past psychiatric history, she was first admitted with postnatal depression at 27 years of age, for a period of 3 months and had required ECT. She was discharged on a depot antipsychotic (flupentixol 40 mg 2 weekly), lofepramine 70 mg three time a day, thioridazine 50 mg three time a day and orphenadrine 50 mg three time a day. She continued on the depot for the next 5 years. At age 32, she needed another admission to hospital for 5 months for a mixed affective state. She required ECT, the depot was stopped and she was discharged on lithium 2.6 g daily; dothiepine 100 mg nocte and droperidol 5 mg nocte. At age 40 and 42 years, she developed further hypomanic episodes and was stabilised with lithium without needing further hospitalisation. She expressed her reluctance to continue lithium due to perceived adverse effects on her memory (which was however disproved by neuropsychology) and polyuria. Lithium was replaced by valproate, which unfortunately caused hair loss and sedation, therefore, was changed to carbamazepine (CBZ). She was maintained on CBZ 400 mg and olanzapine 10 mg daily in the community for 1 year prior to current deterioration which seems to have been precipitated by a major life event. She developed hypomanic symptoms about 2 months prior to the current admission. The dose of CBZ was increased to 800 mg during this period to which she initially reported the side effects of being unable to focus her eyes, dizziness and ataxia.

She needed admission to hospital in February 2004, when she presented with labile mood, formal thought disorder, psychomotor agitation and delusional ideas. There was no significant family psychiatric history or medical history apart from long standing intermittent urinary incontinence. Socially, the patient was unemployed, lived alone and was in a supportive relationship with a man who lived nearby.

INVESTIGATIONS

The physical examination and all routine blood tests (full blood count, liver function tests, urea and electrolytes, thyroid function test, sugar and lipids) were normal. There was no history of substance misuse and urine drug screen was negative. Urine microscopy and culture was negative at admission.

TREATMENT

She was continued on CBZ 800 mg modified release (m/r) nocte, and the dose of olanzapine was increased to 20 mg nocte with addition of as required diazepam 5 mg four times a day and temazepam 20 mg nocte. Serum CBZ level was 8 mg/l at the time of admission. No improvement in mental state was noted; she rather became increasingly hostile and disorganised in behaviour and required frequent use of haloperidol and zuclopenthixol acuphase to contain her agitation. A month after admission (March 2004), she

required transfer to the PICU. In the PICU she was treated for a urinary tract infection (UTI) with trimethoprim 200 mg twice daily for 3 days, but it did not lead to any improvement. She became delirious and presented with agitation, disorganised behaviour, incontinence and grabbing staff members. Emergency ECT with unilateral stimulation was started. In addition, oral benzodiazepines, including lorazepam were increased and sodium valproate was added to her ongoing regimen of olanzapine 20 mg and CBZ m/r 800 mg daily. The dose of valproate was gradually increased to 1200 mg/day. Serum levels of valproate and CBZ were maintained at 61 and 8 mg/l, respectively. At one point the serum level of CBZ increased to 11 mg/l, after addition of valproate. After six ECT treatments agitation was reduced but her mood remained labile and she continued to present disorientated. She was transferred to an open ward (May 2004). All blood tests as above were reported normal at this point and a CT brain scan was normal.

On the open ward, she remained unsettled and appeared ataxic. A review of treatment was conducted and it was felt that she had not shown any significant response to an adequate trial of CBZ, valproate or 10 treatments with ECT. There were concerns that she was experiencing adverse effects from the medication including ataxia (CBZ) and severe alopecia (valproate). Therefore, it was planned to discontinue ECT and slowly reduce CBZ and valproate with increase in olanzapine to 30 mg and commencing lithium with as required use of haloperidol and lorazepam. No improvement in mental state was noted with continued need for zuclopentixol acuphase to contain agitation. She needed another transfer to the PICU (July 2004) where signs of catatonia were observed – excitement, immobility/stupor, mutism, staring, posturing, verbigeration, rigidity, withdrawal, impulsivity, positive grasp reflex, perseveration, and combativeness. An opinion from a neurologist was sought who could not identify any focal cause and suspected that she might be presenting with drug induced parkinsonism or atypical signs of neuroleptic malignant syndrome (NMS). Creatine kinase levels were raised (2534 U/l) and liver enzymes were slightly raised. Other blood tests, including syphilis, HIV and immunology screen were normal with no evidence of UTI. It was then decided to stop all antipsychotics. Sedation was continued with high dose benzodiazepines and promethazine. This resulted in gradual reduction in neurological signs but recurrence of hostility. Lithium 600 mg was continued and quetiapine was introduced cautiously. Gradually, a notable improvement in mental state was observed including improved sleep pattern, diet, weight and compliance with oral medication. She became less hostile towards staff members and there was reduced need for as required intramuscular medication. Creatine kinase levels returned to 96 U/l. She was then transferred to an open ward (September 2004).

The dose of lithium was gradually increased to 1000 mg (serum levels 0.7 mmol/l) and quetiapine 300 mg twice daily. Blood test revealed borderline hypothyroidism, so she was started on levothyroxine 50 µg daily. Further improvement was gradually observed in terms of reduced hostility, better sleep and cooperation but she remained disorientated with monosyllabic speech, staring, psychomotor retardation and repeating one phrase – 'I am alright'. Quetiapine was cautiously cross tapered with olanzapine 15 mg daily but did not result in any further improvement. The dose of lithium was then cautiously increased to 1200 mg (serum levels 0.8 mmol/l in March 2005). Marked improvement in mental state was observed. The patient became well orientated in time, place and person, more stable in mood, and able to hold appropriate conversations. The family corroborated this improvement with evidence of good autobiographical memory. Prior to this time, it was difficult to test autobiographical memory as she was agitated and disorientated. Physical examination revealed remission of motor signs. She however appeared blunted in affect, exhibited delayed responses, presented impatient, somewhat repetitive, and anxious. In order to rule out any frontal lobe pathology an MRI scan was performed, which was reported normal.

After about a month, deterioration in mental state was observed again. Urine microscopy and culture revealed UTI, which was treated with trimethoprim but her mental state did not improve. She again became agitated with disorganised behaviour, incontinence and grabbing staff members. A multidisciplinary review was held and it was decided to stop olanzapine and consider a trial of clozapine. As the patient was detained under the Mental Health Act and the second opinion appointed doctor did not agree for concomitant lithium with clozapine, it was decided to withdraw lithium. The dose of clozapine was gradually increased to 500 mg/day with clozapine levels being 594 µg/l and desmethyl clozapine 230 µg/l. Mental state, however continued to deteriorate, and she required transfer to the PICU (September 2005). Lithium and valproate were restarted with as required chloral hydrate and lorazepam for sedation. As the patient started refusing oral medication and became delirious, aggressive and floridly manic, spending most of the time in seclusion, ECT was commenced and clozapine stopped. Improvement in mental state was noted after four ECT sessions. A course of 12 ECTs was administered with continued improvement. Lithium was gradually increased to 1000 mg/day and valproate increased to 1400 mg/day (serum lithium 0.7 mmol/l and valproate 81 mg/l). Gradually the patient returned to her normal premorbid self and was eventually discharged home in February 2006. She was discharged on lithium 1000 mg, sodium valproate 1400 mg, levothyroxine 50 µg and lorazepam 1 mg daily.

OUTCOME AND FOLLOW-UP

She continues to remain stable about a year after discharge from hospital and is caring for her elderly parents.

DISCUSSION

The clinical presentation in our patient was similar to that described by Karmacharya *et al*, 2008 in their report on 16 cases with delirious mania – female, prior diagnosis of bipolar disorder, acute onset of severe symptoms, incontinence, extremely disorganised thought and behaviour and affective lability.[3]

On analysis of this case it becomes apparent that the patient developed catatonia early during admission. Catatonia is frequently associated with mania,[5] and clinical diagnosis can be supported by using a catatonia screening and rating instrument.[6] Catatonic symptoms are a marker of severe mania with poorer outcome. Prevalence studies in mania discovered

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that manic patients with catatonia present with more mixed episodes, more severe manic symptoms, more frequent admission to acute care unit, a longer hospitalisation, more general psychopathology and lower Global Assessment of Functioning scores than non-catatonic manic patients.[7 8] Catatonic symptoms can co-occur in delirious mania and may be linked with NMS due to the common pathophysiology of central dopamine deficiency.[2 9 10] It is important to diagnose a catatonic syndrome in order to use appropriate treatment with lorazepam and ECT, which are particularly effective in catatonia.[11] We hypothesise that in our patient the use of typical antipsychotics – haloperidol and zuclopentixol acuphase – to contain agitation might have led to the deterioration in catatonic symptoms.

The increased dose of olanzapine after admission might have been only of limited usefulness as CBZ significantly enhances olanzapine metabolism.[12] Further worsening in mental state might be explained by neurotoxic side effects from CBZ when combined with valproate as this increases 10,11 CBZ-epoxide by inhibiting epoxide hydrolase and/or glucuronidation of CBZ-10,11-*trans*-diol.[13 14]

We believe that the first course of ECT was not effective due to a number of factors. The patient was on two antiepileptic medications – CBZ and valproate in addition to benzodiazepines (lorazepam), which most likely affected the effectiveness of ECT.[15] As documented in the ECT protocols (table 1), the duration of observed and EEG measured epileptic activity repetitively decreased with the introduction or an increase of the valproate dose. In addition, she was administered unilateral ECT which might be less effective, particularly in the presence of anticonvulsants, limiting generalisation of seizure activity. The potential neurotoxicity associated with CBZ epoxide may have led to more pronounced disorientation as a consequence of ECT.

Table 1 First course of ECT

Date	Treatment number	Stimulus strength (mC)	Placement of electrodes	Duration of fit (visual, in s)	Duration of fit (EEG, in s)	Regular medication
5 April 2004	1	75	Right unilateral	21	27	Olanzapine 20 mg/day, CBZ 800 mg/day, diazepam 5 mg four times a day and temazepam 20 mg
10 April 2004	2	300	Right unilateral	12	15	Same
12 April 2004	3	300	Right unilateral	9	25	Same
16 April 2004	4	300	Right unilateral	15	21	Same
19 April 2004	5	300	Right unilateral	16	18	Same
23 April 2004	6	300	Right unilateral	0	0	Valproate added on 21 April 2004 1000 mg/day
23 April 2004	6	350	Right unilateral	0	0	All of the above
26 April 2004	7	400	Right unilateral	11	19	All of the above
3 May 2004	8	550	Right unilateral	9	27	27 April 2004, valproate increased 1600 mg/day
8 May 2004	9	550	Right unilateral	9	19	As above
10 May 2004	10	600	Right unilateral	0	24	As above

As required medication used (oral/intramuscular): lorazepam, zuclopenthixol acuphase, haloperidol.

Table 2 Second course of ECT

Date	Treatment number	Stimulus strength	Placement of electrodes	Duration of fit (visual, in s)	Duration of fit (EEG, in s)	Regular medication
15 September 2005	Zero	75	Bilateral	0	0	Lithium 700 mg/day, valproate 1000 mg/day
125	Bilateral	31	43			
18 September 2005	1	200	Bilateral	19	32	Same
22 September 2005	2	200	Bilateral	22	30	Same
25 September 2005	3	200	Bilateral	18	31	Same
29 September 2005	4	500	Right* unilateral	10	29	Same
2 October 2005	5	500	Right unilateral	10	13	Same
6 October 2005	6	550	Right unilateral	10	23	Same
13 October 2005	7	550	Right unilateral	10	23	Same
16 October 2005	8	550	Right unilateral	8	24	Same
20 October 2005	9	600	Right unilateral	10	29	Same
23 October 2005	10	600	Right unilateral	8	30	Same
27 October 2005	11	600	Right unilateral	4	35	Same

As required medication used (oral/intramuscular): promethazine, lorazepam.
* ECT changed from bilateral to unilateral as patient showed signs of improvement and the family was concerned about potential cognitive effects of ECT.

The second course of ECT was effective as at that time she was not on CBZ and, while she was on valproate, was poorly compliant with medication at commencement of ECT. Another factor is that she was initiated on bilateral ECT (see table 2) which may be more effective in severe mania.[16]

With respect to treatment response in our patient, ECT and combination of lithium and valproate were clearly beneficial as shown previously by Karmacharya *et al*.[3] It is important to recognise that therapeutic serum levels of valproate (at least 80 µg/ml) are achieved in order to get a response in mania.[17] The atypical antipsychotics (quetiapine and olanzapine) showed some benefit in treating agitation. Clozapine can be beneficial in delirious mania,[3] however, in our patient it did not seem to be effective. It is possible that any benefit was overshadowed by a relapse potentially caused by discontinuation of lithium.[18]

Learning points

- Treatment of delirious mania, especially when accompanied by catatonic symptoms, remains a clinical challenge.
- It is important to recognise catatonia as a symptom of delirious mania early to initiate appropriate treatment.
- ECT and mood stabilisers (lithium and valproate combination) were effective treatments in our case of catatonic delirious mania.
- As treatment regimens become more complex, chances of complications also increase due to drug–drug interactions, treatment discontinuations, eg, of lithium, or suboptimal preparation and execution of ECT.

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Patient consent Obtained.

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