Adjuvant Metformin Worsens Psychosis in Schizophrenia: A Case Report

To the Editor: Metformin has been reported to be a useful add-on medication in reversing metabolic complications due to antipsychotic treatment in schizophrenia patients.[1] However, treatment with metformin can reduce the levels of insulin-like growth factor-1 (IGF-1).[2] Since IGF-1 deficiency might be associated with the pathogenesis of schizophrenia,[3,4] it is possible that metformin treatment might result in worsening of psychosis.[5] In this letter, we provide the first report of a patient with schizophrenia whose psychosis worsened after adjuvant treatment with metformin.

Case report. Ms A, a 20-year-old woman with a diagnosis of schizophrenia (*ICD-10*), had experienced onset of symptoms in November 2007. She was treated with risperidone (4 mg/d) and trihexyphenidyl (2 mg/d). She had near total improvement in her symptoms in March 2008 and started attending her college regularly. Over a period of 5 months, she gained 12 kg. She had developed menstrual disturbances, acne, and hirsutism; her serum prolactin level was elevated (141.5 ng/mL); and ultrasonogram revealed polycystic changes in the ovary. In view of these side effects, her risperidone dose was reduced to 3 mg/d in April 2008, and regular physical exercises were advised.

Over the next 1-month period, Ms A maintained clinical improvement but was distressed about her weight gain. Hence, in May 2008, metformin 250 mg/d was added to her treatment. After 2 days, she started experiencing features suggestive of thought broadcast. Metformin treatment was stopped, and her risperidone dose was increased to 3.5 mg/d. Thought broadcast symptoms resolved completely. After 1 week, on repeated request by the patient as well as her family members, metformin was restarted at 250 mg/d and increased to 500 mg/d after a few days, as there was no initial worsening of psychosis. However, after 2 days of treatment with metformin 500 mg, thought broadcast symptoms reemerged, and metformin treatment was stopped. By the next day, these symptoms resolved completely.

Over the 6-month follow-up period (ie, up to December 2008), the patient maintained the clinical improvement with optimal functioning.

To the best of our knowledge, this is the first report of adjuvant metformin worsening psychotic symptoms in schizophrenia. Although one might argue that the worsening of symptoms could be a part of the illness course, the following factors make this explanation unlikely: (1) on both occasions, the symptoms were time-locked to either metformin initiation or dosage increase in metformin; (2) the symptoms disappeared completely after metformin treatment was stopped—importantly, during the second time, even with no increase in antipsychotic dosage; and (3) after metformin treatment was stopped, no further psychotic symptoms were observed over the follow-up period of 6 months.

Metformin can decrease IGF-1 level.[2] Recently, antipsychotic-naive schizophrenia patients were demonstrated to have deficient IGF-1 levels, lower than those of healthy controls.[4] Moreover, in that study, the lower the IGF-1 levels, the more severe were the positive symptoms.[4] Although metformin-induced IGF-1 reduction might have played a role in the worsening of psychotic symptoms in this patient, confirmation of this is needed by concurrent assessment of serum IGF-1 in further studies.

References

1. Wu RR, Zhao JP, Jin H, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA*. 2008;299(2):185–193.
2. Fruehwald-Schultes B, Oltmanns KM, Toschek B, et al. Short-term treatment with metformin decreases serum leptin concentration without affecting body weight and body fat content in normal-weight healthy men. *Metabolism*. 2002;51(4):531–536.
3. Gunnell D, Holly JM. Hypothesis: do insulin-like growth factors underlie associations of birth complications, fetal and pre-adult growth with schizophrenia? *Schizophr Res*. 2004;71(1):191–193.
4. Venkatasubramanian G, Chittiprol S, Neelakantachar N, et al. Insulin and insulin-like growth factor-1 abnormalities in antipsychotic-naive schizophrenia. *Am J Psychiatry*. 2007;164(10):1557–1560.
5. Venkatasubramanian G. Antipsychotic-induced weight gain in patients with schizophrenia. *JAMA*. 2008;299(16):1899–1900.

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