Serum Angiotensin-Converting Enzyme in Healthy and Sarcoidotic Children: Comparison with the Reference Interval for Adults

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Angiotensin-converting enzyme (ACE) was measured in serum of 187 healthy children between the ages six months and 18 years. Results were pooled for five-year age intervals and compared with the reference values for adults that we previously determined [Clin Chem 1986;32:884–6]. Results for each age group were also studied as a function of sex. Children had higher ACE activities in serum than did adults (P <0.001), but these activities were age-related only from age four to 18 years. Adolescents showed sex-related differences, with higher serum ACE activities in boys than in girls (P <0.05). Both sex- and age-related differences may be related to a steroid hormonal regulation of ACE biosynthesis. We also verified that children with sarcoidosis (n = 20) had significantly increased serum ACE activity. Such physiological variations in serum ACE activity must be taken into account for diagnosing sarcoidosis in children, for following the course of the disease, and for evaluating the accuracy of therapy.

Additional Keyphrases: sex- and age-related effects • pediatric chemistry • steroids • monitoring therapy • hypertension • enzyme activity

Angiotensin-converting enzyme (ACE; EC 3.4.15.1, dipeptidyl carboxypeptidase I) catalyzes the conversion of angiotensin I to angiotensin II, a potent vasopressor, and inactivates bradykinin, a vasodilator. Thus it is important in homeostasis of blood pressure. ACE is primarily synthesized by endothelial cells but also by macrophages under certain conditions of stimulation—e.g., in the course of sarcoidosis. Determination of ACE activity in serum or plasma is of particular interest in the diagnosis of clinically active sarcoidosis and the management of the disease after corticotherapy or without drug treatment (1, 2). Reference intervals for ACE in serum of human adults have been determined for several enzymatic assays (2, 3), but little is known about the reference values for serum of children, even though sarcoidosis has been widely described in children and young adults (4, 5). The substrate N-[3-(2-furyl)acryloyl]-L-phenylalanyl-L-glycyl-L-glycine (FAPGG) permits kinetic assays of ACE activity. We previously reported an automated determination of serum ACE activity based on use of this substrate with a discrete analyzer and demonstrated the reliability, rapidity, and simplicity of the assay that makes it suitable for routine use and for clinical investigations of ACE (6).

In the present study, using the same enzymic assay, we measured ACE in serum of 187 healthy children, ages six months to 18 years, to determine whether there were age- and sex-related differences in the normal reference interval.

Subjects and Methods

Subjects. We obtained serum samples from 187 apparently healthy children (95 girls, 92 boys) during a consultation for routine health control in the Center of Preventive Medicine of Vandoeuvre-les-Nancy (ages six months to four years) and the Pediatric Medical Center of Paris 12 (ages four to 18 years). We arbitrarily grouped the 187 subjects into five-year age intervals. We also studied the results for each group according to sex.

We also collected sera from 20 children with active sarcoidosis confirmed by clinical findings plus a positive biopsy (Department of Pediatric Pneumology, Hôtel-Dieu Hospital, Paris).

Determination of ACE in serum. ACE activity was determined according to the automated method previously described, with FAPGG as the substrate (6). One unit (U) of ACE activity is the amount of enzyme that hydrolyzes 1 µmol of FAPGG per minute at 37 °C.

Data analysis. For statistical comparison we used Student’s t-test for non-paired data.

Results

Table 1 summarizes the ACE activity in serum of
Table 1. Variations of ACE Activity in Serum of Healthy Children as a Function of Age and in Comparison with Healthy Adults

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>n</th>
<th>Serum ACE (mean ± SD, U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–2</td>
<td>40</td>
<td>109 ± 33</td>
</tr>
<tr>
<td>2–4</td>
<td>47</td>
<td>100 ± 30</td>
</tr>
<tr>
<td>4–9</td>
<td>31</td>
<td>124 ± 42&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9–13</td>
<td>38</td>
<td>138 ± 47&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>13–18</td>
<td>15 boys</td>
<td>126 ± 34&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>16 girls</td>
<td>102 ± 30</td>
</tr>
<tr>
<td>Children (&lt;18)</td>
<td>187</td>
<td>118 ± 30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adults (&gt;18)</td>
<td>156</td>
<td>100 ± 35&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a,b</sup> Significantly different from the adult values: *P* < 0.01; B P < 0.001.
<sup>c</sup> From reference 6.

healthy children as compared with the reference interval in adults (6).

Overall, the children had higher mean serum ACE activity than did adults: 118 (SD 30) vs 100 (SD 35) U/L.

A more detailed analysis, however, demonstrated an age-related dependence. Between six months and four years we observed no difference; from four years to 13 years, serum ACE progressively increased; after 13 years, serum ACE gradually decreased until it reached values for adults. Furthermore, between 13 and 18 years, a sex-related difference was apparent: serum ACE decreased to normal adult values faster in girls (102 ± 30 U/L) than in boys (126 ± 34 U/L) (P < 0.05) (Figure 1).

We also verified statistically significant (P < 0.01) high serum ACE activity in subjects with sarcoidosis, both in adults (n = 15, 220 ± 48 U/L) and in children (n = 20, 200 ± 30 U/L). However, the difference between the sarcoidotic adults and the sarcoidotic children was not significant.

Discussion

Serum ACE has been widely studied in normal adults and in those with sarcoidosis, but little is known about physiological sex- and age-related differences for this enzyme in children. We previously reported a reference interval for serum ACE activity in normal adults, enzyme activity being determined by an automated kinetic method with FAPGG as the substrate. There was no significant difference either by age or by sex in adults, but we noticed higher values in newborns, premature infants being no different from full-term infants. Now we show that serum ACE activity is returned to the adult value in six-month-old infants and is stabilized at this concentration until the age of four years. Then, serum ACE gradually increases until puberty; afterward, it decreases during adolescence to again reach adult values, but ACE activity stays at high values for a longer time in boys than in girls.

Our results are comparable with those reported by Rodriguez et al. (5), who found higher values for normal children than for adults but no age- or sex-related differences. This discrepancy could be explained by the fact that they used another substrate, hippuryl-histidyl-leucine, in a less sensitive assay.

The high ACE activities determined in serum from newborns have been explicated as the consequence of the rapid development of lung capillaries after parturition (7), capillary endothelial cells being the principal source of circulating ACE. This phenomenon cannot explain the increased ACE values between four and 18 years. Rather, such an increment may be related to a hormonal regulation of ACE synthesis, because it is well known that hormones from the renal cortical and thyroid glands can stimulate ACE biosynthesis, as shown in vivo studies (8) as well as in vitro in cultures of endothelial cells (8, 9). On the other hand, the difference encountered between boys and girls during puberty may be related more specifically to a steroid hormonal regulation of ACE synthesis. Testicular and epididymal ACE are known to develop at puberty and depend on pituitary function (10). In particular, the development during puberty and the maintenance during adulthood of testicular ACE require the presence of an intact pituitary gland, and thus they are under endocrinological control (11).

In conclusion, the high ACE activities frequently encountered in serum from boys four years to 18 years old and from girls four years to 13 years old must be taken into account for diagnosing sarcoidosis and monitoring therapy in this disease.

References


Fig. 1. Comparison of serum ACE activity (U/L, y-axis) between the different age-groups, by sex

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Aminotransferase as a Prognostic Index in Infants with Liver Disease

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To assess the utility of the serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio in a group of infants with liver disorders, we retrospectively analyzed the charts of 73 infants with chronic liver disorders. Patients were considered as having either a good outcome (n = 40) or a poor outcome (n = 33), based upon the clinical course. AST and ALT in serum were measured simultaneously at the time of initial presentation and at various follow-up visits during the first 13 months after birth. At presentation (mean age 1.65 months), there was no difference in the AST/ALT ratios between the good (1.61 ± 0.62; mean ± SD) and poor (1.65 ± 0.78) outcome groups (P = 0.81). However, over time, the AST/ALT ratio increased in patients in the poor-outcome group and decreased in patients in the good-outcome group. Calculating the AST/ALT ratio appears to be an easy, early, and reliable prognostic indicator for infants with hepatic disease, and may be a useful measure for evaluating liver-disease patients.

Advances in the diagnosis and treatment of pediatric liver disorders have markedly improved survival rates for children with liver disease (1). Unfortunately, a substantial number of children continue to die from complications of their primary hepatic pathology while awaiting liver transplantation. Given the limited number of donor organs, identification of the infants at greatest risk who might benefit from earlier hepatic transplantation could be of considerable utility.

The ratio between aspartate aminotransferase (AST, EC 2.6.1.1) and alanine aminotransferase (ALT, EC 2.6.1.2), AST/ALT, has been found to be a useful indicator of hepatic disease in adults (2). In adult patients with nonalcoholic liver disease, an AST/ALT ratio increasing to >1.0 suggests cirrhosis, whereas a ratio <1.0 is usually seen in patients with chronic hepatitis, survivors of acute viral hepatitis, and patients with chronic cholestatic syndromes (2-5). An AST/ALT activity concentration ratio >2.0 has been reported in adult patients with alcoholic liver disease (5, 6).

In an attempt to identify an easily measured and reliable index that would assist in the early evaluation of infants with liver disorders and offer a prognostic guide to their outcome, we assessed the utility of the AST/ALT ratio in the serum of a group of such infants.

Patients and Methods

We retrospectively analyzed the charts of 73 infants with chronic liver disorders, who had been referred to our division for evaluation and treatment between October 1976 and September 1988. Diagnoses were confirmed on the basis of appropriate clinical, microbiological, radiological, biochemical, and histological criteria. The study population included 42 infants with extrahepatic biliary atresia, 12 infants with cytomegalovirus (CMV) hepatitis, 11 with idiopathic neonatal hepatitis, six with alpha-1-antitrypsin deficiency liver disease, and two with arteriohepatic dysplasia (Alagille's syndrome). There were 39 boys and 34 girls.

Patients were assigned to either a good-outcome (n = 40) or poor-outcome (n = 33) group, based on their clinical course. Poor outcome was defined as evidence of cirrhosis, portal hypertension, esophageal varices, ascites, liver transplantation, or death. Patients in the good-outcome group had no signs of chronic liver disease or any of the findings used to define a poor outcome. Follow-up assessments were made from three months to 10 years later (mean 23 months).

AST and ALT activity concentrations were measured simultaneously in serum of each patient at the time of initial presentation and at various intervals at follow-up visits with an automated procedure (Abbott Bichromatic Analyzer, ABA-100; Abbott Labs., Abbott Park, IL) in our clinical chemistry laboratory under standard laboratory conditions (7). The serum AST/ALT ratios during the first 13 postnatal months were calculated from these serial values. We used Student's t-test (two-tailed) to compare values obtained for the two groups.

This study was approved by the Committee on Clinical Investigations and Publications of the Childrens Hospital of Los Angeles.

Results

For the good-outcome group, serum AST values ranged