anoxic birth. His death during an acute infection could be interpreted as indicating that he was merely living on borrowed time and that a fatal catabolic illness was inevitable at some stage. However, we believe that the unfortunate delay in recognizing the severity of this episode and in starting effective treatment provides an adequate explanation. As emphasized by Wick et al. (1973), every intercurrent illness must be treated energetically; fluid and glucose sufficient to meet caloric requirements must be given by intravenous infusion if necessary.

Unfortunately, the opportunity for presumptomatic treatment of citrullinaemia arises only occasionally in new babies born into families in which previous cases have been diagnosed, and in rare families like the present one in which a new baby is investigated because of previous unexplained deaths (Danks, 1974).

Fluctuations in the clinical condition of this baby corresponded closely to the blood ammonia levels, supporting the idea that this is the noxious compound in citrullinaemia (Wick et al., 1973). His ability to develop normally while serum citrulline levels were 100 times that of normal infants appears to contradict claims that citrulline itself is harmful (Okken et al., 1973). Arginine supplements form an important part of the treatment, for arginine becomes an essential amino acid in these patients.

Summary

Diagnosis of citrullinaemia was achieved at 36 hours in a baby whose 2 sibs had died in the newborn period without diagnosis. Control of blood ammonia levels by a low-protein diet allowed normal development until the age of 7 months, when delayed treatment of an acute infection allowed fatal hyperammonaemia to develop.

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References


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Maternal histidinaemia

Maternal histidinaemia was first reported in 1971 by Neville et al., who described a 4-year-old boy whose 23-year-old mother had histidinaemia. The child appeared to be normal and of average mental development (IQ 107).

Our interest in this condition dates from 1969, when an expansion of the New Zealand phenylketonuria (PKU) neonate screening programme providing Guthrie Inhibition Assays (GIA) of blood phenylalanine, methionine, leucine, and tyrosine levels was extended to include a GIA for blood histidine. This resulted in the discovery of considerable numbers of transient elevations of neonatal blood histidine. At least one case of maternal PKU has been discovered by examining the mother of a newborn child with hyperphenylalaninaemia (Coffelt, 1964), and it has been a long-standing practice in our laboratory to request a dried blood spot from the mother of each child with hyperphenylalaninaemia. We instituted a similar procedure for mothers of children who had an initial GIA for histidine of 8 mg/100 ml or greater. From 1 January 1970 to 31 October 1973, 1556 such mothers were tested without the detection of a single case of maternal histidinaemia. However, in studying the relatives of a case of histidinaemia found in a mental hospital survey, we discovered a 37-year-old female sib with this condition. She had 5 children. Her family, and our study of it, are described here.

Family study

In the course of a biochemical study of 1780 mentally retarded and psychiatric patients in two institutions in 1972, using blood GIAs and early morning urine specimens, a mentally retarded 27-year-old male with
histidinaemia was detected. The initial GIA histidine was 12 mg/100 ml, fasting plasma histidine 12·9 mg/100 ml, 24-hour urinary excretion of histidine 1040 mg, a histidine loading test was abnormal, and no skin urocanic acid was detected. Though no formal psychological assessment has been done, it was said to have 'always been backward'. He attended school, but by the age of 17 years had only reached standard 2 (8- to 9-year-old level), and it is clear that this promotion was on age rather than merit, for he had not learned to read, write, or do the simplest arithmetic. After leaving school at 17 years, problems of social maladjustment increased, and his admission to a psychiatric hospital in 1963 was precipitated by episodes of antisocial behaviour. Since his admission he has presented no difficulty in management except, perhaps, for persistent nocturnal enuresis. Physical examination was unremarkable.

He had 7 sibs, all apparently mentally, physically, and socially normal, whom we tested. 2 had histidinaemia: his 52-year-old brother, a member of a TV production team, had a GIA histidine of 11 mg/100 ml; and his 37-year-old sister, a housewife, had a GIA histidine of 10 mg/100 ml. They certainly would have never been examined but for the discovery of the condition in their retarded brother.

We studied the sister, who had 5 children, in more detail. Her fasting plasma histidine of 9·6 mg/100 ml, her histidine loading test, and absence of skin urocanic acid indicated that her biochemical lesion was the same as that of the index case. Her 5 children were aged 19, 17, 14, 13, and 3 in 1973. Their perinatal and medical histories are unremarkable. Each had a GIA histidine of 2 mg/100 ml. A formal psychological assessment was performed on the parents and on all the children except the 3-year-old, whose hyperactivity made the procedure so difficult it was abandoned. The results of testing are set out in the Table.

Discussion

The problem of maternal PKU has been reviewed by MacCready and Levy (1972). Mothers with untreated PKU have given birth to children with profound mental retardation, microcephaly, and other congenital malformations. The high frequency of such retardation in the offspring of PKU mothers, ascertained other than through their retarded children, indicates that this relation is almost always found. Dietary management in pregnancy may prevent the ill effects of maternal PKU (Allen and Brown, 1968).

There is the possibility that maternal histidinaemia could similarly be a cause of mental retardation and/or other developmental abnormalities. The child born to a histidinaemic mother reported by Neville et al. (1971) did not appear to have suffered any difficulties by the age of 4½ years. In the family described, 4 of the children were old enough to undergo precise psychological assessment. Their IQs are closely grouped, with a mean full scale IQ of 86·5–96·5. This is about 20 points less than the midparent value (106·5–116·5). The mean IQ of the children would be expected to approximate the midparent value. The fact that it is considerably lower, and on the other side of the population mean, we regard as suggestive of a causal relation with the maternal histidinaemia.

Recent studies of histidinaemic mice (Kacser, Bulfield and Wallace, 1973; Bulfield and Kacser, 1974) are relevant to the present discussion. These workers have discovered what appears to be a useful animal model, in that the disorder is biochemically similar, and that it is associated with central nervous system abnormalities in the offspring of homozygous (his/his) mothers. The nervous defect—circling and head tilting—was often present in the offspring of his/his × his/his matings, though it was present in a milder form (head tilting) where the mother was his/his and the father normal (+/—). The offspring of his/his male × +/+ female matings, and of his/+ × his/+ matings (including the his/his progeny) did not have the balance defect. The authors concluded that the evidence strongly supported the view that the maternal histidinaemia had caused the balance defect.

<table>
<thead>
<tr>
<th>Age at test (yr)</th>
<th>Test used</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>Full scale IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>Wechsler Bellvue form 2</td>
<td>110–120</td>
<td>100–110</td>
<td>108–118</td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td>100–110</td>
<td>107–117</td>
<td>105–115</td>
</tr>
<tr>
<td>Child 1</td>
<td></td>
<td>90–100</td>
<td>86–96</td>
<td>87–97</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>77–87</td>
<td>83–93</td>
<td>78–88</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>91–101</td>
<td>95–105</td>
<td>93–103</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>81–89</td>
<td>95–105</td>
<td>87–97</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Not able to be tested</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WISC, Wechsler Intelligence Scale for Children.
The early evidence from mice and men, therefore, suggests that maternal histidinaemia and a central nervous system defect, obvious or subtle, may be related as cause and effect. Clearly, more studies are required before this can be substantiated. We suggest that it become a routine procedure that mothers of children with mental retardation of undetermined cause have their blood histidine (as well as blood phenylalanine) measured. Perhaps all mothers could be examined antenatally by a ‘ferric chloride’ type of urine test, which would detect both maternal PKU and histidinaemia. Whether or not histidinaemic women should have a low histidine diet in pregnancy will not become clear until further studies have been done.

Summary

A 37-year-old sister of a mentally retarded 27-year-old male with histidinaemia was shown to have the same biochemical condition. She had 5 children aged between 3 and 19 years, all of whom had normal blood histidine levels. The IQ of 4 of the 5 children was assessed and in all 4 the IQ was much less than the mean parental value. The possibility that this was attributable to maternal histidinaemia is considered.

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References


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Minimal rates of oxygen consumption in small-for-dates babies during the first week of life

Scopes and Ahmed (1966) showed that the minimal rates of oxygen consumption in small-for-dates babies remained low during the first 3 days of life but rose abruptly at 4 days and thereafter rates were similar to those of mature babies. During a different study involving metabolic rates (Bhakoo and Scopes, 1971), we had reason to repeat these observations on oxygen consumption in small-for-dates babies with quite different findings.

Material and methods

The birthweights and gestation periods of the 11 babies studied ranged from 1940 to 2700 g and 37 to 40 weeks. Gestational age was calculated from the first day of the mother’s last menstrual period in all cases. All babies were below the 10th centile birthweight for gestational age (Butler and Bonham, 1963). The mother’s permission was obtained for each study.

Oxygen consumption was measured in an apparatus working on the closed circuit principle as described by Scopes (1965). The study was performed during postprandial sleep over a period of 20 to 30 minutes. The temperature of the environment was kept within the neutral range and was confirmed by measurement of the skin temperature of the exposed abdominal wall. 48 observations were made.

Observations

Table I shows the minimum rates of oxygen consumption in these babies during the first week of life. In the first 12 hours only 2 observations were made. However, the rates of oxygen consumption during this period are the same as the larger number of observations made by Scopes (1965) and by Hill

<table>
<thead>
<tr>
<th>Age (hr)</th>
<th>No. of studies</th>
<th>O₂ consumption (mean) (ml/kg per min)</th>
<th>SD</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>2</td>
<td>5.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-36</td>
<td>10</td>
<td>6.50</td>
<td>0.68</td>
<td>0.20</td>
</tr>
<tr>
<td>37-60</td>
<td>9</td>
<td>6.54</td>
<td>0.55</td>
<td>0.18</td>
</tr>
<tr>
<td>3 dy ±12</td>
<td>8</td>
<td>6.85</td>
<td>0.80</td>
<td>0.28</td>
</tr>
<tr>
<td>4 dy ±12</td>
<td>8</td>
<td>6.65</td>
<td>0.70</td>
<td>0.25</td>
</tr>
<tr>
<td>5 dy ±12</td>
<td>7</td>
<td>7.00</td>
<td>0.41</td>
<td>0.16</td>
</tr>
<tr>
<td>6 dy ±12</td>
<td>4</td>
<td>7.9</td>
<td>0.92</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Note: The time intervals are the same as those used by Scopes and Ahmed (1966).