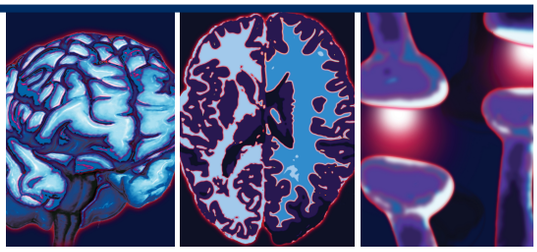
CASE REPORT



Psychosis in a boy with ADHD treated with stimulants and acute lymphocytic leukemia treated with chemotherapy and steroids

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Practice points

- Psychosis can be a rare side effect of stimulant treatment in children with ADHD.
- Psychosis can also be a side effect of steroid treatment in children treated with chemotherapy for leukemia.
- Since regular steroid and chemotherapy treatments for leukemia can continue almost monthly for 3 years, a preventive approach to recurrent psychotic episodes is required in such instances.
- A brief several-day course of risperidone, which precedes and corresponds to the steroid treatment, can prevent recurrence of psychotic episodes secondary to steroid treatment.

SUMMARY This article describes the case of a 14-year-old boy who presented at the emergency room with acute psychotic symptoms, ADHD treated with stimulants and acute lymphocytic leukemia treated with chemotherapy and steroids. The stimulants were discontinued and not reinstated; the course of chemotherapy and steroids were continued; and the psychosis was treated with risperidone. The psychotic symptoms resolved and the risperidone was discontinued. The patient presented again as a psychiatric emergency 1 month later with acute anxiety and paranoia after he began a further course of chemotherapy and steroids. The risperidone course was again initiated and the symptoms resolved. As the chemotherapy and steroids would be continued almost on a monthly basis to treat the leukemia, a prophylactic protocol was established. Very small dosages of risperidone were administered prophylactically a day before the steroids and chemotherapy course began and were continued throughout the course (5–6 days). This treatment approach has been repeated over several months of treatment and there has been no recurrence of the acute psychosis. This case report highlights the possibility of developing steroid psychosis and the potential effectiveness of intermittent small doses of risperidone in preventing the recurrence of the steroid-associated psychotic symptoms.

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Presentation of case

John (not the patient's real name) is a 14-year-old boy who presented to the psychiatric emergency room for assessment and management of acute-onset auditory and visual hallucinations, agitation, rapid speech and feeling like he was on an 'emotional rollercoaster'. John was diagnosed with T-cell acute lymphocytic leukemia 2 weeks before this, which was immediately followed by the first stage of treatment, induction. This treatment stage included several medications: intrathecal cytarabine, intrathecal methotrexate, prednisone, vincristine, daunorubicin and PEG asparaginase.

John was diagnosed with ADHD 2 years before this. He was also noted to experience significant anxiety, as well as oppositional and impulsive behavior. A concurrent neurological examination demonstrated some difficulties with balance and coordination. Attentional difficulties were treated with an unsuccessful Ritalin® trial (Novartis Pharma, Basel, Switzerland; 10-mg twice daily) and then successfully treated with Concerta® (Janssen Pharmaceuticals Inc., NJ, USA; 36-mg once daily) 18 months prior to the current presentation. Pregnancy and birth were described as within normal limits. John was born with craniosynostosis, which has been associated with increased intracranial pressure and behavioral problems. He was not breastfed due to difficulty with his sucking reflex. There was a reported developmental difficulty in fine motor movements. The family history includes ADHD, obsessive-compulsive disorder, Rett's syndrome, a completed suicide, and mood and bipolar disorders.

Hypotheses as to the etiology of the psychotic symptoms included that they may have been due to a psychotic and/or mood disorder with psychotic features secondary to the stimulants or to some of the agents used in the leukemia treatment, such as steroids or intrathecal medications. Furthermore, John seemed to be at risk of developing psychiatric symptoms due to his developmental history and family psychiatric history, in the context of an oncological diagnosis and treatment regimen.

The initial approach to the treatment of his acute psychotic symptoms was to discontinue the stimulants and to initiate antipsychotics. All other potential medication contributors (i.e., vincristine and prednisone) were continued due to the urgent need to treat the leukemia. The medication prescribed for the psychotic symptoms was low-dose risperidone. John was treated on an outpatient basis with frequent phone discussions with his mother in order to monitor target symptom changes and potential medication side effects, and to plan medication adjustments including any 'as needed' medication. Risperidone 0.5 mg in the morning and evening was administered regularly over the course of 3 weeks. After 3 weeks, John's psychotic symptoms resolved completely, except for some residual anxiety, and he was gradually weaned off the risperidone.

Shortly after the beginning of the next course of chemotherapy and steroids (John was no longer on stimulants), he was again urgently referred to psychiatry. At this time he was extremely fearful and paranoid, clinging to his mother, not permitting her to leave his room or break physical contact with him. He cried frequently for no apparent reason, was very emotionally labile and difficult to calm down. Lorazepam 0.5 mg was administered as needed and John was started on Zoloft® (Pfizer, NY, USA; sertraline HCL; 50 mg). His overall level of anxiety had been high for a few months, to the point that he was not able to engage in the therapies offered to him for his anxiety and agitation. The pediatric oncology service has excellent psychosocial resources, including child life specialists, music and art therapists, pastoral care workers, a psychologist and a social worker. John's anxiety was generalized to many areas, but a significant amount was focused around his illness, worries about death, being in the hospital and receiving treatments, and separation from his mother. He would experience mild improvement at home if he did not return to the hospital for several days but his anxiety would increase significantly upon return to the hospital. John's marked anxiety and psychiatric symptoms occurred when he was at home being treated with steroids and chemotherapy and were not limited to the hospital setting. Thus even though the anxiety was present a good deal of the time, the psychotic symptoms clearly corresponded to receiving high dosages of steroids and not hospitalization *per se*.

At this time, the differential diagnosis in accordance with the five Axes of the DSM-IV included the following. On Axis I (primary diagnosis), in addition to the history of ADHD, the differential diagnosis for his anxiety which was almost of psychotic proportions included: an adjustment disorder with significant anxiety and a behavioral component; anxiety secondary to medications and/or the medical condition; and a generalized

anxiety disorder. There was no Axis II (personality diagnosis) diagnosis; however, on history, John had been temperamentally anxious. The Axis III (medical diagnosis) diagnosis was T-cell acute lymphocytic leukemia. On Axis IV (contributing factors), John was distressed about missing school and his minimal access to friends; and the family members (mother, father and older sibling) were readjusting their life functioning in the context of a new serious illness diagnosis and concomitant treatments. Axis V (overall level of functioning) was variable: 45–60.

His condition did not significantly improve and risperidone 0.5 mg twice daily was restarted. After a few days, his condition improved with a return to his previous state of mood and functioning. At this point, a regime of prophylactic risperidone treatment was instituted. Risperidone at 0.5 mg *hora somni* was started the day before the steroids and chemotherapy were due to begin. This was increased to risperidone 0.25 mg in the morning, 0.25 mg at noon and 0.5 mg *hora somni* the following day, and 0.5 mg in the morning and 0.5 mg *hora somni* each day for the duration of the steroid treatment (usually 5 days). The risperidone was then decreased to 1 day of 0.25 mg twice daily, 1 day of 0.25 mg in the morning and then discontinued.

This regime was repeated for all subsequent months of his steroid and chemotherapy regime (5 months to date) with no recurrence of any psychotic episodes or severe uncontrollable anxiety. The hypothesis that the psychotic symptoms were related to stimulant treatment for John's ADHD had to be abandoned because these psychotic side effects appear in patients receiving high steroid doses who do not have ADHD and do not receive stimulant treatment. In addition, the cessation of stimulant treatment did not improve the clinical picture nor did it prevent the recurrence of the psychosis when high dosages of steroids were reintroduced. Furthermore, repeated development of psychotic symptoms with the administration of high dosages of steroids was too coincidental to ignore, as was the absence of these symptoms with the intermittent use of risperidone corresponding to the time of the steroid administration.

John has continued to do well and has returned to school on a modified educational program.

Outcome & implication

The prophylactic use of intermittent (6 days/month) small dosages (0.5 mg twice a day) of risperidone has been successful in preventing the recurrence of steroid-induced psychosis related to the treatment of acute lymphocytic leukemia in a 14-year-old boy. There have been no significant antipsychotic medication side effects associated with this regime. Risperidone is started at a very low dose the day before the steroids and chemotherapy begin, continued at this low dose twice a day during the 5 days of leukemia therapy, tapered on the day after the therapy ends and then discontinued. This strategy of intervention has been effective for John. This suggests that when the repeated use of steroids is unavoidable and when steroid-linked psychotic symptoms have repeatedly developed, these symptoms can be prevented with the use of low doses of risperidone concurrently with the steroids. Initiating the risperidone treatment the day prior to beginning steroid treatment may be more effective in preventing the development of the steroid psychosis. The use of risperidone shortly before the steroids and chemotherapy begin has been very effective in decreasing the anxiety of the child and family that had developed around the steroid and chemotherapy treatment.

Discussion & conclusion

Most of the literature that describes steroid-induced psychiatric disturbances, such as mood and/or psychotic symptoms, has been reported in the adult population [1–6]. The Boston Collaborative Drug Surveillance Program reported that psychiatric reactions may be dose dependent and seen in 1.3% of 403 patients receiving less than 40 mg/day, 4.6% of 175 patients receiving 40–80 mg/day and 18.4% of 38 patients receiving more than 80 mg/day [4]. In a meta-analysis of 13 studies involving 2555 patients treated with corticosteroids, Lewis and Smith reported an average of 5.7% incidence of severe psychiatric symptoms [5]. Since cancer patients generally receive high dosages of corticosteroids, Stiefel *et al.* reported a 5–10% incidence of psychiatric symptoms in this population [7].

A review by Sirois on steroid psychoses suggested that 35% were mania, 26% depression, 12% mania and depression, 13% delirium, and 11% psychosis [8]. However, the literature pertaining to serious psychiatric reactions in children treated with corticosteroids is much more sparse [9]. A recent literature review (1979–2008) reported 17 pediatric case reports of steroid-induced psychosis [10,11]. These pediatric case

reports have limited treatment data in them. Generally, a discontinuation of steroids is recommended, although this is often not feasible. One case was successfully treated with chlorpromazine and another reported the use of electroconvulsive therapy treatment for an adolescent, while a third reported some benefits with promethazine. Three cases were treated with risperidone.

Patients with acute lymphocytic leukemia seem to be at an elevated risk for this side effect because they require high steroid dosages. Generally, psychotic symptoms resolve after discontinuation or a reduction in steroid dose. However, this is not an option in acute leukemia and hence treating these psychotic symptoms in the presence of continued steroid treatment is a challenge. A PubMed search on steroid-related psychosis in pediatric oncology revealed only three papers: a case review of a 14-year-old girl with acute lymphoblastic leukemia treated with risperidone [12], a 2-year old with acute lymphoblastic leukemia treated with promethazine [13], and a description of three patients aged 8, 10 and 16 years with acute lymphoblastic leukemia, all of whom were treated with risperidone [9]. In all three cases it was recommended that risperidone treatment be started concurrently with every cycle of prednisone during the chemotherapy routine. In some cases it was also recommended that risperidone be continued for a week after the steroids are discontinued. In another case, intermittent episodes of recurrent steroid-induced mood symptoms continued and responded to risperidone. A prophylactic or preventative approach was not used in any reported cases with risperidone started 1–2 days before the steroid treatment began, thus minimizing the development of steroid-related psychiatric symptoms and keeping the number of days on risperidone treatment to a minimum. In all cases, the dosages of risperidone that were used were small and ranged from 0.5 to 1.5 mg per day (usually in two divided dosages in the morning and *hora somni*). The intermittent use of risperidone and the small dosages may be important in decreasing the side effects of risperidone (e.g., weight gain and metabolic syndrome).

Clearly, more systematic research is needed to determine the best protocol to employ in treating serious psychiatric side effects of steroid treatment in children. Since the acute lymphoblastic leukemia population of children requires long-term intermittent high dosages of steroids as part of their chemotherapy regime, this population may be particularly suitable for such systematic explorations.

The mechanism by which steroids exert their psychiatric effects, particularly psychosis, is not well understood and needs further research. Such understanding may also provide clues about how to prevent the serious and destabilizing psychiatric side effects.

In the interim, we can conclude that risperidone administered during the treatment with steroids is useful prophylactically for steroid-induced psychosis in children who have shown themselves to be susceptible to these side effects and who require ongoing steroid treatment.

Informed consent

This is a case report and the family provided verbal and written consent for the authors to present their child's medical and treatment history within this case report.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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