Metalloproteinase Polymorphisms and Bicuspid Aortic Valves

To the Editor,

We have read with great interest and admiration the work of Dr Pastora Gallego on vascular disease of the arterial wall in congenital cardiopathies, recently published in the supplement that the journal dedicated to congenital cardiopathies in adults.[1] Of special interest was the paragraph dedicated to the bicuspid aortic valve (BAV), which has great relevance due to both its prevalence (between 0.5% and 2% of the population, as mentioned in the article) and its clinical implications. However, this remains a poorly understood disease with regard to its pathogenic mechanisms and genetic basis.

As mentioned by other authors, BAV patients also represents a heterogeneous population with a wide spectrum of symptoms.[2] As Dr Gallego mentioned with regards to pathogeny, Fedak et al[3] observed a reduction in fibrillin 1 content in the vascular walls of BAV patients. This led to increased production of matrix metalloproteases (MMP) capable of fragmenting and weakening extracellular matrices, which finally leads to degeneration and dilation of the aortic wall.[3] The analysis of MMP gene expression in BAV patients has also been studied with no definitive results; on the other hand, a study was recently published correlating the plasma concentrations of matrix metaloprotease-2 (MMP-2) with proximal dilation of the aorta in BAV patients.[4,5]

In connection with the genetic basis of BAV and the increased expression of MMP in the aortic wall of these patients, our group is currently analyzing

the frequencies of various polymorphisms in the promoter region of the MMP-1 related to protein concentrations in BAV patients and a control group of patients with tricuspid aortic valves (TAV). To date, we have analyzed 72 patients with BAV and 63 controls with TAV diagnosed by echocardiogram. We have analyzed -1607 1G/2G, -519 A/G and -340 T/C polymorphisms using polymerase chain reactions (PCR)-restriction fragment length polymorphisms and then compared these with allelic, genotypic, and haplotypic frequencies using statistical tests. The BAV group was 79% males, with a mean age of 50 (15) years in our results. Over half had significant aortic regurgitation; valvular stenosis was the main condition in the rest of the patients. Aneurysm of the ascending aorta (AAA) was also found in 47% of cases, and a previous family history was implicated in 12.5%, which supports the hypothesis of familial grouping. To date, we have found no significant differences in frequency between test cases and controls in any of the polymorphisms under study, nor have we found any differences in the BAV group between those with stenosis, regurgitation, and AAA.

At this point, these preliminary data indicate that the increase in MMP activity in the aortic wall of these patients is not secondary to the polymorphisms that we have analyzed. Our study continues, and we hope that in the future, with the analysis of other candidate genes, we can contribute to improving the understanding of this common and heterogeneous disease, of major interest to the general practitioner and the researcher, not just because of its severe complications, but also due to the significant lack of knowledge as to its pathogenic mechanisms.

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