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LETTER

Folate Deficiency in Chronic Pancreatitis

Gopalakrishna Rajesh[1], Banavara Narasimhamurthy Girish[2], Kannan Vaidyanathan[3], Menon Saumya[1], Vallath Balakrishnan[1]

Departments of [1]Gastroenterology, [2]Physiology and [3]Biochemistry, Amrita Institute of Medical Sciences. Cochin, Kerala, India

Dear Sir,

While there has been a spurt of interest in genetic alterations associated with pancreatitis in the past few years, interest in the role of environmental factors has largely focused on alcoholism and smoking with insufficient attention being paid to the contributions of nutritional deficiency, and the role of environmental toxins in the pathogenesis of pancreatitis. Braganza and Dormandy [1] argue convincingly about the role played by cytochrome P450 monooxygenases (especially CYP1A) enzyme induction by xenobiotics and the resultant oxidative stress, as also the now increasingly recognized reductive stress posed by the metabolites in initiating pancreatic injury. Their article underlines the important part played by the deficiency of methyl and thiol molecules in different stages of the progression of pancreatic damage. Furthermore, they attempt to establish a link between environmental and genetic factors and bring in a holistic view on the etiopathogenesis of chronic pancreatitis.

We have recently demonstrated lower plasma methionine levels in two cohorts of chronic pancreatitis patients; one of tropical chronic pancreatitis and the other, of alcoholic chronic pancreatitis as compared to healthy controls [2] which suggests that deficiency of methyl groups may be a factor in various forms of pancreatitis. Similarly, we have shown lower red cell glutathione levels in chronic pancreatitis patients with tropical chronic pancreatitis and alcoholic chronic pancreatitis, indicating deficiency of thiol molecules. In addition, we have demonstrated significantly higher levels of plasma total homocysteine in chronic pancreatitis patients than in healthy controls. Moreover, our study has shown that there is a deficiency of red cell folate in the majority of chronic pancreatitis patients, more so in tropical chronic pancreatitis; and that folate deficiency appeared to be the key factor in hyperhomocysteinemia in chronic pancreatitis patients. Whether the high plasma homocysteine levels have any pathogenetic implications through possible vascular damage in the pancreas, or merely serve as a marker of the disease, is yet to be elucidated.

Braganza and Dormandy have made a case for nutrient supplementation in the prevention of pancreatitis in a susceptible population [1]. We feel there is emerging evidence for long-term studies on folate supplementation in chronic pancreatitis. Apart from the liver, the pancreas is the other organ in the body which has the maximum folate content. Furthermore, folate plays a crucial role in the integrity and normal physiology of the pancreas [3], which becomes altered in folate deficiency [4]. Folate plays an important role in one carbon transfer involving remethylation of homocysteine to methionine, which is a precursor of S-adenosylmethionine, a ubiquitous methyl donor. In fact, we have demonstrated that those patients who had low levels of methionine in chronic pancreatitis also had low levels of red cell folate [2]. There is epidemiological evidence linking folate deficiency to the development of pancreatic cancer [5]. Aberrant DNA methylation could be a leading mechanism for development of carcinogenesis in chronic pancreatitis, an area which needs closer scrutiny, as the effects of folate on DNA methylation seem to be complex [6].

Braganza and Dormandy have described how deficiency of methyl and thiol groups could affect cystic fibrosis transmembrane conductance regulator (*CFTR*) gene expression [1], which, apart from its effect on water and bicarbonate secretion and flushing out of the nascent pancreatic secretion into the pancreatic ductules, also interferes with apical exocytosis in the acinar cell. The latter leads to

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Correspondence Vallath Balakrishnan
Department of Gastroenterology, Amrita Institute of Medical Sciences, AIMS Ponekkara P.O., Cochin - 682 041, Kerala, India
Phone: +91-484.400.1225; Fax: +91-484.280.2020
E-mail: vbalakrishnan@aims.amrita.edu

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intracellular accumulation of activated trypsin resulting in cell damage in a cascading scheme. Abnormalities of the *CFTR* gene have been described earlier in alcoholic chronic pancreatitis and idiopathic chronic pancreatitis [7, 8] and more recently in tropical chronic pancreatitis [9, 10]. It may be worthwhile to study *CFTR* mutations in pancreatitis patients with folate deficiencies. Recently reported effects of steroids on *CFTR* mislocalisation in autoimmune pancreatitis and the possibility of *CFTR* mislocalisation in other forms of pancreatitis are valuable additions to the attempt to find a unifying mechanism [11].

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