Malignant osteopetrosis: hypercalcaemia after bone marrow transplantation

Dr J R Corrondent 1991;66:639-41

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Dr Skeoch.

abnormalities were no worse, and her osteosclerosis had improved both histologically and radiologically. The graft was intact and of donor origin. She was well, intellectually bright, and attending a preschool for the blind.

Discussion
In this case engraftment was followed by a rapid rise in the calcium concentration, and hypercalcaemia occurred on a number of occasions. A management plan to control the serum calcium concentration during these acute phases and to maintain long term normocalcaemia evolved with experience. In the acute phase the hypercalcaemia seemed to be controlled primarily by a combination of rehydration, intravenous phosphate infusions, and a bisphosphonate. Calcitonin was useful as a maintenance agent but was not completely effective alone.

Phosphate infusions produced a rapid, dose dependent reduction in the serum calcium concentration, which is directly related to the rise in the serum phosphate concentration. The serum phosphate concentrations returned to their pretreatment values within 24 to 36 hours of the infusion. The risk of soft tissue calcification after a phosphate infusion is therefore likely to be short lived. In our patient there was no radiological evidence of soft tissue calcification or of nephrocalcinosis, despite repeated phosphate infusions.

APD is thought to be localised and concentrated in hydroxyapatite, making bone more resistant to osteoclastic activity; to inhibit osteoclast formation from stem cells at low concentration; and to have a direct antiosteoclast effect at high concentrations. It should therefore be an effective drug in the management of hypercalcaemia after bone marrow transplantation for osteopetrosis as it would control osteoclast recruitment and activity. APD has not, to our knowledge, previously been used for this condition. The number of infusions required to regain control of the serum calcium became less with time, presumably reflecting the progressive reduction in total skeletal calcium load. Its long term use might, however, be associated with defects in mineralisation. For this reason salmon calcitonin, given by subcutaneous injection, was used as maintenance treatment. There was an incomplete (but nevertheless clinically useful) response to calcitonin, and at one year after bone marrow transplant the need to suppress accelerated bone remodelling disappeared.

CONCLUSION
Successful engraftment of older children with osteopetrosis is often complicated by severe hypercalcaemia. Acute episodes of hypercalcaemia can be controlled by resalination together with APD given intravenously and a phosphate infusion. The latter, although rapid may introduce a risk of soft tissue calcification and nephrocalcinosis. Salmon calcitonin was useful for maintenance treatment.

We thank Dr SH Ralston for his help and advice.


Genetic aspects of admissions to a paediatric intensive care unit

D R FitzPatrick, C H Skeoch, J L Tolmie

Abstract
Of 821 consecutive admissions to a paediatric intensive care unit, 47 (5.7%) were for chromosomal or monogenic disorders. These patients had more readmissions, longer mean stays, and a higher mortality rate than the group as a whole. In two of the four cases that died of single gene disorders, failure to store DNA made genetic counselling difficult.

In developed countries genetic disorders account for about 6% of the admissions to general paediatric wards. New molecular genetic, cytogenetic, and obstetric techniques offer families the prospect of avoiding recurrences of an increasing number of serious inherited conditions.

The aims of this study were to find out what proportion of the admissions to the paediatric intensive care unit were for the treatment of genetic diseases, and to audit the storage of DNA or tissues that are important for the subsequent counselling of families.

Patients and methods
The intensive care unit at this hospital is a 12 bedded unit and serves the west of Scotland, a population of roughly three million people. It
combines the regional paediatric cardiothoracic unit and the general paediatric intensive care unit. Basic data including length of stay, outcome, discharge diagnosis, and any readmissions were recorded for 821 consecutive admissions to the unit between January 1987 and 31 June 1988. Each patient was assigned to one of five diagnostic categories that were described in a previous study of paediatric hospital admissions. (1) Single gene, chromosomal, or mitochondrial DNA disorders. (2) Multifactorial/polygenic conditions—for example, cleft palate, asthma, most congenital heart diseases, and seizures. (3) Congenital malformations not assigned to category 2—for example, renal anomalies and multiple congenital anomalies syndromes. (4) Familial disorders not included in the above categories—for example, prematurity, malignancy, and near miss cot death. (5) Non-genetic disorders—for example, trauma and infections.

Statistical analysis was by the \( \chi^2 \) test, and a probability of 0.05 was accepted as significant.

**Results**

Of 821 admissions to the unit during the 18 months of the survey, 14 (1.7%) could not be assigned to categories because of lack of information or follow up.

**ADMISSIONS BY CATEGORY**

**Category 1**

Forty seven admissions (6%) were due to clearly genetic disease (table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Genetic disorders for which children were admitted to the paediatric intensive care unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Chromosomal:</td>
<td></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>10</td>
</tr>
<tr>
<td>Ring chromosome 8</td>
<td>8</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1</td>
</tr>
<tr>
<td>Autosomal dominant:</td>
<td></td>
</tr>
<tr>
<td>Malignant hyperpyrexia</td>
<td>6</td>
</tr>
<tr>
<td>Velocardiofacial syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Crouzon’s disease</td>
<td>1</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>1</td>
</tr>
<tr>
<td>Benign familial pemphigus</td>
<td>1</td>
</tr>
<tr>
<td>Autosomal recessive:</td>
<td></td>
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<tr>
<td>Aminioaciduria</td>
<td>16</td>
</tr>
<tr>
<td>Mucopolysaccharidosis</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>2</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic arterial calcification</td>
<td>1</td>
</tr>
<tr>
<td>Congenital cataract</td>
<td>1</td>
</tr>
<tr>
<td>Ataxic telangiectasia</td>
<td>1</td>
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<tr>
<td>X linked:</td>
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<tr>
<td>Geitz syndrome</td>
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<tr>
<td>Chronic granulomatous disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypergammaglobulinaemia</td>
<td>1</td>
</tr>
<tr>
<td>Lowe’s syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

**Category 2**

There were 392 admissions (48%) for multifactorial disorders. Of these 235 (60%) were due to congenital heart disease, the remaining 157 were due to epilepsy (n=60), cleft lip and/or palate (n=29), asthma (n=26), diabetes (n=11), neural tube defects (n=9), scoliosis (n=9), hydrocephalus (n=7), and cerebral palsy (n=6).

**Category 3**

Thirty four children admitted (4%) had congenital anomalies; single malformations occurred in 22 (65%) and multiple abnormalities in 12 (35%).

**Category 4**

Eighty six children admitted (10%) had familial disorders. Of this group 31 (36%) had malignancies, 21 (24%) the sequelae of prematurity, 19 (22%) renal disorders, and 15 (17%) 'near-miss' sudden infant death syndrome.

**Category 5**

There were 248 admissions (30%) for non-genetic disease. Of these 149 (60%) were due to infection, the remaining 99 were due to trauma (n=31), drug ingestion (n=20), surgical abdominal emergencies (n=19), scald or burn (n=11), smoke inhalation (n=8), inhaled foreign body (n=5), non-accidental injury (n=4), and adder bite (n=1).

**LENGTH OF STAY AND OUTCOME (TABLE 2)**

In category 1 there was a significantly higher rate of readmission compared with category 5 \( (\chi^2=20.6, p<0.001) \) and the whole group \( (\chi^2=8.14, p<0.01) \), a longer mean length of stay, and a significantly higher mortality rate than both the whole group \( (\chi^2=5.04, p<0.05) \) and category 5 \( (\chi^2=7.08, p<0.01) \).

**RISKS OF RECURRENT AND COUNSELLING**

The risks of recurrence for the families of the 36 patients (47 admissions, 11 readmissions) with category 1 diagnoses were 1-5% or less in 13 cases (10 new chromosomal aberrations, three presumed new mutations of autosomal or X linked dominant genes); 25% in 19 cases (16 autosomal and three X linked recessive disorders); 50% in two cases (autosomal dominant phenotypes with a positive family history); and unknown in two cases with autosomal dominant conditions in which the parents were not examined.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Number of patients and admissions and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>No of patients</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
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<tr>
<td>2</td>
<td>360</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
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<tr>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>237</td>
</tr>
<tr>
<td>Unclassified</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>738</td>
</tr>
</tbody>
</table>
Seventeen of the 36 category 1 families (47%) had received formal genetic counselling. Of these, four probands had conditions that can be diagnosed prenatally by established techniques. In two of these families, however, failure to store DNA or a fibroblast cell line made this impossible. The disorders in these two cases were Lowe's syndrome (oculocerebrorenal syndrome) and Hurler's syndrome (mucopolysaccharidosis type 1).

Discussion

The incidence of genetic disease in this study (5-7%) is within the range 3-5-7-1% reported in other studies of paediatric inpatients.1 2 Half of the deaths in category 1 were of recessive conditions (two X linked, two autosomal) with risks of recurrence of 25%. The single gene and chromosomal disorders also had a higher rereception rate and longer stay in the intensive care unit. Their prevention thus assumes importance for both affected families and health care planners.

Storage of DNA or cell lines, or both, is recommended for any single defect, mapped or unmapped, so that the diagnosis may be confirmed at a molecular level, and to facilitate carrier detection or prenatal diagnostic tests. 3 As the importance of storing such samples is easily overlooked during resuscitation and stabilisation of a critically ill child it is vital that within any paediatric intensive care unit there is a protocol for appropriate use of genetic diagnostic services. The clinical geneticist is best placed to provide the staff with advice about conditions that can be diagnosed and confirmed by genetic testing, and about sampling techniques and appropriate storage.

Although our study showed that single gene disorders accounted for a small but important proportion of the intensive care unit caseload, it is probably an underestimate. For example, in a recent survey of cases of Reye's syndrome, it was found that in 36% the diagnosis was revised to 'inborn errors of metabolism'. 4 Thus there are almost certainly genetic disorders awaiting delineation that will account for some cases in diagnostic categories such as sudden or 'near-miss' infant death. 5 In the light of this we recommend that all children and infants with unexplained life threatening illnesses that require intensive care should have urine, serum, and whole blood (EDTA) stored at -70°C. Careful consideration should also be given to obtaining a skin biopsy specimen for fibroblast culture, and storing samples of other tissues (such as muscle and liver) at -70°C.

Teratogenic effect of carbamazepine

V Vestermark, S Vestermark

Abstract

A girl was born to a mother who had undergone treatment for epilepsy with carbamazepine during pregnancy. The infant had dysmorphic features and was physically and mentally retarded. We consider that the malformations were the result of the maternal treatment with carbamazepine.

Antiepileptic drugs taken during pregnancy increase the risk of malformations in the offspring, but the teratogenicity is lower if the mothers are on one drug alone rather than a combination. 1 Carbamazepine is generally considered not to be teratogenic, but recently a pattern of malformations among the offspring of mothers treated with carbamazepine alone has been reported. 2

Case report

The mother was 19 years old, para 1, and had been taking carbamazepine alone for more than two years. She had had no epileptic symptoms for the two years before delivery. The serum carbamazepine concentrations were monitored regularly during the pregnancy and were all in the range 3-8 mg/l (therapeutic range 6-11 mg/l). The daily dose of carbamazepine was increased during the pregnancy from 500 to 1700 mg.

A caesarean section was done during week 38, and a dysmature girl was delivered. The birth weight was 2280 g, length 44 cm, and head circumference 34 cm. The Apgar scores were 8 at 1 minute and 10 at five minutes.

The forehead was prominent, and the ears were large but not malformed. The palpebral fissures slanted downwards. The nasal bridge was flat and the nostrils were antverted. The philtrum was normal. The palate was arched and the tongue protruded. There was no hypoplasia of finger or toenails, and the hair was normal. Chromosome analysis was normal. Total skeletal radiography was done when the

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