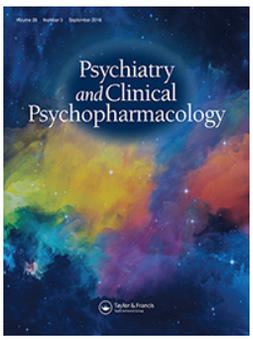

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CASE REPORT

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Imipramine-induced mania in a child diagnosed with attention-deficit/hyperactivity disorder (ADHD): a case report

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ABSTRACT

Children and adolescents treated with antidepressants (ADs) are at higher risk for developing hypomania and mania compared with adults. It was suggested that AD-induced mania represent a predisposition to bipolar disorder (BD) so it may accelerate the course of BD in this risky population. According to the literature, susceptibility to manic conversion with the use of ADs is higher in BD patients treated with tricyclic ADs compared with selective serotonin reuptake inhibitors (SSRIs) and placebo. Here, we report a six-year-old girl who was diagnosed with attention-deficit/hyperactivity disorder (ADHD) and primary nocturnal enuresis who developed manic symptoms after imipramine treatment. While using tricyclic antidepressants or SSRIs for different indications in the paediatric population, clinicians should be alert for the manic switch or behavioural activation symptoms, which may show a bipolar predisposition.

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Imipramine; mania; behavioural activation; ADHD; children and adolescents; bipolar disorder

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioural disorder characterized by persistent, pervasive impairment and developmentally inappropriate inattention and/or hyperactivity-impulsivity [1]. ADHD is among the most common childhood disorders with an estimated prevalence rate of 5.3% [2]. Oppositional defiant disorder (ODD), conduct disorder (CD), anxiety and mood disorders, and learning disorders are the most common comorbidities with ADHD [3,4].

Elimination disorders, nocturnal enuresis (NE) foremost among them, are also frequent comorbidities with ADHD. Clinical studies revealed prevalence rates of 11.7–17.1% for NE among children with ADHD [5]. Treatment strategies include both psychosocial interventions (psychoeducation, monitoring of symptoms, voiding exercises, alarm devices, etc.) and pharmacotherapy in case of comorbidity of ADHD and NE [6,7].

Long Acting forms of methylphenidate (MPH) are the most commonly used FDA approved drugs for the treatment of ADHD. Although stimulants do not have known anti-enuretic effects and are not indicated in enuretic children without ADHD, there are case reports of resolution of NE with stimulant treatment [8,9]. Atomoxetine, a selective Noradrenaline reuptake inhibitor, is effective in the treatment of ADHD and may also have a positive effect on bladder control in children with NE [10]. Among tricyclic antidepressants (TCAs) (ADs), imipramine has been documented to be effective in the treatment of NE and could be a treatment option for children with treatment-resistant NE in children with ADHD [5,7].

The most commonly reported side effects of imipramine are; tremors, increased weight, dry mouth, constipation, and cardiovascular problems. Psychiatric side effects of imipramine are; confusional states (especially in the elderly), hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia, nightmares, exacerbation of psychosis, sleep disorders, emotional instability, and swings from depression to hypomania to mania [11].

Here, we report a seven-year-old girl diagnosed with ADHD who exhibited manic symptoms after imipramine treatment. Informed consent of parents and the verbal assent of the child were obtained before case presentation.

Case presentation:

A six-year-old girl was brought to our Child and Adolescent Psychiatry Clinic with irritability, increased motor activity and impulsivity, agitated behaviours, mood elevation, decreased need for sleep, suicidal thoughts, and inflated self-esteem. The symptoms were ongoing for the last two weeks. According to parents, the symptoms started after prescription of imipramine 25 mg/day for ADHD and primary NE by a Child and Adolescent Psychiatrist.

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Past history revealed a problematic, irritable, overactive infancy with crying spells and problems in sleep and feeding. Motor developmental milestones were within normal limits. She had uncomplicated febrile seizures at 18th and 26th months. Hyperactivity and behaviour problems continued during early childhood and kindergarten, and she was diagnosed with ADHD and NE by the first grade.

Family history revealed no psychiatric history or diagnoses. Laboratory and neurological evaluations were within normal range. Baseline mental status examination revealed an overactive and restless school child with limited cooperation. Spontaneous attention was increased while sustained attention and concentration were impaired. The mood was dysphoric while affect was labile. Thought content was notable for grandiosity ("I'm so strong and will not be injured even if I would jump off," "I know everything"), impaired reality testing ("I can make magic."), and passive suicidal ideation. Loose associations were noted. The speech was increased, and she was hard to interrupt at times. Need for sleep and appetite were decreased while motor activity was increased.

Baseline Young Mania Rating Scale (YMRS) score was 13 (Above cut-off of 12 for acute mania), Clinical Global Impressions-Severity Score was 5 ("markedly ill"). An evaluation with Naranjo Adverse Drug Reaction Probability Scale yielded a score of 6 (probable ADR) [12].

According to clinical and psychometric evaluations and history of complaints, she was diagnosed to have a manic episode that emerged during antidepressant medication according to DSM-5 criteria. Imipramine was discontinued immediately and risperidone 0.25 mg/day was started. Risperidone was titrated to a dosage of 0.50 mg/ day over three days. After cessation of imipramine and with risperidone her symptoms resolved dramatically within a few days. Follow-up assessments at the second and fourth weeks were non-remarkable and her last YMRS score reduced to 3 points. Her parents and teacher have not reported any problems at home or school.

Discussion

Here, we report a female patient who was diagnosed with ADHD and primary NE who developed manic symptoms after imipramine treatment. For our case; increased motor activity and impulsivity, agitated behaviours, mood elevation, decreased need for sleep, and inflated self-esteem symptoms prompted us for tentative diagnosis of imipramine-induced mania. Children and adolescents treated with ADs are at higher risk for developing hypomania and mania compared with adults. Martin et al. found the rate of mania-hypomania symptoms as 5.4%, in a large young aged population under treatment with an AD [13]. According to a review comparing 29 single case studies and randomized controlled trials (RCTs), it was determined that youth who develop manic symptoms as a result of antidepressant treatment have genetic vulnerabilities and have a family history for bipolar disorder (BD) [14]. It was suggested that AD-induced mania represent a predisposition to BD so it may accelerate the course of BD in this risky population [15,16]. According to the literature, susceptibility to manic conversion with the use of ADs is higher in BD patients treated with tricyclic ADs (11.7%) compared with selective serotonin reuptake inhibitors (SSRIs) (3.7%) and placebo (4.2%) [17]. However, Cheung et al. found a 2% mean rate of antidepressants induced Mania in paediatric population without a family history of BD, with the highest incidence of manic symptoms induced by fluoxetine (6%) while the incidence for placebo was 0–2% [18]. In the literature, there are some case reports of AD treatment-induced new-onset episodes of mania or hypomania in children and adolescents [19–21]. Especially in younger persons, such new-onset symptoms may predict an undiagnosed BD. These switch like symptoms can also be explained by adverse drug effects or de novo induction of BD by mood-elevating treatments [15]. Mood elevation risk may be greater in treatment with tricyclic ADs than with SSRIs [17]. On the other hand, treatment with ADs in the paediatric population has also been associated with "behavioural activation"; a more broadly defined phenomenon by comparison with treatment-induced mania [13]. The term of "behavioural activation" which occurs at higher rates in paediatric patients than adults refers to; hyperactivity, impulsivity, insomnia or disinhibition and, importantly shows a distinct clinical pattern from treatment-emergent mania [22,23]. A meta-analysis including nine RCTs in children and adolescents showed that behavioural activation is strongly associated with antidepressant treatment compared to placebo [24]. Activation appears to be more common in prepubertal children with an average rate of 10.7% than in adolescents (2.1%) [25].

To the best of our knowledge, this is the first case mentioning manic symptoms induced by imipramine during ADHD and NE treatment of a six-year-old paediatric patient. Tricyclic ADs seem to be effective for the management of enuresis in children. Co-occurring ADHD and enuresis is a predictor of persistent enuresis, so imipramine; a tricyclic antidepressant can be a suitable treatment option for the management of NE and ADHD symptoms together [26]. But while using TCAs or SSRIs for different indications in the paediatric population, clinicians should be alert for the manic switch or behavioural activation symptoms which may show a bipolar predisposition. Titration dosage of AD's and monitoring adverse events seem to be very important for clinical management and prognosis for those children who may be at risk for BD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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