Acute liver failure induced by carbamazepine

N Hadžić, B Portmann, E T Davies, A P Mowat, G Mieli-Vergani

Abstract

Two children developed acute liver failure while taking carbamazepine. Clinical and laboratory findings suggested an immunological reaction, but only one child improved on steroids. Determination of liver function during the first few weeks of treatment and early detection of signs of idiosyncrasy may prevent this rare but severe complication.

Since 1970, 14·5 million adults and children are estimated to have taken carbamazepine. Unwanted effects mainly or exclusively affecting the liver have been reported in 499 instances, but often other causes of liver damage were not excluded. In about half of these cases alteration in the results of liver function tests was the only abnormality reported (Ciba-Geigy, personal communication). There have been 17 deaths from liver disease, five in children, 1, 2 but in only one of these was carbamazepine the sole hepatotoxin. We describe two children receiving carbamazepine who developed life threatening liver disease.

Case reports

CASE 1

A girl aged 11·6 years developed a severe maculopapular rash, intermittent fever, arthralgia, cough, anemia, anorexia, diarrhoea, and vomiting four weeks after starting carbamazepine (16 mg/kg/24 hours) for focal epilepsy. Her medical history was negative. Carbamazepine was stopped, the blood concentration being 32 μmol/l (therapeutic range: 16–50 μmol/l). Two weeks later she developed jaundice. On admission, six days later, she was pale and jaundiced, with a generalised exfoliative rash, periorbital oedema, generalised lymphadenopathy, and stomatitis. Firm liver and spleen

Sialic acid concentrations in urine and cultured fibroblasts

Patient Controls

<table>
<thead>
<tr>
<th>Urine (μmol/mmol creatinine)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free</td>
<td>994</td>
<td>93, 78</td>
</tr>
<tr>
<td>Bound</td>
<td>109</td>
<td>71, 52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibroblasts (nmol/mg protein)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free</td>
<td>25</td>
<td>2·6</td>
</tr>
<tr>
<td>Bound</td>
<td>17</td>
<td>8·6</td>
</tr>
</tbody>
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Sialic acid concentrations were measured by the thioarbituric acid method before and after hydrolysis.

Discussion

Stevenson et al described two unrelated cases of severe infantile sialic acid storage disease and reviewed five other cases in 1983.4 The main features he identified were coarse facies, growth delay, appreciable mental retardation, hepatosplenomegaly, recurrent pneumonias, and in five, evidence of lysosomal storage with raised free sialic acid in cells and urine. The infant reported here displayed all these features, and she also showed a more pronounced respiratory impairment. Cardiac failure was also prominent, suggesting either a storage disorder of the myocardium, or a response to the respiratory problems. The presence of multiple widespread telangiectasias, presumably related to liver disease, is also a new finding.

The exact role of sialic acid in cellular function is unclear, but it is known to be an important constituent of many glycolipids and glycoproteins. It has been suggested that the underlying defect is impaired transport of free sialic acid across the lysosomal membranes, but the precise defect has yet to be identified.5 Antenatal diagnosis is available by assaying free sialic acid in amniotic fluid or by chorionic villus biopsy.6 Severe infantile sialic acid storage disease should be considered in a child presenting with coarse facial features, growth and developmental delay, hepatosplenomegaly, and evidence of abnormal storage in cells.

We are grateful to Dr AW Boon for allowing us to report his patient.

edges were palpable 6 and 7 cm below the costal margin. Temperature was 38.5°C. Her haemoglobin concentration was 76 g/l; red cell indices, reticulocyte, white cell, platelet, and differential counts were normal, with no eosinophilia; prothrombin time was 20 seconds (control 13 seconds).

Biochemical investigations were as follows (reference range in parentheses). Total bilirubin concentration was 212 μmol/l (20-30) with a conjugated fraction of 198. Activities of enzymes were: aspartate aminotransferase 165 IU/l (<50); γ glutamyl transpeptidase 299 IU/l (<50); and alkaline phosphatase 407 IU/l (<300). Albumin concentration was 31 g/l (35–50) and concentrations of plasma sodium and proteins were normal. Concentration of IgA was normal but IgG, IgM, and IgE were increased (22-3 g/l, 5 g/l, and 30 kU/l (<18, <2-2, and <10) respectively). C3 and C4 complement components were decreased (0·35 g/l and 0·13 g/l (0·55–1·2 and 0·20–0·60) respectively). Autoantibodies were negative. A 99mTc colloid liver scan showed reduced liver uptake, with increased bone and spleen uptake. Bone marrow aspirate contained many plasmacytoid lymphocytes and moderate erythrophagocytosis by macrophages. A specimen taken at liver biopsy, performed 12 days after admission, showed an acute hepatitis, with both portal and parenchymal cell infiltrates rich in plasma cells (fig 1A). After 10 days of supportive treatment (blood and albumin transfusions, oral iron, Ketovite (Paines and Byrne), and intravenous vitamin K) without improvement, she was given prednisolone (0·7 mg/kg/24 hours). This was followed by a dramatic symptomatic and biochemical improvement, although the prothrombin time had already returned to normal before starting steroid treatment (fig 2). She was discharged one week later after complete resolution of symptoms. Her serum bilirubin concentration was 31 μmol/l, γ glutamyl transpeptidase 214 IU/l, and aspartate aminotransferase, alkaline phosphatase, albumin, and prothrombin time were normal. Prednisolone was stopped after 18 days. Three years later the girl is well with normal liver function.

CASE 2
A girl aged 7·8 years presented with fever, generalised maculopapular rash, arthralgia, and lymphadenopathy four weeks after starting carbamazepine (16·5 mg/kg/24 hours). Seventeen days later she developed jaundice, ascites, and generalised oedema. She had had convulsions from the age of 8 months. At 3 years grand mal epilepsy was diagnosed. She received sodium valproate for two months at the age of 7 years, but she had been on no anticonvulsant treatment for four months before starting carbamazepine. On admission she was jaundiced, with generalised peeling maculopapular rash, oedema, and ascites. A firm liver was palpable 3 cm below the costal margin; her spleen was not palpable.

Concentrations of carbamazepine in the blood was 28 μmol/l. Her haemoglobin concentration was 105 g/l with normal white cell, platelet, and differential counts; there was no eosinophilia, and the prothrombin time was 24 seconds (control 15 seconds). Total bilirubin concentration was 236 μmol/l and activities of aspartate aminotransferase 946 IU/l, γ glutamyl transpeptidase 206 IU/l, and alkaline phosphatase 151 IU/l. Ammonia was 94 μmol/l (10–47), total protein 43 g/l, albumin 24 g/l, and plasma sodium 126 μmol/l. IgG was 5·9 g/l (6·5–18),
Acute liver failure induced by carbamazepine

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Abstract

An infant girl with arachnoidactyly, spontaneously resolving contractures, dolichostenomelia, iridodonesis, and mitral and tricuspid incompetence died in cardiac failure. We confirm that congenital contractual arachnoidactyly may exhibit serious cardiovascular and ophthalmic complications like Marfan's syndrome. The presence of iridodonesis further obscures the differentiation between classical Marfan's syndrome and congenital contractual arachnoidactyly.

We thank Dr TK Hanif and Dr DM Cook for referring the patients. NH is a British Council Research Fellow, GMV is supported by the M McCouph Foundation Against Liver Disease in Children.


Addendum

Since this paper was accepted we have admitted and successfully transplanted a 3 year old child who had fulminant hepatic failure due to carbamazepine toxicity.

Contractural arachnoidactyly with mitral regurgitation and iridodonesis

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