Arterial Hypertension and Posterior Reversible Cerebral Edema Syndrome Induced by Risperidone

abstract

Posterior reversible cerebral edema syndrome is a generally reversible neurologic condition that is diagnosed based on distinctive clinical and radiologic findings. The condition, which is mostly associated with severe arterial hypertension, has also been reported to be induced by several medications. We made the diagnosis of hypertension with posterior reversible cerebral edema syndrome in a lean 12-year-old girl treated with the second-generation antipsychotic risperidone. We applied the Naranjo Adverse Drug Reaction Probability Scale and the World Health Organization–Uppsala Monitoring Centre system for causality assessment to the present case. Both scales indicated that a relationship to risperidone was likely. Second-generation antipsychotic agents may occasionally induce an increase in blood pressure even in the absence of overweight. Given this possibility, we recommend routine monitoring of blood pressure during therapy with these agents. Pediatrics 2014;133:e771–e774

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KEY WORDS
arterial hypertension, posterior reversible cerebral edema syndrome, risperidone, second-generation antipsychotic drugs

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The second-generation antipsychotic agent risperidone is approved, along with other agents, for the treatment of children and adolescents with schizophrenia or bipolar disorders. It is well tolerated, with 10% of children withdrawing from treatment because of adverse events. Similar to other antipsychotic drugs, the adverse effects of risperidone include insomnia, agitation, anxiety, headache, somnolence, dizziness, tiredness, poor concentration, nausea, extrapyramidal symptoms (including tremor, dyskinesia, rigidity, and akathisia), weight gain, and low blood pressure. We describe here the occurrence of severe arterial hypertension with posterior reversible cerebral edema syndrome that we believe are directly attributable to long-term management with risperidone.

CASE REPORT
A previously normotensive 12-year-old Italian girl was admitted to the emergency department with a 2-day history of asthenia, lack of appetite, mild generalized headache, insomnia, and 2 episodes of visual impairment lasting ~5 minutes.

Since she was 8 years old, the girl had experienced episodes with decreases in emotion, cognition, and energy associated with sadness, isolation, poor concentration, and low activity affecting the normal psychosocial functioning. Periods of abnormally elevated and irritable mood lasting 8 to 10 days as associated with a decreased need for sleep and her attention being easily drawn to insignificant external stimuli had also been reported. Based on these data, the diagnosis of bipolar type I disorder was made, and oral risperidone 0.75 mg twice daily was started when she was 10 years old. No adverse effects were noted, and her parents reported improved health-related quality of life, scholarly activities, and social interactions. The girl was free of any other medication, and there was no known social drug or alcohol use.

On admission, general conditions and results of visual and neurologic examinations were unremarkable; body weight was 38.9 kg (36th percentile), body height was 1.512 m (62th percent), BMI was 17.0 (35th percent), axillary temperature was 36.3°C, oxygen saturation was 96%, and heart rate was 66 beats per minute. Blood pressure was increased, with systolic values ranging between 140 and 155 mm Hg (stage 2 hypertension: >135 mm Hg) and diastolic values ranging between 95 and 105 mm Hg (stage 2 hypertension: >93 mm Hg). A few minutes later, the girl experienced 3 generalized convulsions lasting 3, 5, and 8 minutes, respectively; these were managed with intravenous diazepam. Intravenous nitroprusside (initially 0.3 mg/kg per minute, subsequently increased to 3 μg/kg per minute), later given with oral amlodipine 0.15 mg/kg daily, decreased systolic and diastolic blood pressure by ≤10 and ≤5 mm Hg, respectively.

Results of initial investigations were normal, including renal function; circulating sodium, potassium, and calcium; and other laboratory tests. Table 1 lists the drugs associated with posterior reversible cerebral edema syndrome.

TABLE 1
Drugs Associated With Posterior Reversible Cerebral Edema Syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer agentsa</td>
<td>Alkylating agents: carboplatin, chlorambucil, cisplatin, cyclophosphamide (mostly used in combination with corticosteroids)</td>
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<tr>
<td></td>
<td>Antimetabolites: cytarabine, fluorouracil, gemcitabine, methotrexate</td>
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<tr>
<td></td>
<td>Inhibitors of angiogenesis: inhibitors of vascular endothelial growth factor (bevacizumab), thalidomide</td>
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<tr>
<td></td>
<td>Tyrosine kinase inhibitors: pazopanib, sorafenib, sunitinib</td>
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<tr>
<td></td>
<td>Inhibitors of epidermal growth factor receptor: cetuximab, pazopanib</td>
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<tr>
<td></td>
<td>Inhibitors of cytotoxic T-lymphocyte antigen 4: ipilimumab</td>
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<tr>
<td></td>
<td>Inhibitors of B-cell receptor signaling: rituximab</td>
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<tr>
<td></td>
<td>Lasparaginase</td>
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<td></td>
<td>Topoisomerase inhibitors</td>
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<tr>
<td></td>
<td>Vinca alkaloids: vinblastine, vincristine, vinflunine, vinorelbine</td>
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<tr>
<td>Corticosteroids (high doses)</td>
<td>Immunosuppressants</td>
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<tr>
<td></td>
<td>Calcineurin inhibitors: cyclosporine, tacrolimus</td>
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<td></td>
<td>Rapamycin (sirolimus)</td>
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<tr>
<td></td>
<td>Antitumor necrosis factor agents: etanercept, infliximab</td>
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<td></td>
<td>Inhibitors of interleukin-12 and interleukin-23: ustekinumab</td>
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<tr>
<td></td>
<td>Interferon-α</td>
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<tr>
<td>Miscellaneous</td>
<td>Levarusomide</td>
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<tr>
<td></td>
<td>Polyclonal intravenous immunoglobulin</td>
</tr>
<tr>
<td></td>
<td>Toxicity: alcohol abuse, cocaine, ephedra overdose</td>
</tr>
</tbody>
</table>

a Many anticancer agents included in this section are also used for nononcologic conditions (eg, renal diseases, systemic lupus erythematosus).

FIGURE 1
Brain MRI of a 12-year-old Italian girl with recurrent episodes of mania and major depression. (A) Fluid-attenuated inversion recovery images document the extent of cerebral lesions with oral risperidone 0.75 mg twice daily; and (B) their complete normalization 2 weeks after discontinuing this second-generation antipsychotic agent.
urinalysis; urinary toxicology screening; abdominal ultrasound; and cerebrospinal fluid testing. A brain computed tomography scan, performed 4 hours after admission, was unremarkable. Twenty-four hours later, a brain MRI showed many infra- and supratentorial high signal intensities distributed bilaterally in the cortical and subcortical parieto-occipital regions on fluid-attenuated inversion recovery sequences (Fig 1).

The subsequent diagnostic evaluation failed to reveal possible causes of hypertension, including altered thyroid function, mercury poisoning, cardiac diseases with left ventricular hypertrophy (by electrocardiography and echocardiography), renal artery stenosis (by Doppler ultrasonography), or catecholamine-secreting tumors (by both abdominal computed tomography and measurement of urinary catecholamine levels).

Risperidone was discontinued after considering the aforementioned normal results on investigations and the data suggesting that both first- and second-generation antipsychotic agents have occasionally been associated with an increase in blood pressure. Within 5 days, the patient’s blood pressure was 95th percentile (ie, 123/81 mm Hg), and the drug management with nitroprusside and amlodipine was discontinued. A repeat brain MRI, performed 2 weeks after admission, revealed a complete resolution of the abnormalities (Fig 1). One year later, the girl was doing well with family-focused cognitive behavior therapy and no drug medication. Her blood pressure was 108/56 mm Hg.

To objectively establish the causal relationship between risperidone and arterial hypertension with posterior reversible cerebral edema syndrome, we applied the Naranjo Adverse Drug Reaction Probability Scale and the probabilistic causality assessment system proposed by the World Health Organization—Uppsala Monitoring Centre. Their use has been widely advocated in clinical practice and in the literature because of their simple structure and easy reproducibility. Both scales indicated that a relationship between risperidone and arterial hypertension with posterior reversible cerebral edema syndrome was likely.

**DISCUSSION**

Posterior reversible cerebral edema syndrome, first described by Hinchey et al in 1996, is also referred to as posterior reversible encephalopathy syndrome, posterior reversible leukoencephalopathy syndrome, hyperperfusion encephalopathy, and brain capillary leak syndrome. It is a potentially reversible clinicoangiologic entity characterized by insidious onset of headache, confusion, visual disturbances, and seizures associated with brain edema, which predominates in the posterior areas and in the white matter on imaging. Most cases of this condition occur in patients with severe hypertension. Very rarely, these agents paradoxically produce high blood pressure. Most cases of hypertension associated with these agents occur in patients who are overweight or being concurrently treated with selective serotonin reuptake inhibitors. At this stage, the mechanism by which these drugs increase blood pressure in a small minority of patients is still unclear.

**CONCLUSIONS**

Risperidone is an effective medication for children and adolescents with bipolar type I disorders. The current case report supports the notion that second-generation antipsychotic agents may occasionally induce an increase in blood pressure. Given this possibility, we recommend routine monitoring of blood pressure during therapy with these agents.

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