

Editorials

Association between angiotensin II receptor gene polymorphism and serum angiotensin converting enzyme (SACE) activity in patients with sarcoidosis

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It is now 23 years since Lieberman first reported that serum angiotensin converting enzyme (SACE) levels were raised in patients with sarcoidosis.¹ He concluded that raised SACE levels appeared to be associated with the active disease process and not a familial inherited enzyme abnormality. The paper by Takemoto and colleagues in this issue of *Thorax*² provides new evidence that the sarcoid granuloma load in patients is not the only factor to account for circulating SACE levels in sarcoidosis and that polymorphisms in both the ACE and angiotensin II receptor genes may also play a part.

Angiotensin converting enzyme (ACE), a zinc metalloproteinase, catalyses the hydrolysis of carboxyterminal dipeptides, particularly the largely inactive peptide angiotensin-1 to the active angiotensin-2. This enzyme has been hypothesised to be a marker of disease activity in sarcoidosis. It is thought that ACE is produced by epithelioid cells³ and other components of the sarcoid granuloma and is likely to be important both in mediating and modulating inflammation.⁴ Circulating SACE probably originates from proteolytic cleavage of the hydrophobic anchor, thus allowing passive leakage of the membrane bound enzyme. Measurement of SACE has been found to be a useful adjunct in both the diagnosis and longitudinal evaluation of patients with sarcoidosis.⁵⁻⁶ It has been postulated that SACE levels can reflect whole body granuloma mass, a hypothesis supported by recent work in an animal model of granulomatous inflammation.⁷ However, raised SACE levels are found in no more than 60% of patients with sarcoidosis,⁸ and SACE concentrations are also influenced by other granulomatous diseases such as miliary tuberculosis and silicosis.⁹ Additionally, familial clustering of normal and raised SACE levels has been reported in large samples of healthy families,¹⁰⁻¹¹ suggesting the possibility of genetic control of SACE levels.

It has recently been shown that polymorphism exists both at the ACE gene locus¹² and in the angiotensin II type 1 receptor.¹³ It has not been determined how these polymorphisms influence the SACE level, although there is some suggestion that the ACE gene insertion/deletion (I/D) polymorphism may be in linkage disequilibrium with regulatory elements of the ACE gene.¹² Although the nature of the ACE molecule itself does not differ due to genotype, ACE polymorphism accounts for nearly half of the total phenotypic variance of SACE concentrations in healthy adults.¹² Genetic analysis of polymorphisms in genes of the renin-angiotensin system has been extensively conducted in patient populations with cardiovascular diseases,¹⁴⁻¹⁶ showing a significant difference in ACE and ACE receptor genotype and allele frequencies between affected and non-affected groups. These results implicate

ACE gene polymorphisms in the causation of a number of disease states.

Polymorphism in the ACE gene has now been studied in differing sarcoidosis populations.¹⁷⁻¹⁹ There appears to be no link between the genotype distribution of the ACE gene and sarcoidosis. SACE values in both patients with sarcoidosis and healthy control subjects are, however, loosely influenced by the ACE genotype, values in a group of Japanese patients reaching significance with the DD genotype associated with the highest mean value of SACE.¹⁹ The results of the present study by Takemoto and co-workers lend support to these findings,² but also provide new evidence that angiotensin II receptor gene polymorphism manifests an additional predisposition to high SACE activity in sarcoidosis. Interestingly, when the combined results of ACE and angiotensin II receptor gene polymorphisms were analysed it appeared that, rather than a synergistic effect on SACE values, an inverse effect was found. This is contrary to the findings in patients at risk of myocardial infarction as described by Tiret *et al.*²⁰

With these recently discovered polymorphisms it is now likely that concomitant determination of these genotypes with measurement of SACE concentration will improve discrimination between normal and abnormal SACE values. By determining the genotype of patients with sarcoidosis, it should be possible to reduce the size of the reference range to which a given measurement of the SACE level can be compared, thus allowing more clinically relevant conclusions to be drawn about the significance of SACE levels in individual patients. It may also be possible that further polymorphisms in the ACE gene complex exist, and these need to be identified and characterised to enhance our understanding of this complex disease process.

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