

# PISA SYNDROME INDUCED BY RAPID INCREASE AND HIGH DOSAGE OF RISPERIDONE

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Pisa syndrome (PS) is a rare condition of acute or tardive dystonia characterized by a body involuntary sustained lateral flexion with the head to one side, creating a “leaning tower” posture. The essential symptoms for the diagnosis of PS are the presence of persistent dystonia of the trunk, and lateral flexion with mildly backward axial rotation of the trunk, the absence of other dystonic regions of the body, a history of medication preceding or concurrent with the onset of dystonia, the absence of known reasons for secondary dystonia, and a negative family history for dystonia<sup>1</sup>. The referential items supporting the diagnosis of the syndrome are worsening of the posture abnormality in walking, indifference to posture abnormality without agony (anosognosia), and improvement in the abnormality of the posture by withdrawal of the causal agents<sup>1</sup>. Different from other side effects related to antipsychotic treatment<sup>2</sup>, there are putative risk factors described for PS, including previous prolonged treatment with typical antipsychotics, combined pharmacological treatment, female gender, old age, presence of an

organic brain disorder<sup>3</sup>. Most of PS cases have been described as adverse effects of prolonged exposure to conventional antipsychotics, however more recently, other drugs, including atypical antipsychotics, have been implicated in the pathophysiology of PS<sup>4</sup>.

We describe the case of a patient with no classical risk factors for PS, who developed the disorder induced by rapid increase and high dosage of risperidone.

## CASE

An 18-year-old man was admitted to our inpatient unit because of a severe psychotic exacerbation. Since the diagnosis of DSM-IV hebephrenic schizophrenia, two years ago, he had been treated with risperidone, a maximum of 4 mg/day, presenting a good clinical control. However two months before the admission, the patient discontinued his medication and began to present thought and behavioral disorganization, delusions, auditive hallucinations, agitation, insomnia.

In the beginning of the admission, he was administered risperidone 4 mg/day and diazepam 30 mg/day for one month. As the clinical features were not improving with such medication, the dosage of risperidone was increased until 6 mg/day and diazepam was switched to clonazepam 6 mg/day with the aim to control the episodes of agitation and insomnia. After three weeks with such medication, risperidone was increased to 12 mg/day because of the inadequate control of the psychotic symptoms. One week after risperidone augmentation, an acute dystonic reaction (tonic flexion of trunk and head toward the left along with a slight backward axial rotation) was observed (Figure). Risperidone was immediately discontinued and an adjunctive treatment with biperiden, an anticholinergic drug, was initiated. Biperiden was introduced in a dosage of 6 mg/day by oral administration. In addition, in the period of three days that followed the beginning of PS the patient has received 20 mg of biperiden by intramuscular administration. PS completely disappeared within 3 days after risperidone discontinuation and complementary anticholinergic therapy. After that, risperidone

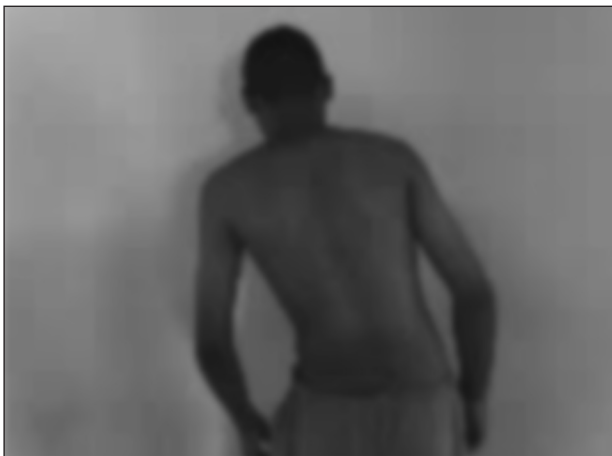


Figure. Patient presenting tonic flexion of trunk and head toward the left along with a slight backward axial rotation.

## SÍNDROME DE PISA INDUZIDA POR AUMENTO RÁPIDO E DOSAGEM ELEVADA DE RISPERIDONA

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was switched to olanzapine, until a dosage of 10 mg/day, with a good antipsychotic response.

On admission, the physical examination revealed non-focal neurological deficits. No evidence of other extrapyramidal symptoms was found. The patient had no personal history of drug abuse, no history of head trauma or other neurological problems, and no family history of dystonia or other movement disorders. Secondary dystonias resulting from metabolic disorder, organic disorder, or infection were ruled out.

## DISCUSSION

A dysfunction of cerebral dopaminergic pathways, which are strategic in the regulation of axial muscle tone, has been related as a possible central factor in PS pathophysiology<sup>5</sup>. Risperidone is a selective monoaminergic antagonist with a high affinity for dopaminergic D<sub>2</sub> receptors. Blockade of D<sub>2</sub> receptors by classical antipsychotics ameliorate the positive symptoms of schizophrenia. However, this blockade is considered responsible for the occurrence of extrapyramidal symptoms. At therapeutic dosages, risperidone's combined serotonin and dopamine antagonism is supposed to be responsible for its effectiveness on positive and possibly negative symptoms of schizophrenia and its lack of extrapyramidal side effects at dosages lower than 6 mg/day. The reported incidence of acute dystonia with risperidone is greater than placebo at high dosages (16 mg/day), however no greater than placebo in dosages lower than 6 mg/day<sup>6</sup>. In clinical populations, risperidone has been associated with dosage-dependent induction of extrapyramidal adverse effects occurring in the upper dosage range (>6 mg/day)<sup>6,7</sup>. Therefore, high dosages of risperidone may be associated with extrapyramidal side effects, such as dystonia<sup>7</sup>. In the present report, such phenomenon may be happened, as the patient has received a high dosage of risperidone (12 mg/day) before the occurrence of acute dystonia.

Rapid increase of a dopaminergic antipsychotic may also be involved in the onset of dystonia<sup>7</sup>. A previous case of dystonia appearance related to rapid increase of risperidone dosage was reported, however with no PS manifestation<sup>8</sup>. Moreover other case reports of PS-induced risperidone have also been described<sup>9</sup>, nevertheless in the

present case the patient had no history of putative risk factors described for PS.

Once the PS begins, the treatment remains empirical, which reflects the poor understanding of its underlying pathophysiology<sup>10</sup>. The first-line treatment for PS has been the reduction in dosage or discontinuation of antipsychotics, while the second-line treatment has been the introduction of an anticholinergic medication, as PS is a side effect caused by the central dopaminergic blockade<sup>9</sup>.

In the follow-up of patients who presented PS with risperidone, the substitution to other atypical antipsychotics that does not present high affinity for dopaminergic D<sub>2</sub> receptors, as olanzapine, may provide an interesting alternative for their treatment, as occurred in the present case report<sup>9</sup>.

In summary, clinicians should be aware of rapid upward titration and high dosage of risperidone because these conditions may precipitate PS even in patients without risk factors for the development of such adverse effect. Once the patient presents PS, the treatment may include the reduction in dosage or discontinuation of the antipsychotic drug, associated to the introduction of an anticholinergic medication, and in the follow-up drugs with low affinity for dopaminergic D<sub>2</sub> receptors must be used.

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