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Folate and vitamin B12 reduce disabling schizophrenia symptoms in some patients

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Adding the dietary supplements folate and vitamin B12 to treatment with antipsychotic medication improved a core symptom component of schizophrenia in a study of more than 100 patients. The study focused on negative symptoms of schizophrenia – which include apathy, social withdrawal, and a lack of emotional expressiveness. While the level of improvement across all participants was modest, results were more significant in individuals carrying specific variants in genes involved with folate metabolism. The report from a team based at Massachusetts General Hospital (MGH) will appear in the journal *JAMA Psychiatry* (formerly *Archives of General Psychiatry*) and has been issued online.

"The symptoms of schizophrenia are complex, and antipsychotic medications provide no relief for some of the most disabling parts of the illness. These include negative symptoms, which can be particularly devastating," says Joshua Roffman, MD, MMSc, of the MGH Department of Psychiatry, corresponding author of the *JAMA Psychiatry* paper. "Our finding that folate plus vitamin B12 supplementation can improve negative symptoms opens a new potential avenue for treatment of schizophrenia. Because treatment effects differed based on which genetic variants were present in each participant, the results also support a personalized medical approach to treating schizophrenia."

An essential nutrient, folate (or folic acid) is required for the synthesis of DNA and neurotransmitters and plays a role in the control of gene expression. Adequate folate intake during pregnancy can reduce the risk of birth defects – in particular neural tube defects – and studies have

suggested that folate deficiency during pregnancy significantly increases the risk of schizophrenia among offspring. Earlier research by members of the MGH-based team associated low blood folate levels with more severe negative symptoms among patients with schizophrenia.

The current study was designed specifically to investigate whether supplementation with folate and B12 – which can magnify the effects of folate – reduced negative symptoms of schizophrenia. A 2011 pilot study found symptom improvement only among patients carrying a variant in a folate-pathway gene called MTHFR that reduced the gene's activity. To get a clearer picture of folate's effect on negative symptoms, the current study enrolled 140 patients with schizophrenia at community mental health centers in Boston, Rochester, N.Y., and Grand Rapids, Mich.

Participants were all taking antipsychotic medications – which have been shown to alleviate positive symptoms, such as hallucinations and delusions, but not negative symptoms – and were randomized to receive daily doses of either folate and vitamin B12 or a placebo for 16 weeks. Every two weeks their medical and psychiatric status was evaluated, using standard symptom assessment tools along with measurements of blood levels of folate and homocysteine, an amino acid that tends to rise when folate levels drop. Nutritional information was compiled to account for differences in dietary intake of the nutrients. Participants' blood samples were analyzed to determine the variants they carried of MTHFR and three other folate-pathway genes previously associated with the severity of negative symptoms of schizophrenia.

Among all 140 participants in the study protocol, those receiving folate and vitamin B12 showed improvement in negative symptoms, but the degree of improvement was not statistically significant compared with the placebo group. But when the analysis accounted for the variants in the genes of interest, intake of the two nutrients did provide significant improvement in negative symptoms, chiefly reflecting the effects of

specific variants in MTHFR and in a gene called FOLH1. Variants in the other two genes studied did not appear to have an effect on treatment outcome.

While a low-functioning variant in FOLH1 had been associated with more severe negative symptoms in previous research, in this study it was the high-functioning FOLH1 variant that predicted a better treatment outcome. Measurement of participants' blood folate levels throughout the study provided an explanation for this unexpected finding. Those with the low-functioning FOLH1 variant started the trial with substantially lower folate levels, suggesting a problem with folate absorption. Although supplementation enabled their blood folate levels to eventually catch up with those of participants with the high-functioning variant, it was probably too late to produce symptom improvement during the 16-week trial period.

"For participants who did show a benefit, it took the full 16 weeks of treatment for that benefit to appear," Roffman explains. "While we don't know why this is the case, changes in gene expression – which take time – are a likely explanation. Folate plays a critical role in DNA methylation, which regulates gene expression, so it's plausible that its effects on negative symptoms act through gene expression changes. Participants with the low-functioning FOLH1 variant might eventually show a benefit of folate supplementation if treated for a longer period of time, but that needs to be investigated in future studies."

He adds that, while the benefits of supplementation for the overall group were modest, the lack of effective treatment for negative symptoms and the safety of folate and vitamin B12 supplementation support the need for larger-scale trials. In addition, the impact of genotype on this study's results suggests the need to investigate the role of folate pathway variants in conditions such as dementia and cardiovascular disease, in which low folate appears to increase risk but supplementation trials have had

inconclusive results.

"We are now conducting a clinical trial of 1-methylfolate, which bypasses some of these folate-pathway enzymes and might have greater efficiency among individuals with low-functioning variants," explains Roffman, an assistant professor of Psychiatry at Harvard Medical School. "Understanding more about the basic neural mechanisms of folate in patients with schizophrenia could help us generate more targeted and effective interventions to reduce and possibly even prevent symptoms."

Provided by Massachusetts General Hospital