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Patophysiology of metabolic syndrome in mentally ill patients treated by antipsychotics

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ABSTRACT

The metabolic syndrome is increasingly named as epidemic of our time. It affects about 20-25% of the world's population and is associated with a twofold increase in the risk of death and a threefold increase in the risk of heart attack and stroke. Numerous scientific studies confirm the more frequent occurrence of the metabolic syndrome among the mentally ill patients than in the general population.

It is related not only to common inflammatory etiology of psychiatric disorders and metabolic syndrome, endocrinopathies accompanying mental illness, unhealthy lifestyle of psychiatric patients or genetic predispositions of this group of patients to the development of metabolic disorders, but also with the use of psychiatric drugs such as antipsychotics or mood stabilizers.

METABOLIC SYNDROME

The metabolic syndrome, also known as the metabolic syndrome X or the insulin resistance syndrome[1], is a set of interrelated risk factors for the development of coronary and cerebrovascular diseases and diabetes. To establish a diagnosis of the metabolic syndrome according to IDF criteria from 2005, it is necessary to meet 3/5 the following conditions:

- abdominal obesity (waist circumference in men in Europe ≥ 94 cm, while in women ≥ 80 cm)
- Triglyceride levels ≥ 150 mg/dl or dyslipidemia treatment
- HDL cholesterol
    - o <40 mg/dl in men
    - o <50 mg/dl in women
    - o or treatment of dyslipidemia
- arterial pressure ≥ 130/85 mm Hg or treatment of hypertension
- fasting glucose ≥ 100 mg/dl or type 2 diabetes mellitus

The metabolic syndrome is increasingly named as the epidemic of our time.[2] It affects about 20-25% of the world's population and is associated with a twofold increase in the risk of death and a threefold increase in the risk of heart attack and stroke (International Diabetes Federation 2006).[3]

METABOLIC SYNDROME IN MENTALLY ILL PATIENTS

The increased incidence of metabolic syndrome among mentally ill patients is confirmed by numerous scientific studies. Among patients with schizophrenia, the risk of developing metabolic syndrome is 5 times higher than in the general population. In 36-50% of patients suffering from depression, the metabolic syndrome is additionally diagnosed. Higher risk of developing metabolic syndrome also affects patients with post-traumatic stress disorder, binge eating disorders (affects 50-60% of patients) or patients with borderline personality (ZM twice as much as in the general population). Elderly people burdened with metabolic syndrome are at higher risk of developing cognitive disorders and Alzheimer's syndrome or vascular dementia.[3]

Increased incidence of metabolic syndrome in mentally ill patients is not only related to common inflammatory etiology of psychiatric disorders and metabolic syndrome, endocrinopathies accompanying mental illness, unhealthy lifestyle of psychiatric patients or

genetic predispositions of this group of patients to the development of metabolic disorders, but also with the use of psychiatric drugs such as antipsychotics or mood stabilizers.[3]

ANTIPSYCHOTICS – METABOLIC HIGHWAY

An important and confirmed risk factor for the development of the metabolic syndrome among mentally ill patients is the use of second generation antipsychotics (SGAs). These drugs cause fewer side effects associated with the extrapyramidal system and allow better control of symptoms from the affective and cognitive spheres compared to the first generation antipsychotics, but they are burdened with a much higher risk of weight gain.[3] Initially, the relationship between weight gain, obesity and SGAs was noticed, but later on the SGAs was associated also with an increased risk of developing dyslipidemia, diabetes, cardiovascular disease and premature death. The "metabolic highway" begins with increased appetite and weight gain and leads to obesity, insulin resistance and dyslipidemia with increased triglyceride levels. In the end, hyperinsulinaemia turns into a failure of pancreatic beta cells, pre-diabetes and diabetes. When it comes to diabetes, the risk of cardiovascular disease increases, as does the risk of premature death.[4]

PATOMECHANISM OF ANTIPSYCHOTICS-RELATED METABOLIC CHANGES

A multifactorial pathomechanism of weight gain in patients using SGAs is postulated.[4] Certainly, a selective antagonism of 5-HT2C, H1 and D2 receptors is essential. Antipsychotics associated with the greatest weight gain have the strongest antagonistic activity at the same time at the H1 and 5HT2C receptors. Antagonism in relation to these receptors leads to stimulation of hypothalamic appetite regulation. Antagonism of 5-HT2C receptors also increases insulin resistance and reduces skeletal muscle glucose consumption. The antihistaminergic effects of antipsychotics contribute to sedation and reduce the rate of metabolism.[3]

Antipsychotic drugs affect also glucose metabolism, although the pathomechanism of changes under their influence is not entirely clear. Probably the etiology of carbohydrate disorders caused by SGAs is multifactorial.[5] Under the influence of olanzapine and clozapine (but not after haloperidol), insulin secretion increases.[6] In the Glucose Tolerance Test, olanzapine and clozapine cause a markedly greater increase in glycaemia compared to classical neuroleptics and risperidone.[7] It has been shown that insulin resistance occurs within the first few days of using olanzapine[6], so obesity would be difficult to account for.

There is one more rare but potentially life-threatening metabolic problem related to use of SGAs - diabetic ketoacidosis with sudden onset or a similar state - hyperglycemic hyperosmolar syndrome. The pathomechanism of these states is probably complex and multifactorial, and is the subject of intense research. It is possible that in some patients with undiagnosed insulin resistance, pre-diabetes or diabetes, on the metabolic pathway compensated for hyperinsulinemia, decompensation occurs after administration of specific antipsychotics due to the pharmacological mechanisms associated with them. Perhaps the reason for this condition in some patients taking olanzapine or clozapine is antagonism of the muscarinic receptor M3 cholinergic receptor. Insulin secretion is known to be partially regulated by the parasympathetic cholinergic neurons innervating the pancreas, which act on post-synaptic M3 receptors located on beta-cells of the pancreas that secrete insulin. The results of preclinical studies suggest that M3 receptor blockers on pancreatic beta cells may reduce the release of insulin. If this occurs in a patient dependent on cholinergic regulation of insulin release, it may be a factor responsible for insulin deficiency and leading to diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome.[4]

Antipsychotics can affect lipid metabolism, contributing to an increased risk of developing metabolic syndrome. The published results, so far indicate a significant effect of olanzapine and clozapine on lipid metabolism (increase in total cholesterol and LDL and triglycerides). Other SGAs: risperidone and quetiapine exert far less influence on lipid metabolism, whereas aripiprazole, ziprazidone and sertindole do not affect the lipid profile.[5,8,9,10]

RECOMMENDATIONS

Patients with mental disorders should be examined for the risk of developing or having a metabolic syndrome both before and after psychiatric treatment. Psychoeducation ought to be implemented in every case. Patients should be encouraged to use a healthy, balanced, low-calorie diet rich in vegetables, to do moderate physical activity for 30-40 minutes a day, 3-4 times a week and to control body weight, blood pressure and lipid profile before starting treatment.[3] In the case of ineffectiveness of such a procedure, the patient should be referred to a diet counseling center and treatment of obesity. In patients at risk for developing metabolic syndrome or already suffering from metabolic syndrome, the use of drugs that increase appetite or cause a rise in blood pressure should be avoided. Such decisions are worth to be taken under consideration at the stage of psychiatric treatment planning, because in the case of development

of metabolic syndrome characteristics in the patient with simultaneous stabilization of the mental state, any changes in treatment may cause worsening the mental state.

CONCLUSIONS

With no doubt, treatment with SGAs increases risk of developing metabolic syndrome and its complications. Pathophysiology of metabolic changes caused by SGAs is only partially known. Although treatment with SGAs is burdened with negative metabolic consequences, some disadvantages of such a treatment can be avoided by proper patient's supervision.

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