Elevation of serum angiotensin converting enzyme (S-ACE) activity is associated with active sarcoidosis [1], and with a number of pulmonary and extra-pulmonary diseases, such as pneumoconiosis [2], Gaucher’s disease [3], diabetes mellitus [4], liver cirrhosis [5] and leprosy [6]. In sarcoidosis in particular, serial S-ACE determinations are helpful in the diagnosis and assessment of disease activity [7], so that S-ACE assay is currently required on the diagnostic procedures of interstitial lung disease (ILD). However, in sarcoidosis and in other known causes of S-ACE elevation, S-ACE activity rarely exceeds the values found in normal relatives severalfold. HyperACEemia seemed to be inherited as an autosomal dominant trait. Immunogenetic studies were performed, but we did not find a genetic marker for this condition. The S-ACE activity was inhibited in vitro by edetic acid (EDTA) and SQ 14,225 (captopril). The S-ACE activity was also determined after 1:8 dilution and dialysis against saline of sera. From these experiments we deduced that Lieberman’s intrinsic ACE inhibitor was lacking in the hyperACEemic sera. In the presence of remarkable increase, a congenital elevation of S-ACE should be considered and it would be useful to perform a familial investigation.

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Keywords: Alpha-1-antitrypsin typing; Gm, Km immunoglobulin allotypes; HLA particular histocompatibility locus antigen (HLA) supratypes. Moreover, the presence of immune suppression gene(s) closely linked to the HLA-D subregion [13] has recently been postulated. For these reasons it seemed interesting to investigate the epistatic interaction of major histocompatibility complex (MHC) genes in the control of serum levels of ACE.

Furthermore, a correlation has recently been found between congenital elevation of S-ACE levels and a rare variant (Z) of alpha-1-antitrypsin [9]. Genes coding for alpha-1-antitrypsin allotypes have been mapped on the lowest end of chromosome 14, close to the immunoglobulin heavy chain gene cluster. It would not be a coincidence if an unusual Gm haplotype occurred in the relatives with hyperACEemia. For this reason we extended our genetic study of this rare condition to the characterization of the Gm polymorphism and the alpha-1-antitrypsin phenotype of the whole family under study.

It has previously been reported that human serum may contain an intrinsic ACE inhibitor [14]. The presence of the inhibitor is particularly frequent in sera with elevated ACE levels and its effect can be eliminated by serum dilution [15]. For this reason, a study of intrinsic S-ACE inhibitor is included in this report.
Subjects and methods

\textbf{S-ACE determination}

S-ACE activity was determined by colorimetric assay (ACE Color, Fujirebio Inc., Japan), using the substrate p-hydroxyhippuryl-1-histidyl-1-leucine [16]. Since it has previously been described that elevated S-ACE levels obtained with one method are not necessarily confirmed when other methods are used [17], the colorimetric S-ACE values were checked by radiometric assay (substrate p-[3H]-benzoylglycylglycylglycine) [18].

\textbf{Proband history}

The proband, a 61 yr old female, was first admitted to our department in October, 1986. Since 1984 she had complained of cough and exertional dyspnoea, with progressive worsening of symptoms. The clinical characteristics of the proband are summarized in Table 1. Scalene lymph node and liver biopsies were negative and the patient resolutely refused other biopsy procedures. The S-ACE activity was extremely high (103.95 U·ml\(^{-1}\)), pathological increases over 45 U·ml\(^{-1}\) being rare in our laboratory (normal values: mean±sd 15.53±5.03).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
Initials & Sex & Age yrs & Chest X-ray pattern & Other clinical signs & Respiratory function tests & Ga\(^{75}\)-scan BAL findings & S-ACE value U·ml\(^{-1}\) \\
\hline
R.P. & \female & 61 & ILD (reticulo-nodular pattern) with hilar lymph node enlargement & Liver steatosis (hepatic biopsy) & FVC 60* positive & 150x10\(^{6}\)-ml\(^{-1}\) & 103.95 \\
\hline
&  &  &  &  & TLC 56 & MØ 80* & \\
&  &  &  &  & FEV\(_1\) 48 & Ly 18 & \\
&  &  &  &  & DLco 45 & Neu 2 & \\
&  &  &  &  & PaO\(_2\) 10.2** &  & \\
&  &  &  &  & PaCO\(_2\) 5.4** &  & \\
\hline
\end{tabular}
\caption{Clinical characteristics of the proband}
\end{table}

*: % predicted; \(^{1}\): total count·ml\(^{-1}\) recovered fluid; \(^{2}\): differential count (%); \(^{3}\): kPa; MØ: macrophages; Ly: lymphocytes; Neu: neutrophils; BAL: bronchoalveolar lavage; S-ACE: serum angiotensin converting enzyme; ILD: interstitial lung disease; FVC: forced vital capacity; TLC: total lung capacity; FEV\(_1\): forced expiratory volume in one second; DLco: single breath diffusing capacity for carbon monoxide; PaO\(_2\) and PaCO\(_2\): arterial oxygen and carbon dioxide tension, respectively.

The patient was suspected of having sarcoidosis and started receiving prednisone 40 mg daily, orally, in November, 1986. The prednisone was continued until August, 1987, with progressive dose tapering. At the moment of prednisone withdrawal, the chest X-ray was unchanged and the respiratory function tests only slightly improved. Surprisingly, S-ACE activity did not decrease during the prednisone administration. The behaviour of S-ACE in the proband aroused the suspicion of a lack of connection with the ILD and/or the hepatic disease and, therefore, we decided to study the other members of the family.

Family history

The genealogical tree is shown in Figure 1. The proband family consists of four siblings (four brothers, none of whom had offspring), three offspring (2 sons and 1 daughter) and one grand-daughter (daughter of a son). The four brothers were not affected by known causes of S-ACE elevation: their blood pressure was normal, except for R.S. who showed a mild hypertension. The daughter of the proband (D.C.) was healthy. A son (D.G.P.) was affected by chronic aggressive hepatitis and it was subsequently found that he was a human immunodeficiency virus (HIV)-infected drug addict: therefore, he was no longer studied. D.G.L., the second son, was affected by diabetes mellitus; his daughter (D.F.) was healthy.

Genetic studies

Alpha\(_1\)-antitrypsin phenotyping (Pi-typing) was determined by isoelectric focusing of sera [19]. HLA class I and II polymorphisms were identified by a standard microlymphocytotoxicity test on T and B enriched lymphocyte suspensions from peripheral blood samples [20]. Specificities were assigned according to the 10th International Histocompatibility Workshop definitions [21]. Complement typing was performed: six subjects were analysed for Bf, C4A and C4B polymorphisms; one individual was only defined for Bf. Bf alleles were determined by immunofixation electrophoresis using the standard method proposed by Alper et al. [22]. C4 allotypes were defined by immunofixation electrophoresis of neuraminidase treated serum samples according to the method of Awdesh and Alper [23]. Gm and Km typing was performed: all subjects were typed for G1m (1, 2, 3, 17), G2m (23), G3m (5, 10, 11, 13, 14, 21, 28) and Km (1) allotypes, respectively located on IgG1, IgG2, IgG3 subclasses and on K light chain. The standard haemagglutination inhibition assay was used with reagents described elsewhere [24].
Identification of hyperACEmic family

The S-ACE values in the subjects studied are shown in figure 1. Elevated S-ACE levels were found in two brothers and in two sons. Interestingly, there was no difference between S-ACE values in the two healthy subjects (R.L. and R.S.: mean±sd 95.8±30.68 U·mL⁻¹) and those obtained in the three subjects with known causes of S-ACE elevation [4, 5] (R.P., D.G.P. and D.G.L.: 112.55±23.89 U·mL⁻¹; p=0.05).

The relationship between colorimetric and radiometric assays in determining S-ACE values in subjects studied is shown in figure 2. A very good correlation was found (r=0.98; p<0.001).

In vitro S-ACE studies

Extrinsic inhibition. To demonstrate the specificity of the determination, the S-ACE assay was performed in the presence of the ACE inhibitors: EDTA 0.05 mM [25] and SQ 14,225 0.05 mM (captopril, Squibb & Sons; a kind gift of Prof. R. Fogari) [26].

Intrinsic S-ACE inhibition. To eliminate the influence of intrinsic S-ACE inhibitor, S-ACE activity was determined after 1:8 dilution of sera with saline, according to LIEBERMAN and SASTRE [14]. It has been suggested elsewhere that sera with high ACE activity might show S-ACE increase after dilution because of linearity of the assay [15]. In order to discriminate the S-ACE increase due to linearity of the assay from that due to the elimination of the intrinsic inhibitor, the S-ACE activity was checked after overnight dialysis against a large amount of saline at 4°C, followed by 1:8 dilution [14].

Statistical analysis

When necessary, data were analysed by two-tailed Student's t-test or linear regression analysis. Linkage analysis between affected status (hyperACEemia) and HLA supratypes was performed according LATRHOPE and LALOUEL [27] linkage programme, version 3.5. A set of Lod scores have been calculated for various recombination fractions (θ = 0.0, 0.1, 0.2, ...0.5) between HLA and the supposed susceptibility gene. A Lod score of +3.00 is considered as significant evidence in favour of linkage and a score of -2.00 is generally taken as evidence against linkage.

Results

Identification of hyperACEmic family

The S-ACE values in the subjects studied are shown in figure 1. Elevated S-ACE levels were found in two brothers and in two sons. Interestingly, there was no difference between S-ACE values in the two healthy sons; open squares: subjects with normal S-ACE levels. S-ACE: serum angiotensin converting-enzyme.

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Familial HIGH S-ACE ACTIVITY

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Genetic studies

Analysis of the biochemical and clinical data obtained in the family under study demonstrates that hyperACEemia appears to be inherited as an autosomal dominant trait.

The pedigree of the family under study is drawn in figure 3. The HLA haplotypes could be unambiguously assigned to the grandfather or grandmother of the hyperACEmic condition in this family. The hyperACEemia seems rather unlinked to a specific supertype, although they could not be assigned to the grandfather or grandmother of their relatives.

The Km system is also uninformative as we can find two Km (I) positive brothers (R.G. and R.P.) with different haplotypia combinations associated with the hyperACEmic condition in this family. The hyperACEemia seems rather unlinked to a specific supertype, although they could not be assigned to the grandfather or grandmother of their relatives.

The Gm system is less informative than HLA mainly because it was not possible to assign the parental haplotypes. In fact, only the two most common Caucasian haplotypes Gm (3; 10; 11, 13, 14) and Gm (3; 5, 10, 11, 13, 14) were present in the propositi and their relatives.

Finally, all tested subjects showed Pi-MM phenotype.
The effect of extrinsic ACE inhibitors is shown in Table 2. The addition of EDTA 0.05 mM and SQ 14,225 0.05 mM fully abolished S-ACE activity in all tested sera.

Data concerning studies of intrinsic S-ACE inhibitor are reported in Table 2. The 1:8 dilution of sera resulted in an increase of S-ACE values in 3 out of 4 tested sera (mean % increase 18.71), whilst the 1:8 dilution in 4 subjects of the family with normal S-ACE levels did not show this increase. This result is consistent with the observation of Lieberman and Sastre [14] who found the S-ACE increase particularly frequent in sera with high basal S-ACE activity. This should suggest the presence of a potent intrinsic ACE inhibitor in sera from hyperACEmic subjects, eliminated by 1:8 dilution. The samples were then dialysed and undiluted: an increase in S-ACE activity that paralleled the S-ACE increase obtained in pre-dialysis samples (mean % increase 19.80) was observed. According to Lieberman et al. [15] any increase with dilution after dialysis should reflect linearity of the assay rather than the presence of the inhibitor.

**Discussion**

To our knowledge, this is the second hyperACEmic family so far reported, the first having been described in Japan in 1985 and represented by a woman, a sister and two sons of the sister [10].

In the family described here, 2 out of 5 members are in good health and without known causes of S-ACE elevation. By contrast, 3 out of 5 members were affected by diseases in which S-ACE may be elevated: ILD, chronic hepatitis and diabetes mellitus. Nevertheless, the similarity of S-ACE levels between healthy and affected members, as well as the marked S-ACE increases that exceed severalfold the S-ACE values usually found in those conditions, strongly suggest that S-ACE values in the three affected members are independent of the diseases.

**Table 2. In vitro studies of extrinsic and intrinsic S-ACE inhibition**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Basal</th>
<th>+EDTA</th>
<th>+SQ 14,225</th>
<th>1:8 dilution</th>
<th>After dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.P.</td>
<td>103.95</td>
<td>ND</td>
<td>1.57</td>
<td>105.80</td>
<td>89.07</td>
</tr>
<tr>
<td>R.L.</td>
<td>117.51</td>
<td>ND</td>
<td>2.03</td>
<td>130.72</td>
<td>110.60</td>
</tr>
<tr>
<td>R.S.</td>
<td>74.11</td>
<td>ND</td>
<td>0.86</td>
<td>101.50</td>
<td>57.22</td>
</tr>
<tr>
<td>D.G.L.</td>
<td>139.56</td>
<td>ND</td>
<td>0.35</td>
<td>172.20</td>
<td>111.91</td>
</tr>
<tr>
<td>D.F.</td>
<td>17.85</td>
<td>ND</td>
<td></td>
<td>16.60</td>
<td>-</td>
</tr>
<tr>
<td>R.G.</td>
<td>13.56</td>
<td>ND</td>
<td></td>
<td>9.80</td>
<td>-</td>
</tr>
<tr>
<td>D.C.</td>
<td>15.22</td>
<td>-</td>
<td></td>
<td>10.50</td>
<td>-</td>
</tr>
<tr>
<td>R.T.</td>
<td>19.07</td>
<td>-</td>
<td></td>
<td>18.90</td>
<td>-</td>
</tr>
</tbody>
</table>

**S-ACE inhibitor studies**

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Assay errors were excluded by checking S-ACE activity with radiometric assay (Fig. 2) and the specificity of the determination was supported by extrinsic inhibitory profile (Table 2).

We did not find any relationship between hyperACEmia and MHC genetic markers or immunoglobulin Gm and Km allotypes. On the contrary, there is evidence that this anomalous condition is unlinked with HLA region and uninformative for Gm and Km Ig variants. No singular HLA supertype or Gm haplotype seems to segregate in the proposed or in their relatives. Unfortunately, we did not type the grandparents and, as a consequence, we were unable to assign to each parent their own haplotypes. In addition, hyperACEmia is not related to the presence of alpha_1-antitrypsin variants.

The results of 1:8 dilution of sera (Table 2) are intriguing, but interpretation is not easy. Lieberman et al. [14, 15] first reported an increase of S-ACE activity in
25.4% of 280 sera tested after 1:8 dilution of samples. This increase was particularly frequent (47%) in sera with higher S-ACE values (>35 U·ml⁻¹, spectrophotometric assay). The method of Lieberman [1] requires a 1:1 ratio of serum:substrate solution.

According to Lieberman and Sastre [14] when sera with a significant elevation after 1:8 dilution by the spectrophotometric assay are investigated by the colorimetric assay (that requires a 1:6 ratio of serum:substrate solution), the further 1:8 dilution resulted in minimal increase of S-ACE activity (1%). We deduce that the increase that was found in 3 out of 4 hyperACEemic sera is noteworthy, particularly considering that an overall 1:14 dilution was performed.

Lieberman and Sastre [14] ascribed the post-dilutional increase to a circulating ACE inhibitor, eliminated by 1:8 dilution. The nature and role of the inhibitor are uncertain, but it seems to possess a molecular weight (MW) over 50 kDa and to be labile at 60°C. A peculiar feature of Lieberman's inhibitor is the irreversible inhibition after dialysis [14]; the further 1:8 dilution of the sample does not produce any increase in S-ACE activity, if the pre-dialysis increase was really due to the inhibitor's effect. The authors' explanation of this phenomenon is a continued irreversible inhibition, rather than a loss of an inhibitor by dialysis [14]. In our samples (table 2), the undiluted and 1:8 diluted post-dialysis S-ACE values are notably lower than pre-dialysis values, but the post-dialysis 1:8 dilution percentage increase was unchanged when compared with pre-dialysis increase. Thus, saline dialysis seems to be helpful in discriminating the presence of the inhibitor from the S-ACE increase due to linearity of the assay, that is not affected by dialysis.

According to Lieberman et al. [15] it is, therefore, likely that in hyperACEemic sera an intrinsic inhibitor is lacking, the after dilution increase of S-ACE activity being better ascribed to linearity of the assay; that is understandable in view of the extremely high S-ACE values. Alternatively, it is possible to hypothesize the presence of an inhibitor other than that described by Lieberman and colleagues, not affected by dialysis. There is growing interest in intrinsic S-ACE inhibitors [28, 29] and the characterization of such agents will soon provide the complete profile of circulating and tissue ACE inhibitors. Another question concerns the source of S-ACE. It is known that in normal conditions S-ACE is mainly supplied by endothelial cells [30] whilst in granulomatous disorders the S-ACE increase is due to monocyte/macrophage hyperfunction [31, 32]. In non-granulomatous disorders it is likely that pathological increase of S-ACE could be due to endothelial cells [9], although direct evidence is so far lacking.

An interesting finding coming from hyperACEemic subjects is the resistance of hyperACEemia to a high dose corticosteroid regimen, whilst the S-ACE decrease occurring in treated sarcoidosis patients is related to suppression of inflammatory process [33]. It is likely that molecular biological techniques [34, 35] will soon provide information about site and regulation of S-ACE production in normal and pathological conditions.

In conclusion, this report would suggest that in the presence of a markedly increased S-ACE activity (severalfold exceeding the normal values), even in patients with known causes of S-ACE increase, a possible familial elevation must be considered.

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24. Martinetti M, Tafi A, Dugoujon JM, Mazzacane D, Blanc M, Cuccia J.M, Dugoujon J.M. - Possibility of interaction between HLA Ig and Ig light chain markers in susceptibility to uveitis. Disease Markers, 1988, 6, 257-262.


RESUMÉ: Une agglomération de hauts niveaux d’enzyme de conversion de l’angiotensine sérique (S-ACE) a été mise en évidence dans une famille italienne. Cette élévation concernait une femme, deux de ses quatre frères, et deux de ses trois descendants. Deux d’entre eux (les deux frères) étaient complètement normaux et ne portaient aucune des causes connues d’elevation du taux de S-ACE. Les valeurs de S-ACE (mesure colorimétrique) chez les 5 sujets en question (k=0.105.85±24.60) dépassaient plusieurs fois les valeurs trouvées chez leurs familiers normaux (16.45±2.49). Cette élévation du taux d’angiotensine semble être héréditaire, sous forme d’un trait dominant autosomique. Des études immuno-génétiques (HLA, classes I, II et III, et le tytype Gm, Km) ont été réalisées, mais l’augmentation du taux d’angiotensine n’est pas due à un phénotype particulier HLA, ni à un phénotype d’immunoglobuline. L’activité S-ACE était inhibée en vitro par l’EDTA 0.05 mM et par SQ 14.225 (Captopril) 0.05 mM. L’activité S-ACE a également été déterminée après dilution des seras à 1:8, afin de déterminer l’inhibiteur intrinsèque d’ACE, qui est éliminé par la dilution de l’échantillon; dans 3 de ces 4 seras, cette procédure a montré une augmentation marquable des valeurs de S-ACE (augmentation x: 18.71%), suggérant la présence de l’inhibiteur. Afin de distinguer entre celle-ci et l’absence de linéarité de l’essai, qui peut se produire dans des seras à activité élevée en S-ACE, nous avons dialysé pendant une nuit les seras contre de la solution saline. Nous avons trouvé, malgré la dilution, une augmentation significative des valeurs de S-ACE dans les mêmes seras hyperACE dilués au 1:8 (19.80%), et nous en avons déduit que l’inhibiteur intrinsèque de l’ACE faisait défaut dans les seras hyperACEmiques. Nous suggérons qu’en présence d’une augmentation marquable de S-ACE, une élévation congénitale de S-ACE devrait être prise en considération, et qu’une investigation familiale mériterait d’être réalisée. Eur Respir J., 1990, 3, 441-446.