Lethal cardiomyopathy in epidermolysis bullosa associated with amitriptyline

S M Taibjee, P Ramani, R Brown, C Moss

There are previous reports of dilated cardiomyopathy (DCM) in recessive dystrophic epidermolysis bullosa (RDEB), a debilitating blistering skin disorder. The pathogenesis of DCM in RDEB remains uncertain, although dietary deficiency of selenium and carnitine have been implicated. A 6 year old girl with RDEB who died of DCM is reported; attention is drawn to the possible role of two potentially cardiotoxic drugs, amitriptyline and cisapride.

Recessive dystrophic epidermolysis bullosa (RDEB) is a chronic debilitating skin disorder characterised by widespread painful blistering and skin fragility. There are previous reports of dilated cardiomyopathy (DCM) and sudden death in RDEB1–4 (see table 1). Many departments, including our own, employ routine echocardiographic screening in this condition. The pathogenesis of DCM in RDEB remains uncertain, although dietary deficiency of both selenium2 and carnitine3 has been implicated. We report a case where amitriptyline, used for chronic pain in epidermolysis bullosa, may have contributed.

CASE REPORT

The affected girl with typical Hallopeau-Siemens RDEB, homozygous for a collagen VII mutation, was described previously (patient 3, Sidwell et al6). She was under the joint care of Birmingham Children’s Hospital and Great Ormond Street Hospital. She suffered severe blistering and failure-to-thrive, her weight persistently below the 3rd centile. A gastrostomy inserted at 18 months of age required removal due to persistent leakage. A second gastrostomy inserted at Birmingham Children’s Hospital.3 However, there was considerable overlap between other RDEB patients attending Great Ormond Street Hospital despite close nutritional supervision did not improve cardiac function. Nutritional deficiency also seems an unlikely cause of DCM in RDEB given the apparent excess of cases of DCM in patients at Great Ormond Street Hospital despite close nutritional supervision, contrasting with the absence of reports of DCM in 15 years’ cumulative data on 3280 EB patients enrolled in the US National EB Registry (Jo-David Fine, personal communication).

In our case, cardiac histology showed no myocardial fibrosis or necrosis, features described in Keshan disease, an endemic cardiomyopathy due to selenium deficiency.1 Iron overload from repeated blood transfusions was previously implicated in a case of DCM in RDEB,5 but excluded in our case by negative iron staining. The lymphocytic infiltrate would be consistent with an inflammatory, infective, or toxic cause. We could not show a viral infection by PCR, and considered other causes of inflammatory myocarditis such as drugs.

Abbreviations: DCM, dilated cardiomyopathy; RDEB, recessive dystrophic epidermolysis bullosa

DISCUSSION

The cause of DCM in RDEB is uncertain. Micronutrient deficiency has been implicated, particularly selenium and carnitine.2,6 Sidwell et al6 reported mean baseline carnitine levels significantly lower in RDEB patients with DCM than in other RDEB patients attending Great Ormond Street Hospital.1 However, there was considerable overlap between the two groups, and baseline selenium levels and overall mean carnitine and selenium concentrations did not differ significantly. The authors also conceded that correction of carnitine and selenium deficiency via gastrostomy replacement did not improve cardiac function. Nutritional deficiency also seems an unlikely cause of DCM in RDEB given the apparent excess of cases of DCM in patients at Great Ormond Street Hospital despite close nutritional supervision, contrasting with the absence of reports of DCM in 15 years’ cumulative data on 3280 EB patients enrolled in the US National EB Registry (Jo-David Fine, personal communication).

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Table 1 Reports of dilated cardiomyopathy in recessive dystrophic epidermolysis bullosa

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Possible aetiological factors cited</th>
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<tbody>
<tr>
<td>Brook et al (1989)*</td>
<td>Case report</td>
<td>Long term transfusion therapy with secondary iron overload</td>
</tr>
<tr>
<td>Melville et al (1996)*</td>
<td>Case series (n=2)</td>
<td>Selenium deficiency</td>
</tr>
<tr>
<td>Sidwell et al (2000)*</td>
<td>Case series (n=6)</td>
<td>Carnitine deficiency</td>
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<tr>
<td>Morelli et al (2001)*</td>
<td>Case report</td>
<td>Viral myocarditis</td>
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Competing interests: none declared

Consent was obtained for publication of the patient detailed in this case report

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“Medicines for Children” states that amitriptyline is not recommended in children less than 6 years old. Above this age, although licensed for nocturnal enuresis, its use in chronic pain remains unlicensed. Tricyclic antidepressants are well known causes of arrhythmia, especially in overdose. However, publications including the Adverse Drug Reactions Online Information Tracking data from the Medicines Control Agency (MCA) show that amitriptyline, even at recommended doses, is also associated with cardiomyopathy, cardiomegaly, and ventricular failure, in some cases reversed by stopping the drug.10 Getz et al report acute myocarditis after introduction of amitriptyline and hydroxychloroquine, responding to withdrawal of these two drugs.10 Marti et al report two patients with DCM listed for cardiac transplantation showing recovery of cardiac function after withdrawal of tricyclics.10 Early reversible sub-clinical myocardial damage was shown in adults taking standard doses of amitriptyline for depression using In-111-monoclonal anti-myosin antibodies.11

Cisapride is cardiotoxic and may cause QT prolongation and serious ventricular arrhythmias. Caution has been advised in patients with pre-existing cardiac disease and with interacting drugs including amitriptyline.12 In July 2000 the product licences for cisapride were withdrawn by the MCA.

In summary, drug induced cardiac toxicity should be considered in patients with RDEB. Amitriptyline, increasingly used for chronic pain in this condition, may cause cardiomyopathy. Cisapride may have contributed to a final arrhythmic insult in our patient.

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