PATTERN OF MALFORMATION IN
OFFSPRING OF CHRONIC ALCOHOLIC
MOTHERS
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Summary
Eight unrelated children of three
different ethnic groups, all born to
mothers who were chronic alcoholics, have a similar
pattern of craniofacial, limb, and cardiovascular
defects associated with prenatal-onset growth de-
ficiency and developmental delay. This seems to be
the first reported association between maternal alco-
holism and aberrant morphogenesis in the offspring.

Introduction
The purpose of this report is to alert physicians
and other health professionals to a pattern of altered
morphogenesis and function in eight unrelated children
who have in common mothers who were chronic
alcoholics during pregnancy. Ulleland has called
attention to growth deficiency and developmental
delay in such children.

Clinical Findings
Methods of Patient Ascertainment
Eight children born of alcoholic mothers were
brought together and evaluated at the same time by the
same observers (K. J. and D. W. S.). Four of these
children were recognised as having a similar pattern
of altered growth and morphogenesis. Thereafter,
two other children were ascertained by the abnormal
features identified in the first four patients, while the
remaining two affected children were ascertained
because their mothers were chronically alcoholic.

The mothers of the affected patients all satisfied
the criteria for alcoholism as published in 1972 by the
Criteria Committee, National Council on Alcoholism. 2
Complications and duration of maternal alcoholism
as well as general background information are out-
lined in table I. All drank excessively throughout
the pregnancy, the mothers of patients 1 and 7 to the
extent that they were in hospital with delirium tremens.
Patient 3 was born while her mother was in an alcoholic
stupor. None of the mothers was known to be ad-
dicted to any other drug. Features shared by these
eight children are summarised in table II and are
illustrated in figs. 1 and 2. Further pertinent data and
descriptions are found in the case-reports. Palpebral
fissure length was measured from medial to lateral
canthus and is shown in fig. 3. The growth and per-
formance are presented in figs. 4 and 5 and in table III,
and are summarised following the case-reports.

Case-reports
Patient 1, a 1-year-old girl, had asymmetric maxillary
hypoplasia. There was lack of full extension at both
elbows and bilateral hip dislocations. At birth the 5th
fingers overlapped the 4th bilaterally, but they have
subsequently come to be in a normal position. A grade
4 out of 6 systolic murmur was repeatedly noted during
the first 6 months, but is no longer audible. It was inter-
preted as representing a ventricular septal defect which had
closed. A single upper palmar crease was present on the
right hand. Incomplete development of the superior
helix of both ears was present bilaterally. There was a
3 × 3 cm. capillary haemangioma over the lateral aspect of
the right thigh. The labia majora were hypoplastic.

Chromosomal study was normal.

Patient 2, a female, was admitted at 11 weeks of age in
congestive heart-failure secondary to an atrial septal

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TABLE I—GENERAL DATA

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal history of alcoholism:</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>11</td>
<td>2+</td>
<td>10</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Duration (yr.)</td>
<td>26</td>
<td>34</td>
<td>22</td>
<td>31</td>
<td>32</td>
<td>39</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>↓1</td>
<td>?</td>
<td>?</td>
<td>↓5</td>
<td>↓15</td>
<td>↓15</td>
<td>↓19</td>
<td>↓30</td>
</tr>
<tr>
<td>Nutritional anaemia</td>
<td>5/5</td>
<td>7/7</td>
<td>3/4</td>
<td>6/6</td>
<td>4/7</td>
<td>6/6</td>
<td>4/4</td>
<td>5/5</td>
</tr>
<tr>
<td>Gestational age (wk.)</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>36</td>
<td>38</td>
<td>34</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>Birth order</td>
<td>1850</td>
<td>2500</td>
<td>2500</td>
<td>1600</td>
<td>1673</td>
<td>1550</td>
<td>2345</td>
<td>2250</td>
</tr>
<tr>
<td>Birth weight (g.)</td>
<td>45</td>
<td>44</td>
<td>45</td>
<td>47</td>
<td>42</td>
<td>43</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Weight change during pregnancy (lb.)</td>
<td>+ = present; − = absent; ? = unknown.</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Appar score at 1 min. and 5 min.</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

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TABLE II—PATTERN OF ANOMALIES

<table>
<thead>
<tr>
<th>Patient no. and ethnic group</th>
<th>Native American (American Indian)</th>
<th>Black</th>
<th>White</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Growth features and performance:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prenatal growth deficiency</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Postnatal growth deficiency</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Craniofacial:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short palpebral fissures</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Maxillary hypoplasia with relative prognathism</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Limbs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint anomalies *</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Altered palmar crease pattern</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* = present; -- = absent.

...
All patients had prenatal and postnatal growth deficiency. Though the mean gestational age was 38 weeks, the mean birth length and weight were at the 50th percentile for gestation ages of 33 weeks and 34 weeks, respectively. Thus the degree of linear growth deficiency was more severe than the deficit of weight at birth. Since birth, none of the patients has shown catch-up growth either during hospital admission for “failure to thrive” in six children, during which time adequate caloric intake was recorded, or during foster-care placement in three children. The growth pattern for seven of the eight children is depicted in fig. 4. After 1 year of age the average linear growth-rate was 65% of normal and the average rate of weight gain was only 38% of normal. The mean daily weight increment for the eight patients was 9 g., as contrasted to 26.6 g. for upper-middle-class Seattle children and 24.4 g. for high-risk children followed in the maternal and infant care programme in this city.

Head circumference, depicted in fig. 5, was below the 3rd percentile for gestational age in seven of the eight children at birth. By 1 year of age it had dropped below the 3rd percentile for height age as well as for chronological age in five of the six patients for whom these data were available.

Performance

Performance testing, except for patient 5, was done by one of us (A. P. S.). As indicated in table III,
TABLE III—MENTAL, MOTOR, AND SOCIAL DEVELOPMENT

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age* (mo.)</td>
<td>14</td>
<td>3</td>
<td>57</td>
<td>46</td>
<td>18</td>
<td>40</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>Motor age estimate† (mo.)</td>
<td>10</td>
<td>2</td>
<td>31</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Mental age‡ (mo.)</td>
<td>10</td>
<td>2</td>
<td>44</td>
<td>26</td>
<td>11</td>
<td>32</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>I.Q. or M.D.I.§</td>
<td>59</td>
<td>83</td>
<td>75</td>
<td>57</td>
<td>. .</td>
<td>79</td>
<td>70</td>
<td>. .</td>
</tr>
<tr>
<td>Social quotient¶ (mo.)</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
</tbody>
</table>

* Age at time of testing.
† Bayley scales of infant motor development used where appropriate. This is an estimate only, owing to low ceiling on test relative to age of children.
‡ Stanford-Binet intelligence scale, form L-M (yielding a mental age and I.Q.), used for patients 3, 4 (without glasses), 6, and 7. Bayley scales of infant mental development (yielding a mental age and mental development index) used for patients 1, 2, 4, and 8. Denver developmental scale used for patient 5.
§ Vineland social maturity scale administered to one or both parents.

none of the children were performing within the normal range. In all cases, the children’s social and motor performance was more in accord with mental age than chronological age. Fine motor dysfunction, including tremulousness, weak grasp, and/or poor eye/hand coordination was present in five out of the six patients tested, and most of them were delayed in gross motor performance. Five of the children were observed or reported to engage in some type of repetitive self-stimulating behaviour such as head rolling, head banging, or rocking.

**Discussion**

Past evidence from animal experiments and human experience has not given clear indication of an association between maternal alcoholism and aberrant morphogenesis in the offspring.4 This report points strongly to such an association. Eight unrelated children of three different ethnic groups, all raised in the fetal environment provided by an alcoholic mother, had a similar pattern of craniofacial, limb, and cardiovascular defects with prenatal-onset growth deficiency and developmental delay. The similarity in the pattern of malformation among these eight children suggests a singular mode of aetiology, most likely environmentally determined by some as yet unknown effect of the maternal alcoholism. Direct ethanol toxicity is the most obvious possibility. There is good evidence in man and other animals that ethanol freely crosses the placental barrier. Animals studies have shown it to be distributed in the amniotic fluid and in multiple fetal tissues, at least during mid or late gestation. Other direct toxic possibilities include one of the breakdown products of ethanol such as acetaldehyde or an unknown toxic agent in the alcoholic beverages which these mothers were consuming. The adverse effect on morphogenesis could also be the indirect consequence of general maternal undernutrition or the deficiency of a specific nutrient or vitamin. However, this degree of prenatal growth deficiency and the pattern of malformation have not been previously recognised in offspring of undernourished women who were not alcoholics.7

The following comments and interpretations relate to the specific anomalies of this syndrome. The short palpebral fissures were interpreted as being secondary to deficient growth of the eyes. A prenatal onset of this implied ocular growth deficiency was indicated for at least patients 1 and 7, who were noted in the records as having “microphthalmia” at the time of birth. The hypoplasia of the maxilla, most evident in its anterior-posterior dimension, resulted in relative prognathism at an age when this is unusual. The variable alterations in joint mobility and positioning in hands, elbows, hips, and feet could be the consequence of limited movement and/or aberrant position during early fetal life. This is further implied by the altered palmar flexional crease patterns, which are normally determined by 11 weeks. In terms of severity, the hand positioning in patient 1, which has improved in time, was at first similar to that found in babies with the 18 trisomy syndrome. None of the patients have had any serious functional joint disability except for the problem of hip dislocation in patients 1 and 7. Of the five patients with evidence of a cardiac anomaly, three were considered to have had a ventricular septal defect which closed before 1 year of age.

The prenatal growth deficiency was more profound in terms of linear growth than for weight growth. This is in contrast to studies of generalised maternal undernutrition in which the newborn is usually underweight for length,7 and hence suggests that a factor other than nutritional deprivation alone was adversely affecting prenatal growth in these children. Whatever
HYPERCALCÆMIA AFTER ORAL CALCIUM-CARBONATE THERAPY IN PATIENTS ON CHRONIC HÆMODIALYSIS

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Summary

Oral calcium carbonate is widely used in chronic renal failure as a phosphate-binding antacid. Unexpectedly, severe hypercalcæmia developed in three out of ten hæmodialysis patients treated with 3-2 to 6-4 g. calcium carbonate per day for 4-8 weeks. In one patient the serum-calcium reached 15.8 mg. per 100 ml., and he had nausea, vomiting, muscular weakness, personality changes, and subconjunctival calcifications. Two other patients were symptom-free with serum-calcium levels of 12.3 and 12.7 mg. per 100 ml. Hyperparathyroidism, raised dialysate calcium concentrations, and vitamin-D intoxication were excluded as causes of this complication. When calcium carbonate was discontinued, serum-calcium promptly returned to normal, and in the first patient all signs and symptoms disappeared. It is concluded that the hypercalcæmia resulted from intestinal absorption of calcium, probably by passive diffusion not dependent upon vitamin D. Calcium carbonate should be used with caution in patients maintained on chronic hæmodialysis.

Introduction

Patients with chronic renal failure who are maintained on chronic hæmodialysis still face several metabolic problems, including acidosis, disorders of mineral metabolism, and peptic- ulcer disease. Phosphate retention, an important factor in the aetiology of renal osteodystrophy, is both common and difficult to manage. Oral phosphate-binding agents must be used, but the most popular of these, aluminium hydroxide and aluminium carbonate, are unpalatable to many patients. Makoff et al. recommended the use of calcium carbonate in chronic uræmic patients. Since these metabolic disorders potentially respond to treatment with calcium carbonate, which is in addition well tolerated, we substituted this agent for aluminium carbonate. Unexpectedly, moderate to severe hypercalcæmia developed in three of these patients while they were receiving calcium-carbonate therapy.

References

3. Peterson, D. R. Personal communication.