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Cardiac Failure Associated With G6PD Deficiency

To the Editor:

Jain et al¹ made the very interesting suggestion that glucose-6-phosphate dehydrogenase (G6PD) deficiency contributes to cardiac dysfunction through increased susceptibility to oxidative injury and impairment of intracellular calcium transport in cardiomyocytes from rats. Additionally, they demonstrated the development of in vivo adverse structural remodeling and contractile dysfunction over time in a murine model of G6PD deficiency. A clinical finding in our hospital appears to corroborate and extend to humans the concepts enunciated by Jain et al.¹

In 2000, a 64-year-old black woman, originating from Curacao, was referred to the Sarcoidosis Management Center, a tertiary referral center for sarcoidosis in the Netherlands. The diagnosis of sarcoidosis, which she had carried for 6 years, was histologically confirmed by a liver biopsy in another hospital. In 1999, she consulted for the first time a pulmonary physician because of dyspnea and severe fatigue. Her complaints of dyspnea were progressive, especially during exercise. She never smoked and had no prior history of respiratory illness or relevant comorbidity. No environmental or occupational pulmonary risk factors were apparent. She had never been treated for her sarcoidosis. Physical examination revealed biventricular enlargement of the heart, an apical systolic murmur consistent with mitral regurgitation, and signs of right- and left-sided congestion with basal lung crepitations, increased central venous pressure, hepatomegaly, and ankle edema. Lung function tests revealed a mild restrictive defect with a moderate reduction of the CO diffusion test (69% of predicted.) A chest radiograph showed cardiomegaly and minimal pleural effusions on both sides without any other abnormalities. An ECG showed sinus rhythm, left atrial and left ventricular hypertrophy, and no signs of previous infarctions. Dipyridamole thallium scintigraphy was negative for ischemia, scar formation, or sarcoid granulomas. Echocardiography revealed a globally dilated left ventricle with a diminished ejection fraction of 31%, consistent with dilated cardiomyopathy, grade 2 to 3 mitral regurgitation, mitral ring dilatation, and signs of increased right ventricular systolic pressure. Laboratory findings including autoantibody screen revealed no abnormalities. Upon further examination, a strongly reduced G6PD activity (1.5 IU/g Hb) was found. To investigate to which genetic defects in the G6PD gene this was attributed, DNA was sequenced. She appeared to have a homozygous G6PD deficiency with a mutation in the G6PD gene.² This was a combination of 202G→A (Met68 to Val) and 376A→G (Asp126 to Asn) called G6PD A, the most common G6PD mutation in the negroid race.

She received bumetanide, digoxin, and captopril. Moreover, salt and fluid restriction were advised. The deficiency in G6PD that may lead to increased vulnerability to oxidative damage and the cardiac failure prompted us to start treatment with carvedilol. In our patient, a marked clinical improvement was noted after institution of drug therapy. In addition, echocardiographically it was observed that the left atrial dimension decreased from 48 to 40 mm, the ventricular end-diastolic dimension decreased from 60 to 53 mm, the left ventricular ejection fraction rose to 50%, and the mitral regurgitation diminished completely.

Besides a selective antagonist effect on α_1 adrenergic receptors, thereby decreasing the total peripheral vascular resistance, and a cardiac nonselective β -adrenergic receptor blocking action, thereby preventing reflex tachycardia, carvedilol has a potent antioxidant action.³⁻⁵ In line with this, Dandona et al⁴ reported that carvedilol inhibits reactive oxygen species (ROS) generation by polymorphonuclear neutrophils and mononuclear cells. They suggested that this reduction in ROS generation probably contributes to the antioxidant

effects and related benefits. However, the results were based on a study in a healthy subject. Flesch et al⁵ demonstrated that hydroxyl radicals (OH) induce severe contractile dysfunction in human myocardium. Carvedilol had beneficial effects on OH free radical-induced contractile dysfunction in human myocardium. These observations could help explain the improvement of ejection fraction in heart failure trials with carvedilol without a restoration of β -adrenergic receptor density.

The antioxidant action of carvedilol might prevent the effects from the G6PD deficiency in combination with sarcoidosis. As suggested by Jain et al,¹ inactivity of G6PD will prevent adequate formation of NADPH and thus hamper maintenance of glutathione (GSH). Sarcoidosis has been suggested to trigger an oxidative stress response as indicated by an increased activation of NF- κ B.⁶ This may lead to a decrease in cytosolic GSH as well.

This case provides clinical support of the observations reported by Jain et al¹ that deficiency of G6PD may contribute to cardiac dysfunction through increased susceptibility to free radical injury and impairment of intracellular calcium transport in humans. Therefore, we recommend to consider an effective antioxidant treatment in cases of cardiac failure in which an oxidative stress response (in our case sarcoidosis) in combination with a G6PD deficiency occurs. Moreover, the study by Jain et al¹ and our observation may guide interesting and relevant clinical studies in the near future aiming to explore the knowledge and clinical relevance of the relation of oxidative stress and cardiac dysfunction.

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