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Case report

Clonidine in the management of treatment resistant adolescent-onset mania: A case report

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Abstract

Introduction: Treatment of early-onset mania proves to be challenging in the face of chronicity and comorbidities, especially when the conventional anti-manic medications are ineffective or poorly tolerated.

Case history: A 14-year-old girl with moderate intellectual disability, presented with symptoms suggestive of manic episode without psychotic symptoms. Poor tolerability of the first-line antimanic medications namely lithium, valproate, risperidone, quetiapine, and aripiprazole impeded the effective management of the episode. In this background, addition of clonidine was followed by significant reduction in the severity of core manic symptoms.

Discussion: Clonidine has been found to be effective in hyperadrenergic states including mania, particularly in a subset of refractory patients as well as those who have poor tolerability to lithium and antipsychotic drugs.

Key-words: Clonidine, adolescent-onset mania

Introduction

Diagnosis and treatment of early-onset mania have gained the attention of mental health researchers over the years [1]. These cases prove to be challenging in the face of chronicity [2] and comorbidities, more so when the conventional anti-manic drugs are ineffective or poorly

tolerated. This case highlights the dilemmas encountered in treating a manic episode in an adolescent, who had poor tolerability to conventional anti-manic treatments, in the light of which clonidine proved to be effective.

Case history

A 14-year-old girl presented to us with moderate intellectual disability (IQ = 48), and baseline behavioural problems of overactivity and anger outbursts when demands were not met, since her formative years. She had epilepsy, with semiology suggestive of partial seizures with secondary generalisation, and was being treated with carbamazepine at 600mg/day (10 mg/kg/day). She developed an episode of unprovoked seizures, following which clobazam 10 mg was added to the existing regimen. The seizures were controlled; however, she developed irritability, restlessness, mutism and functional deterioration, not amounting to a mood disorder. Since there was temporal correlation with addition of clobazam and improvement in the emergent symptoms on withdrawing the drug, clobazam induced paradoxical disinhibition was considered. Hence, for optimal management of seizures, sodium valproate was added as a second anti-epileptic, at a dose of 1g (20 mg/kg). On a combination of two anti-epileptics, her seizures were under control and she attained her premorbid self.

A month later, she presented with new onset symptoms of elated mood, increased psychomotor activity, disturbed biological functions, and developmentally inappropriate over-familiarity and over-talkativeness over 3 weeks. She continued to have good compliance to anti-epileptic medications and had no relapse of seizures. Given the background of moderate intellectual disability and epilepsy, neuroimaging (MRI) and EEG were done to rule out organicity and were found to be normal. A diagnosis of Mania without psychotic symptoms, according to ICD-10 diagnostic criteria was made. She was treated on an inpatient basis in view of severe dysfunction and failed outpatient-based treatment. At baseline, she scored 40 on Youngs Mania Rating Scale (YMRS), and 20 on C-GAS (Children-Global Assessment Scale).

Serum level estimation of carbamazepine (600 mg) was 9.92 mcg/ml and valproate at 1gm was 65.6 mcg/ml. Further increase in the dose of either of the mood stabilisers was deferred, given the complex pharmacokinetic interactions between the two drugs. Hence, for acute management of mania, combination of antipsychotic was considered. Increased risk of additive metabolic and sedative side effects precluded the choice of olanzapine. Risperidone was started and gradually titrated up to 8 mg, with the valproate and carbamazepine combination. However, risperidone had to be discontinued as she developed marked akathisia. She subsequently developed incapacitating drug induced parkinsonism with 400 mg of Quetiapine and on Aripiprazole at 10 mg, minimizing the option of antipsychotics combination in the acute phase management. Minimal clinical improvement and higher sensitivity to extrapyramidal symptoms were noted at optimal doses of antipsychotics. The child continued to have baseline severity of symptoms at the end of 4 weeks of inpatient management.

Combination of two mood stabilisers for the management of the acute phase of mania was considered, and valproate was gradually up-titrated to 2 gm (36mg/kg) over 3 weeks. Carbamazepine was continued at 600 mg, owing to the enzyme inhibiting property of valproate. At 2 gm of valproate, serum level continued to be low (66 mcg/mL), attributable to pharmacokinetic interactions with carbamazepine and no clinical improvement was noted. Hence, optimization of valproate as monotherapy was considered to minimise drug interactions and adverse events. Following the gradual reduction of carbamazepine, she developed drowsiness, altered sensorium and generalised seizures. Toxic serum levels of valproate (156 mcg/mL at 2g), mild elevation of liver enzymes and hyperammonaemia necessitated dose reduction. There was no past history suggestive of inborn errors of metabolism, storage disorders or susceptibility to hepatic injury. Baseline liver enzymes prior to initiating valproate were within normal limits. Hence, valproate induced hyperammonemia was considered. Valproate was reduced to 1400 mg (25 mg/kg), following which liver enzymes and ammonia

levels normalised. Lacosamide was prescribed for seizures given the safer side effect profile [3].

Valproate monotherapy was ineffective at serum level of 110 mcg/ml, partial response from baseline severity was noted. Given the predominant manic polarity of the mood episode and poor tolerability to antipsychotics, combination of lithium and valproate was considered to achieve remission. Lithium was chosen for its favourable hepatic profile and efficacy in mania in adolescents. Lithium was started at 600 mg. At the combination, symptomatic improvement was noted; however, child did not attain remission of symptoms over 6 months (YMRS 25). Serum lithium levels were 0.9 mEq/L at 600 mg. On lithium 600 mg, she developed polydipsia and polyuria within two months of lithium initiation. Nocturnal polyuria (3-4 times urination) resulted in sleep impairment and worsening of manic symptoms. A serum lithium level at 600 mg was 1.13 mEq/L, which could be explained by polyuria. Dose reduction to 450 mg (0.64 mEq/L) did not improve polyuria, hence lithium was tapered and stopped.

This case posed the following management challenges. 1) Early onset Bipolar disorder with comorbid moderate intellectual disability 2) Persistence of symptoms for duration of 8 months without symptomatic remission. 3) Higher propensity to adverse events with antipsychotics and mood stabilisers 4) Comorbid epilepsy. Relook at the diagnosis focusing on the neurodevelopmental comorbidities such as comorbid ADHD and organic affective disorder was considered. The persistent symptoms were euphoric mood, disinhibited behaviour and increased psychomotor activity, which are core symptoms of mania, and could not be explained by untreated or residual comorbid ADHD. The episode was characterised by a clear onset and prominent affective symptoms, which were different in nature compared to the episodic context-specific irritability that was part of the child's premorbid functioning. Hence, the diagnosis of Bipolar affective disorder with current episode of mania without psychotic symptoms was retained.

At this juncture, given the persistent manic symptoms (YMRS 25 at 8 months from onset), necessitated alternate treatment options. Clonidine was chosen for its sedative properties, favourable CNS side effect profile and anti-manic action. [4] Gradual titration from 25 mcg to 250 micrograms (mcg) (4.5 mcg/kg/day) was done over two weeks, while carefully monitoring for cardiovascular side effects. Improvement in sleep was noted at 100 mcg. Reduction in the severity of manic symptoms was noted when the dose was titrated above 150 mcg (2.7 mcg/kg/day), at the end of 2 weeks. Clonidine was tolerated well, with no serious adverse events. YMRS score reduction from 25 to 14 and improvement in C-GAS score from 20 to 50 was observed. Over three months' follow-up, she had attained remission and continued to maintain the improvement, and was functioning at premorbid level (C-GAS 70) on a combination of valproate 1400 mg and clonidine 250 mcg.

Discussion

This case demonstrates a variety of treatment challenges encountered while treating an episode of mania in a child with intellectual disability. Poor tolerability of the first-line antimanic medications impeded the effective management of the index episode. As per the provisions of The Mental Healthcare Act, 2017 for child and adolescent population, electroconvulsive therapy could not be considered directly by treating team which led to limited treatment options [5]. Clonidine, a central alpha-2 adrenergic agonist, described to be effective in a variety of hyperadrenergic states including mania, was considered as an alternative. The basis for the use of clonidine in mania is the 'Catecholamine hypothesis of affective disorders' which proposes that mania is associated with a relative excess of catecholamines particularly norepinephrine [6]. Clonidine does not cause severe adverse effects that are related to various antipsychotics and mood stabilizers used in the treatment of mania. The rapidity of action of clonidine and its lack of relatively serious side-effects renders it a potential alternative to conventional anti-manic agents, more so in resistant cases [7].

A review of the existing literature suggests that clonidine may be particularly effective in a subset of refractory patients as well as those who have poor tolerability to lithium and antipsychotic drugs [7]. Clonidine monotherapy for mania has been reported, however evidence is based on anecdotal reports. The child had evident manic symptoms and these markedly reduced following augmentation with clonidine. Nevertheless, whether clonidine only improved the hyperkinetic behaviour could not be completely delineated. However, the trajectory of improvement suggests the reduction in core manic symptoms. Literature predominantly focuses on adult population with bipolar disorder [7-9], while research in the early-onset population with comorbid neurodevelopmental disorders is sparse. It would prove to be beneficial to conduct more systematic studies exploring the use of clonidine in the treatment of manic episodes in the paediatric population with comorbid developmental disorders, to increase the effective options for the management of such cases.

Conflict of interest: None declared

References

1. Danner S, Fristad MA, Arnold LE, Youngstrom EA, Birmaher B, Horwitz SM, et al. Early-onset bipolar spectrum disorders: diagnostic issues. Clin Child Fam Psychol Rev 2009, 12(3):271–93.
2. Sareen H, Trivedi JK. Child psychopharmacology: Is it more similar than different from adult psychopharmacology? Indian J Psychiatry 2013, 55(3):301–4.
3. Lancman ME, Fertig EJ, Trobliger RW, Perrine K, Myers L, Iyengar SS, et al. The effects of lacosamide on cognition, quality-of-life measures, and quality of life in patients with refractory partial epilepsy. Epilepsy &Behavior 2016, 61:27–33.
4. Hunt RD, Capper L, O'Connell PA. Clonidine in child and adolescent psychiatry. Journal of child and adolescent psychopharmacology 1990, 1(1):87-102.
5. Ministry of Law and Justice. The Mental Healthcare Act; 2017. Available from: http://www.egazette.nic.in/WriteReadData/2017/175248.pdf.
6. Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. American Journal of Psychiatry 1965, 122(5):509–22.

7. Hardy MC, Lecrubier Y, Widlöcher D. Efficacy of Clonidine in 24 patients with acute mania. Am J Psychiatry 1986, 143(11):1450–3.
8. Tudorache B, Diacicov S. The effect of Clonidine in the treatment of acute mania. Rom J Neurol Psychiatry 1991, 29(3–4):209–13.
9. Shaik S, Sarkar S, Menon V. Difficult to treat mania: Clonidine as an option? Journal of International Research in Medical and Pharmaceutical Sciences 2015, 2(1): 23-25.

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