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WEIGHT GAIN INDUCED WITH OLANZAPINE IN ADOLESCENT

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SUMMARY

Children and adolescents are being treated with antipsychotics more often than before, although the risk of adverse events in this age group still remains unclear.

Because of increased use of antipsychotics in children and adolescents, their endocrine and metabolic side-effects (weight gain, obesity, and related metabolic deviations) are of particular worrying, especially within pediatric and adolescent population that appears to be at greater risk comparing with adults for antipsychotic-induced metabolic adverse events.

In this work we will present the course of treatment of an adolescent girl with psychotic symptoms, within the clinical diagnosis of Organic delusional disorder, who had a considerable weight gain after one year of olanzapine treatment.

Key words: *olanzapine - weight gain - adolescence*

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INTRODUCTION

Children and adolescents are being treated more and more with antipsychotics. The risk of side effects and metabolic abnormalities in this age group remains unclear (Overbeek et al. 2010).

Despite increasing use of psychotropic medication in children and adolescents, their endocrine and metabolic side-effects (weight gain, obesity, and related metabolic abnormalities such as hyperglycaemia and dyslipidemia) are of particular concern, especially within this pediatric population that appears to be at greater risk as compared with adults for antipsychotic-induced metabolic side-effects. In addition to medication, many factors contribute to weigh gain in psychiatric patients, including sedentary lifestyle and poor diet. Excessive weight gain has several deleterious effects in psychiatric patients, including stigmatization and further social withdrawal, and non compliance with medication. Furthermore, excessive corpulence may evolve to a metabolic syndrome with a high-risk state for future cardiovascular morbidity and mortality in adult age. Because youths are still developing at the time of psychotropic drug exposure, in a context of physiological changes in hormonal and endocrine levels and body composition, most reference values need to be adjusted for gender, age and growth charts. Hence, sex- and age-adjusted body mass index (BMI) percentiles are crucial to assess weight gain in children and adolescents (Goeb et al. 2010).

Olanzapine is an atypical antipsychotic that belongs to the thienobenzodiazepine class. Olanzapine binds to a large number of neurotransmitter receptors, including the dopamine D_1, D_2, and D_4 receptors, serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_3 receptors, histamine H_1 receptor, muscarinic receptors, α- and β-adrenergic receptors, γ-amino butyrate $(GABA)_{a1}$receptor, and the benzodiazepine binding sites (Bymaster et al. 1996). Olanzapine is associated with weight gain, dyslipidemia, and transaminase elevations in youth. Extrapyramidal symptoms, neuroleptic malignant syndrome, and blood dyscrasias have also been reported, but appear rare (Maloney & Sikich 2010). In addition, olanzapine-associated weight gain has been linked to genetic variations in the 5-HT_{2A}, 5-HT_{2C}, and β_3-adrenergic receptor, leptin, and the G-protein β_3 subunit genes (Templeman et al. 2005, Ujike et al. 2008).

Jerrell et al. (2008) in their research on side effects in children and adolescents treated with antipsychotics conclude that exposure to multiple antipsychotics and serotonin-specific reuptake inhibitors consistently confers a higher risk of developing a range of neurological adverse events in young patients, especially those with preexisting central nervous system, mental retardation, or cardiovascular disorder (Jerell et al. 2008).

The experts disagree in their opinions on particular issues, such as clustering risk factors, importance of particular diagnostic procedures for the early detection and monitoring of metabolic syndrome and the role of antipsychotics in occurrence of metabolic syndrome. There is, however, unique attitude about importance of early detection and treatment of metabolic syndrome as well as necessity of further investigations (Kozumplik et al. 2010).

The use of antipsychotics in treatment of children and adolescents requires good knowledge of psychopathology, psychofarmacotherapy, developmental processes and family relations (Graovac et al. 2010).

In our country olanzapine is registered for adolescents over the age of 18.

CASE REPORT

The adolescent girl that we are presenting comes to first psychiatric examination in summer of 2007, at the age of 15. She was referred from a neuropediatrician who suspected a psychotic state. From her mother we found out that her daughter began to change at the time of some awkward and unfortunate circumstances during neurological treatment she was submitted to (the retirement of her neuropediatrician, small number of available neuropediatricians, a large number of children in need of a neuropediatrician), she could not influence to change. When she became agitated, started to have hallucinations, with incoherent talk and refusal of food, she was hospitalized on Clinic of pediatry, for correction of antiepileptic medications.

Her mother shows us medical documentation of convulsions on the day the girl was born. Regular course of pregnancy was interrupted with premature labour and complications (umbilical cord wrapped around the neck of the baby, she was not breathing and had to be resuscitated), that required two weeks of treatment in intensive care unit. The recommended therapy was phenobarbital, and she was regularly examined by a neuropediatrician. When she was 9, she had to be hospitalized again on the Ward of neropediatry for epileptic seizures (diagnosis: Epilepsy, secondarily generalized seizures). Carbamazepine was introduced in therapy, and the girl had taken it until a few months ago. In the period between 9 and 15 years of age, she did not have crisis of loss of consciousness.

During the first consiliar psychiatric examination, the psychic state of the patient was evaluated as psychotic and low doses of risperidone (1 mg in the evening) and alprazolame (1 mg per day) were prescribed. The patient continued treatment on Clinic of pediatry, along with regular psychiatric controls, during and after hospitalization.

Routine laboratory blood parameters were in the range of referent values.

A range of neurologic tests was performed: EEG - border result; brain CT - mostly regular; brain MR - signs of bilateral demielinization along occipital horns of lateral ventricles (possibly due to ischemia).

Psychological evaluation shows border degree of intellectual capacities (verbal quotient on the lower end of average scores, nonverbal quotient on level of mental retardation).

An antiepileptic drug, oxcarbazepine 900 mg per day, divided in two daily doses, was introduced in therapy. Diagnoses at discharge: Epilepsy (G 40), Organic delusional disorder (F 06.2), Mild mental retardation (F 70).

During the following year, our patient came to regular psychiatric control examinations, accompanied by her mother. Risperidone was titrated to 6 mg per day, enough for satisfactory control of the symptoms. She continued her education, and had relatively good school marks at the end of her second grade. She also had regular neurologic control examinations and took antiepileptic drugs that were prescribed to her. She had no epileptic seizures.

The deterioration of her psychic state occurred in fall of 2008, when she became distant, introvert, seemed to be deep in her thoughts, staring at one point, laughing with herself. She would leave house to go to school, where she would not come. Mother had to watch over her all the time. To our recommendation for hospitalization of the patient, we did not get mother's approval, and she decided to take her daughter for a second opinion, psychiatric evaluation at another psychiatrist, who removed risperidone from therapy, and introduced sulpyride (100 mg), lamotrigine (100 mg), as well as alprazolame (0,75 mg), promazine (100 mg) and diazepam (5 mg).

On the following control, one year after, we come to know that our patient's psychic condition deteriorated, with periods of psychomotor agitation, aggressiveness and irritability, which were interrupted by periods when she was distant, staring at one point, having hallucinations and listening at sounds. At that time her mother agreed to hospital treatment of the girl. The patient was hospitalized at two occasions, in spring (April) and summer (August) of 2009. During hospitalization in April, a correction of medications was conducted; olanzapine 15 mg per day and lamotrigine 150 mg per day, were prescribed. EEG result was regular, as well as were laboratory blood parameters. With prescribed medication, the patient became calmer, and her sleep was also improved. Despite occasional episodes of agitation, according to mother's information, girl's condition was notably better compared to the period before hospital treatment.

8 to 9 months after olanzapine was introduced to therapy, an abrupt weight gain was observed. We measured and found that the patient's weight was 68 kg (BMI=28), which was a weight gain of 16 kg. Laboratory blood parameters at this point were changed, and revealed increased levels of glucose in blood, cholesterol and thyroid-stimulating hormone.

Weight gain was a valid indication for correction of antipsychotic, switching from olanzapine to quetiapine 500 mg.

Since this medication correction, body weight and BMI were monitored.

After two months, body weight was 62 kg (BMI=25,5), and four months after medication correction body weight was 56 kg (BMI=23). Laboratory blood parameters were completely stabilized six month after correction.

One year after our patient regained her "normal weight" - 52 kg (BMI=21,5).

During the change of therapy her psychic condition was not deteriorated, beside periods of somnolence and psychomotor retardation in the first three weeks after medication change. She did not have epileptic seizures.

At this point, the patient's therapy consists of quetiapine with prolonged action, in the dose of 600 mg, with lamotrigine 300 mg and diazepam 15 mg per day. Her psychic condition is now in partial remission, with occasional hallucinatory experiences of pleasant nature.

DISCUSSION

In this clinical case report our aim was to present the course of treatment of a girl adolescent with olanzapine and the occurrence of a side-effect - weight gain.

Psychotic decompensation in the adolescent patient occurred at the time of inadequately controlled neurologic disorder - epilepsy, coincided with the developmental period of middle adolescence. An increased risk for occurrence of psychic symptoms in our patient is due to verified organic base (anoxia at birth, convulsions, epilepsy), decreased intellectual capacities, as well as interrupted antiepileptic therapy.

Comorbidity is an extremely important issue in comprehensive, individual and personalized patient menagement (Jakovljević 2009).

During one year use of olanzapine (15 mg per day) we achieved relatively good control of psychotic symptoms. In first 8 to 9 months of therapy with olanzapine, body weight was not changed significantly, but the following 2 to 3 months showed notable weight gain.

Comparative studies of olanzapine use in adolescents of Kryzhanovskaya et al., revealed significance of a side-effect - weight gain in adolescents treated with olanzapine in comparison to placebo. Average weight gain in adolescents treated with olanzapine was 3,9 kg. Authors emphasize that the increase in body mass index (BMI) is a more appropriate measure of increased size in youth. In examining the time course of weight gain, there appears a marked reduction in the slope of weight gain after 4 weeks of treatment (Kryzhanovskaya et al. 2009).

We find the fact of abrupt weight gain (16 kg) in an adolescent treated with a stabile dose of olanzapine, during the last 2 to 3 months of one-year treatment, rather interesting.

The literature shows contradictory results, for example, similar findings of rapid weight gain followed by slower weight gain have been observed in other trials (Ratzoni et al. 2002, Fleischhaker et al. 2008, Findling et al. 2010).

The researches of Gebhardt et al. show that female gender and younger age when treated were associated with the magnitude of antipsychotic-associated weight gain independent of medication. Further, individuals with low pretreatment BMI initially show more rapid weight gain than their heavier peers even though total weight gain with treatment is less (Gebhardt et al. 2009).

A more gentle body constitution (156 cm, 52 kg) of our patient, as well as the dose of antipsychotic used, according to findings of Gebhardt, can be taken under consideration in finding an explanation for such abrupt weight gain in a short period of time.

Certainly, weight gain with increased BMI and changed laboratory blood parameters in our patient, showed the seriousness of this side-effect and the potential risk of the development of metabolic syndrome. According to psychopharmacotherapy recommendations we monitored these parameters, along with medication correction and observation of psychic condition of the patient.

With the change of antipsychotic, increased laboratory blood parameters gradually stabilized, and body weight was reduced to previous values. In the contrary, the "window for some new disorders would be still open".

CONCLUSION

In everyday clinical practice we rather often encounter adolescents that, beside psychic disorders, have comorbidities. The specificities of "other" disorders instruct us to the need of interdisciplinary approach and cooperation. It is extremely important to know very well all possible side-effects of the medications we prescribe, so we could promptly intervene, according to achievements and professional rules.

Our clinical presentation of the course of treatment of an adolescent girl with psychotic symptoms, who was diagnosed with Organic delusional disorder and Epilepsy, shows that, beside positive effects antipsychotics have on psychotic symptoms, we also have to take care of possible side-effects of medication.

Measurement of body weight and calculation of BMI are very simple and easily applicable methods, as well as laboratory blood parameters, give a very good insight to some side-effects of antipsychotic therapy.

Olanzapine has played a critical role in alerting scientists to the metabolic consequences of most antipsychotics, particularly within children and adolescents. Weight and metabolic changes observed in olanzapine-treated youth stimulated investigations of such effects among youth treated with other antipsychotics and provided a need for further long-term studies of antipsychotic tolerability in youth.

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