

Chronic Immune Stimulation May Link Ischemic Heart Disease With Depression

To the Editor:

Carney et al¹ reported that greater autonomic heart dysfunction, as reflected by decreased heart rate variability, is a plausible mechanism linking depression to increased cardiac mortality in post-myocardial infarction patients. We want to discuss another possible pathomechanism that might contribute to the fact that depression is an independent risk factor for increased mortality and morbidity after myocardial infarction: from several studies, it is evident that atherosclerotic disease is associated with continuous activation of immunological pathways. Among other markers of immune activation and inflammation, elevated concentrations of neopterin, an indicator of Th1-type immune activation, C-reactive protein, or serum amyloid A are found in plasma of patients with acute or chronic coronary syndromes, indicating the inflammatory nature and correlating with the severity of atherosclerotic disease.² Increased formation of interferon- γ during Th1-type immune response is associated with activation of the enzyme indoleamine (2,3)-dioxygenase (IDO) in a variety of cells including monocytes/macrophages.³ IDO converts the essential amino acid tryptophan to kynurenine within the biosynthetic pathway of nicotinamide-adenine dinucleotide. Because tryptophan is a precursor for the biosynthesis of the neurotransmitter 5-hydroxytryptamine (=serotonin), low tryptophan concentration is associated with decreased availability of serotonin, which finally increases the susceptibility for the development of mood disturbances and depression in the patients.^{3,4}

Increased production of neopterin concomitant with activation of IDO resulting in lower serum tryptophan and higher kynurenine concentrations was found in patients with various immunopathological conditions³ and also in patients with hypertrophic and dilated cardiomyopathy, the changes correlating with left

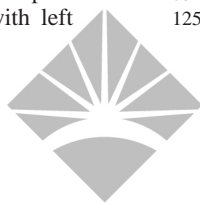
ventricular function tests.⁵ With this background, decreased plasma tryptophan concentrations should parallel the changes of immune activation markers also in atherosclerotic disease; then the development of depression in patients with ischemic heart disease could easily result from chronic immune stimulation and concomitant depletion of tryptophan. We conclude, in patients with ischemic heart disease, a more severe atherosclerotic disease will be associated with a more drastic challenge of the immune system, which is responsible for worse outcome. A higher susceptibility for depression will then result from a parallel depletion of tryptophan and neurotransmitter disturbances.

Christian Murr, MD
Maximilian Ledochowski, MD
Dietmar Fuchs, PhD

Institute for Medical Chemistry and Biochemistry
Department of Clinical Nutrition
University of Innsbruck
Innsbruck, Austria



1. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation*. 2001;104:2024–2028.
2. Schumacher M, Halwachs G, Tatzber F, et al. Increased neopterin in patients with chronic and acute coronary syndromes. *J Am Coll Cardiol*. 1997;30:703–707.
3. Widner B, Laich A, Sperner-Unterweger B, et al. Neopterin production, tryptophan degradation and mental depression: what is the link? *Brain Behav Immun*. In press.
4. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem*. 1994;40:288–295.
5. Rudzite V, Skards JI, Fuchs D, et al. Serum kynurenine and neopterin concentrations in patients with cardiomyopathy. *Immunol Lett*. 1992;32:125–129.



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