Angiotensin converting enzyme activity in infancy is related to birth weight

J S Forsyth, J Reilly, C G Fraser, A D Struthers

Aims: (a) To measure infant angiotensin converting enzyme (ACE) activity in healthy term infants at birth and during the first three months of life. (b) To determine the relation between serum ACE activity and infant feeding practice during this period. (c) To investigate the relation between serum ACE activity and birth weight and other potential contributing factors including acid-base status at birth, gestation, and maternal ACE genotype.

Methods: Prospective study of term infants, with clinical and feeding data collected from parents and medical records, and serum ACE measured in the infant at birth and 1 and 3 months of age, and in the mother at the time of birth and one to three months after birth.

Results: At birth and 1 and 3 months of age, infant serum ACE activity was twice that of maternal ACE activity. Infant ACE activity at birth and 1 and 3 months did not significantly differ between breast and formula fed infants. There was a highly significant negative correlation between infant ACE activity at 3 months and birth weight \[(r = -0.52; \ p < 0.001).\] This persisted after the conversion of birth weights to \[z\] scores \[(r = -0.34; \ p = 0.03).\] ACE activity at 3 months was also related to placental weight \[(r = -0.30; \ p = 0.05).\] The strong correlation between serum ACE activity and birth weight \[z\] score persisted after adjustment for maternal age and placental weight \[(r = -0.34; \ p = 0.03).\]

Conclusion: As ACE is increasingly identified as a risk factor for cardiovascular disease, serum ACE activity in infancy may contribute to the link between low birth weight and later cardiovascular events.

METHODS

The infants were recruited to the study during the early postnatal period, after informed consent had been obtained from their mother or guardian. They were born at term (259–294 days) and had already received their first breast or formula feed.

Clinical data were collected prospectively. These included placenta weight, gestation, mode of delivery, and birth weight. Infant feeding information included type of milk feed at birth and number of breast, formula, and solid feeds at 1 and 3 months of age. Maternal blood pressure was measured one to three months after delivery.

Umbilical cord blood was obtained immediately after birth to measure acid-base status and serum ACE activity. Capillary samples (100 \( \mu l \)) were taken from the infant at 1 and 3 months of age to measure serum ACE activity. A venous blood sample was taken from the mother to determine ACE genotype and also to measure maternal ACE activity at birth and one to three months after delivery.

Serum ACE activity was measured by an automated technique that requires small volumes of blood (100 \( \mu l \)). ACE was assayed by monitoring the change in absorbance at 340 nm caused by the hydrolysis of furylacryloyl-phenylalanine-lysineglycylglycine to furylacryloyl-phenylalanine and glycylglycin (Sigma Aldrich Chemical Co, Poole, Dorset, UK) on an
Values are mean (SD).

Table 3 Maternal and infant angiotensin converting enzyme (ACE) activity (units/l)

<table>
<thead>
<tr>
<th>N</th>
<th>ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Infant</td>
</tr>
<tr>
<td>Birth</td>
<td>1–3 months</td>
</tr>
<tr>
<td>67</td>
<td>43</td>
</tr>
<tr>
<td>29.5 (12.2)*</td>
<td>33.6 (12.5)t</td>
</tr>
<tr>
<td>56.0 (23.2)t</td>
<td>78.3 (40.2)t</td>
</tr>
</tbody>
</table>

Values are mean (SD).
* and t, p < 0.001; †, p < 0.001; ‡, p < 0.05.

Table 4 Relation between feeding practice and infant angiotensin converting enzyme (ACE) activity (units/l)

<table>
<thead>
<tr>
<th>Predominant feed</th>
<th>ACE activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant feed</td>
<td>Birth</td>
</tr>
<tr>
<td>Breast milk</td>
<td>55.0 (15)*</td>
</tr>
<tr>
<td>(n = 21)</td>
<td>(n = 21)</td>
</tr>
<tr>
<td>Formula</td>
<td>57.6 (23)*</td>
</tr>
<tr>
<td>(n = 31)</td>
<td>(n = 31)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
* v, p < 0.05.

Table 2 Feeding characteristics

<table>
<thead>
<tr>
<th>Feed at birth</th>
<th>No of feeds/day at 1 month</th>
<th>No of feeds/day at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Breast</td>
<td>Formula</td>
</tr>
<tr>
<td>5.4 (4.6)</td>
<td>3.0 (3.7)</td>
<td>3.4 (3.6)</td>
</tr>
<tr>
<td>Formula</td>
<td>0.0 (0.0)</td>
<td>6.7 (1.3)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Hitachi 917 clinical chemistry system (Roche, Lewes, East Sussex, UK). ACE genotype was measured by standard techniques.

Data were analysed using SPSS for Windows, version 10.1 (SPSS Inc, Chicago, Illinois, USA). Comparison between groups was analysed using Student’s t test, and effects of confounding variables were assessed by multiple regression analysis.

RESULTS

Sixty eight infants were recruited to the study. Table 1 shows the maternal and infant characteristics. No infant had a positive history of maternal hypertension, and there were no major neonatal problems. All infants started milk feeds within four hours of birth. Table 2 shows feeding details.

Table 3 shows the mean (SD) serum ACE activity for mothers at birth and one to three months after delivery, and the serum ACE activity in infants at birth and 1 and 3 months of age. There were no significant differences between infant serum ACE activity at 1 and 3 months of age but both were significantly higher than at birth. There was also significantly more variance at 1 month of age than at birth and 3 months. At birth and 1–3 months, infant serum ACE activity was twice that of maternal serum ACE activity. Maternal ACE activity measured at the time of birth and at one to three months postnatal did not differ significantly. Maternal ACE activity correlated positively with birth weight, but there was a highly significant correlation persisted after the conversion of birth weights to z scores ($r = -0.34; p = 0.03$; fig 1). ACE activity was also related to placental weight ($r = -0.30; p = 0.02$) and maternal age ($r = -0.30; p = 0.05$). The significant relation between serum ACE activity at 3 months and birth weight z score persisted after adjustment for maternal age and placental weight ($r = -0.34; p = 0.03$).

DISCUSSION

This study of healthy term infants shows that infant serum ACE activity at 3 months of age is related to size at birth but not to breast or formula feeding. A possible implication of these findings is that components of the renin-angiotensin pathway may be directly or indirectly linked to mechanisms that influence fetal growth.

Previous human data on ACE activity have been linked to specific pathological circumstances including maternal hypertension, prematurity, and infant respiratory and acid-base abnormalities. Moreover, measurements of serum ACE activity have been limited to the immediate newborn period. There are no published longitudinal data on healthy term infants and the relation of serum ACE activity to type of infant feeding. Recruits to this study were born at term after a normal pregnancy, they had normal acid-base status at birth, and there was no history of maternal hypertension. The data were therefore not confounded by factors that had
Previously been reported to be associated with raised infant serum ACE activity. Despite this relatively homogeneous study population, a significant correlation between birth weight and infant serum ACE concentration at 3 months of age was noted.

Previous studies have reported higher serum ACE activity in infants than adults. It is known that lung endothelial cells are a rich source of circulating ACE and therefore the raised activities in infants may be related to rapid lung development that occurs during the last trimester and the immediate postpartum period. Several studies have indicated that serum ACE activities are higher in premature infants, suggesting that ACE may be more active in the immature lung.

The variance in ACE activity at 3 months of age was significantly less than that at birth and 1 month. Serum ACE activity at birth and 1 month of age was not related to weight at birth, but there was a highly significant negative correlation between infant ACE activity at 3 months and birth weight. This correlation persisted when the birth weights were converted into z scores. In this cohort of term infants, gestation was not independently related to ACE activity. The serum ACE activities at 3 months were therefore not only more stable, but they also related significantly to variation in birth weights within a narrow gestational range.

This strong association between birth weight and serum ACE suggests that ACE or the renin-aldosterone system may be linked to mechanisms controlling early human growth. There is laboratory evidence indicating that angiotensin II has a specific growth factor-like effect on target tissue, and it has been proposed that the renin-angiotensin system has a pivotal role in fetal development and growth. Data are supported by the adverse findings of growth retardation and pulmonary hypoplasia with ACE inhibitor medication when prescribed antenatally. It is therefore possible that the higher serum ACE activity in infants of lower birth weight may reflect a compensatory mechanism to achieve catch up growth after a period of faltering fetal growth.

Whether the increased serum ACE activities then have long term effects is not known, and it will be important to determine if serum ACE activity tracks into later childhood. As angiotensin II is the main metabolite of serum ACE activity, and as it has been shown to have atherogenic effects, increased serum ACE activity in early life could programme the individual for increased cardiovascular disease in later life.

ACKNOWLEDGEMENTS

We acknowledge the laboratory support from Lesley MacFarlane, Val Godfrey, and Andrew Cassidy, and initial project support from Karen Tosh.

REFERENCES


Authors’ affiliations

J S Forsyth, J Reilly, Tayside Institute for Child Health, University of Dundee, Scotland, UK
C G Fraser, Biochemical Medicine, University of Dundee
A D Struthers, Clinical Pharmacology and Therapeutics, University of Dundee
Infancy is related to birth weight

J S Forsyth, J Reilly, C G Fraser and A D Struthers

Arch Dis Child Fetal Neonatal Ed 2004 89: F442-F444
doi: 10.1136/adc.2003.027896

Updated information and services can be found at:
http://fn.bmj.com/content/89/5/F442

These include:

References
This article cites 18 articles, 4 of which you can access for free at:
http://fn.bmj.com/content/89/5/F442#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Infant nutrition (including breastfeeding) (241)
- Drugs: CNS (not psychiatric) (191)
- Childhood nutrition (297)
- Drugs: cardiovascular system (267)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/