would tend to skew the results of well-controlled dietary therapy in favour of normal mental development and function. Despite these criticisms of past studies, the efficacy of dietary therapy in classical PKU is generally conceded and further controlled trials are unlikely to be ethically acceptable.

Most patients with mild PKU have been diagnosed in the newborn period as a result of mass screening by the Guthrie test. While some of these patients have been treated from early infancy with a low phenylalanine diet, the relatively good prognosis for intellectual attainment in untreated mild PKU raises serious doubts about the need for an expensive and unpalatable low phenylalanine diet. One of the untreated children in the family we describe whose blood phenylalanine was 20 mg/100 ml while on an ordinary diet had an IQ of 104. Further evidence that dietary therapy is probably not necessary in mild PKU is provided by Berman et al. (1969) who reviewed all cases with persistent blood phenylalanine levels of 6 mg/100 ml or higher, with normal blood tyrosine levels, seen during a three-year period in 11 centres in the U.S.A. They arbitrarily divided these patients into group 1 patients with maximum blood phenylalanine levels of 20 mg/100 ml or higher, and group 2 patients with maximum blood phenylalanine levels below 20 mg/100 ml. Group 1 patients had classical PKU, group 2 patients who were regarded as having hyperphenylalaninaemia showed normal mental development whether or not a low phenylalanine diet had been given.

If it is assumed that the lower the IQ the more severe the disease, then it appears that in the family we have described the severity of the mild PKU increases with each successive birth of an affected child, as the IQ of the eldest affected child is 104, of the next 70, and of the next 63. The birth of the fifth child with classical PKU might be regarded as yet a further stage in the increasing severity of the disease.

Summary

A positive Guthrie test in the newborn period led to the diagnosis of classical phenylketonuria in a female infant. 3 of her 4 sibs proved to have mild phenylketonuria which was previously unsuspected. The eldest of these affected sibs has normal intelligence, and the other 2 have IQs of 70 and 63.

We are grateful to Dr. M. S. McBean for her valuable help in the investigation of this family; also to Dr. J. S. Stevenson and his department who carried out the Guthrie tests.

References


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Treatment of Letterer-Siwe Disease

The prognosis in untreated Letterer-Siwe disease is extremely poor; Lahey (1962) found no survivors among 27 infants with the disease who received no treatment. Even with treatment, the majority of those infants who are affected in the first year of life eventually die (Lahey, 1962). Occasional long-term survivors have been reported after no therapy, or after treatment with antibiotics (Bierman, 1966). Apparent cures after steroid or antimetabolite drug therapy have been reported. The antimetabolite drugs used include vinblastine sulphate (Beier, Thatcher, and Lahey, 1963), vincristine sulphate (Hertz and Hambrick, 1968), aminopterin (Freud, 1961), and daunomycin (Segni, Mastrangelo, and Tortorolo, 1968). Cyclophosphamide has also been used with success in some instances (Esterly and Swick, 1969), but in other patients no response was seen.

Case Report

The second child of unrelated parents weighed 3.35 kg at term after a normal pregnancy. At 10 weeks he developed a scaly, erythematous rash on his chest which spread to his limbs. At first this responded to topical steroids but then recurred. At 14 weeks he began to cough and to vomit after meals. He became increasingly breathless and lost 0·57 kg in weight in 7 days.
On examination he was ill and clinically dehydrated. There was a scaly, maculopapular rash on the scalp, face, and trunk. Purpuric spots were noted on the palms, the soles of the feet, and on the trunk (Fig). Central cyanosis was apparent on crying and he had a rapid respiratory rate, intercostal recession, and widespread coarse rales. The liver was firm and palpable 3 cm below the costal margin but there was no lymph node enlargement and no splenomegaly. Apart from general irritability there were no abnormal neurological signs and the fundi were normal.

Chest x-ray showed coarse, nodular opacities scattered throughout both lungs and enlargement of the upper mediastinal glands. No abnormality was seen in x-rays of the skull and long bones. The diagnosis of Letterer-Siwe disease was confirmed by the skin biopsy which showed collections of reticulum cells in the dermis with thinning of the overlying epidermis.

Treatment with ampicillin and cloxacillin was ineffective and he rapidly went into cardiac and respiratory failure which responded poorly to oxygen, digoxin, and diuretics. Prednisolone 4·5 mg/kg per 24 hours was started 3 days after admission, but he continued to deteriorate and 4 days later he was given intravenous vincristine 0·075 mg/kg. Eight weekly doses of vincristine were given, increasing by three increments of 0·025 mg/kg to 0·15 mg/kg per dose and he responded well. An attempt to stop the steroids after 3 weeks was followed immediately by recrudescence of the rash. When he was discharged after 8 weeks in hospital there were only a few purpuric lesions on his hands and feet and his liver was no longer enlarged. There was almost complete clearing of the nodular opacities on the chest x-ray but he still had a raised respiratory rate with subcostal recession.

Prednisolone 2 mg/kg per day was continued but his chest signs worsened, and 6 weeks after discharge he was given a 2-week course of cyclophosphamide 2·5 mg/kg per day. Lung function tests at this time showed evidence of stiff lungs with some increase in airways resistance, and arterial desaturation, presumed to be due to ventilation perfusion imbalance. The chest x-ray 3 weeks later showed increasing pulmonary infiltration, and so cyclophosphamide was restarted and continued for 8 weeks. His skin and liver were not affected by the relapse, and during the second course of cyclophosphamide the rash disappeared leaving a few keratotic nodules on the soles of his feet. Lung function tests immediately after the second course showed no significant change but the x-ray appearances continued to improve until there was no abnormality one year after his first admission. Prednisolone was given for

<table>
<thead>
<tr>
<th>Age</th>
<th>Minute Volume (ml)</th>
<th>Dynamic Compliance (ml/cmH₂O)</th>
<th>Total Pulmonary Resistance (cmH₂O/l. per sec)</th>
<th>Arterial PO₂ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months (during first course of cyclophosphamide)</td>
<td>1900</td>
<td>1200</td>
<td>4·8</td>
<td>26</td>
</tr>
<tr>
<td>9 months (after second course of cyclophosphamide)</td>
<td>2400</td>
<td>1350</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14 months (at completion of course of prednisolone)</td>
<td>1600</td>
<td>1500</td>
<td>10·0</td>
<td>10·0</td>
</tr>
<tr>
<td>19 months (after five months off all therapy)</td>
<td>1800</td>
<td>1600</td>
<td>10·7</td>
<td>10·0</td>
</tr>
</tbody>
</table>

Short Reports

a total of 11 months and though his height and weight remain below the 3rd centiles his rate of growth has subsequently increased. Biopsy of one of the plantar nodules 2 months after stopping prednisolone showed only hyperkeratosis. The results of lung function tests immediately after stopping prednisolone showed that the lungs were no longer stiff but that the airways resistance had increased further. Despite this the arterial oxygen tension had risen to normal levels. Five months later the airways obstruction was less marked (Table). It is now 21 months since the onset of the disease and 10 months since all treatment was stopped; there are no signs of a relapse.

Discussion

The respiratory function tests and the serial chest x-ray suggest that the pulmonary infiltration in this child has now been eradicated.

The clinical course emphasizes the importance of vigorous therapy in this condition. If one antimetabolite drug in combination with steroids fails to produce improvement or, alternatively, if relapse occurs, then a different one should be tried.

In the light of experience gained in treating Hodgkin’s disease (Fairley, 1969), it may be that intensive initial therapy using combinations of more than one antimetabolite and steroids would produce better results.

Summary

The successful treatment of an infant with Letterer-Siwe’s disease using vincristine, cyclophosphamide, and steroids is described. It is suggested that combination therapy using more than one antimetabolite drug might produce better results in this condition.

We are grateful to Dr. U. Shelley, who supervised the care of this child, for permission to publish this report, and to Dr. N. E. France for the interpretation of the skin biopsy.

REFERENCES


C. CHANTLER, A. D. MILNER, and M. H. WINTERBORN


Congenital Hypertrophic Pyloric Stenosis in Phenotypic Female Twins with X/XX Mosaicism

Congenital hypertrophic pyloric stenosis has an incidence of about 1 per 200 (5 per 1000) live male births and 1 per 1000 live female births, with a male to female sex ratio of 5:1 (Carter and Evans, 1969). Its occurrence in both of a set of female twin infants is of interest. To our knowledge, 4 previous reports of pyloric stenosis in female twins have been made (Metракos, 1953; Benson and Lloyd, 1964), but there are no reports of the chromosomes of such patients.

The purpose of this paper is to document the occurrence of pyloric stenosis in a further set of twin female infants, both of whom have X/XX sex chromosome mosaicism.

Case Summaries

Relevant clinical data are shown in Table I. Both infants had symptoms and signs of pyloric stenosis and the diagnosis was confirmed by tumour palpation, radiology, and subsequent operation. Symptoms persisted in spite of formula modification, gastric aspiration before feeds, oral and intramuscular metoclopramide,* and freshly prepared oral atropine methyl nitrate† (given to one infant with severe toxicity, including convulsions). Both infants were submitted to a Fredet-Ramstedt’s pyloromyotomy, after which they progressed well. The subjects were the first children born to a young white Caucasian couple. At the time of the infants’ birth the mother and father were 18 and 20 years of age, respectively, and were unrelated. No history of pyloric stenosis was obtained from the near relatives (parents, grandparents, paternal and maternal sibs, and offspring of paternal and maternal sibs). In spite of dissimilar facial appearance of the infants (Fig.), investigations (Table II) favour development from a single ovum indicating monozygosity.

Cytogenetic Findings

Peripheral blood lymphocytes from the patients (at age 5 months) and their mother were cultured by standard techniques. The mother had a normal female (46,XX) karyotype. Both infants were found to have sex chromosome mosaicism: approximately 66% of the

* Maxolon. Beecham Laboratories.
† Eumydrine. Winthrop Laboratories.