

CASE REPORT

Lethal cardiomyopathy in epidermolysis bullosa associated with amitriptyline

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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 RDEB^{1–4} (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 al*³). 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 3.5 years remained functional until her death.

At times she had documented micronutrient deficiency. At age 3 years plasma selenium was 0.61 µmol/l (0.7–1.7). However, with selenium supplementation, levels as high as 0.8 were subsequently documented. Free carnitine was 9 µmol/l (22–50) and total carnitine 12 µmol/l (26–62) at age 4 years 10 months, but carnitine levels were within the normal range after carnitine replacement was commenced at age 5 years 2 months. Zinc levels fluctuated, with lowest value 7.0 µmol/l (11–24) aged 3 years. Similarly, ferritin varied, with a nadir of <8 µg/l (8–150). Despite iron and folic acid supplements, she remained chronically anaemic, with a typical haemoglobin of 70 g/l, and received 11 blood transfusions in total.

Pain was poorly controlled despite paracetamol and opiates. Amitriptyline was given sporadically before age 4, recommenced at 4 years 10 months at 6 mg *nocte* (0.5 mg/kg), increased to 3.4 mg twice daily (0.5 mg/kg/day) at 5 years 2 months, to 3.4 mg *mane*, 7 mg *nocte* (0.75 mg/kg/day) at 5 years 5 months, and finally to 8 mg twice daily (1.1 mg/kg/day) at 5 years 7 months, continued until her death. For chronic gastro-oesophageal reflux, she received ranitidine, and, from

4 years 8 months until her death, cisapride (highest dose 2.2 mg twice daily).

At 4 years 5 months, a routine echocardiogram was normal. However, at 5 years 10 months, echocardiography showed a moderately dilated left ventricle with reduced systolic function. At 6 years 1 month, she presented with breathlessness. Echocardiography showed deterioration in cardiac function, left ventricular function at only 20%. She was commenced on frusemide and amiloride, but continued to worsen and was admitted a month later to her local hospital with acute dyspnoea and tachycardia. A chest radiograph confirmed massive cardiomegaly. She died the same evening after onset of a suspected tachycardic arrhythmia.

Post mortem, cardiac histology at Birmingham Children's Hospital showed a mild patchy lymphocytic infiltrate with interstitial oedema. Stains for iron and amyloid were negative. There was no evidence of excessive fibrosis or myocyte hypertrophy. Viral PCR on cardiac tissue was negative for adenovirus, cytomegalovirus, enterovirus (including Cocksackie), Epstein-Barr virus, herpes simplex, and parvovirus.

DISCUSSION

The cause of DCM in RDEB is uncertain. Micronutrient deficiency has been implicated, particularly selenium and carnitine.^{2,3} Sidwell *et al* reported mean baseline carnitine levels significantly lower in RDEB patients with DCM than in other RDEB patients attending Great Ormond Street Hospital.³ 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).

In our case, cardiac histology showed no myocardial fibrosis or necrosis, features described in Keshan disease, an endemic cardiomyopathy due to selenium deficiency.⁵ Iron overload from repeated blood transfusions was previously implicated in a case of DCM in RDEB,¹ 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

Table 1 Reports of dilated cardiomyopathy in recessive dystrophic epidermolysis bullosa

Citation	Study group	Possible aetiological factors cited
Brook <i>et al</i> (1989) ¹	Case report	Long term transfusion therapy with secondary iron overload
Melville <i>et al</i> (1996) ²	Case series (n=2)	Selenium deficiency
Sidwell <i>et al</i> (2000) ³	Case series (n=6)	Carnitine deficiency
Morelli <i>et al</i> (2001) ⁴	Case report	Viral myocarditis

“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.^{6–10} Getz *et al* report acute myocarditis after introduction of amitriptyline and hydroxychloroquine, responding to withdrawal of these two drugs.⁶ 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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Consent was obtained for publication of the patient detailed in this case report

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REFERENCES

- 1 Brook MM, Weinhouse E, Jarenwattananon M, *et al*. Dilated cardiomyopathy complicating a case of epidermolysis bullosa dystrophica. *Pediatr Dermatol* 1989;**6**:21–3.
- 2 Melville C, Atherton D, Burch M, *et al*. Fatal cardiomyopathy in dystrophic epidermolysis bullosa. *Br J Dermatol* 1996;**135**:603–6.
- 3 Sidwell RU, Yates R, Atherton D. Dilated cardiomyopathy in dystrophic epidermolysis bullosa. *Arch Dis Child* 2000;**83**:59–63.
- 4 Morelli S, Dianzani C, Sgreccia A, *et al*. Reversible acute global left ventricular dysfunction in a patient with autosomal recessive dystrophic epidermolysis bullosa. *Int J Cardiol* 2001;**79**:321–3.
- 5 Li GS, Wang F, Kang D, *et al*. Keshan disease: an endemic cardiomyopathy in China. *Hum Pathol* 1985;**16**:602–9.
- 6 Getz MA, Subramanian R, Logemann T, *et al*. Acute necrotizing eosinophilic myocarditis as a manifestation of severe hypersensitivity myocarditis. *Ann Intern Med* 1991;**115**:201–2.
- 7 Alexander CS, Nino A. Cardiovascular complications in young patients taking psychosomatic drugs. *Am Heart J* 1969;**78**:757–69.
- 8 Saint-Pierre A, Perrin A, Pouzeratte JP, *et al*. Myocardiopathie chronique induite par l’imipramine. *Coeur Med Interne* 1972;**9**:27–34.
- 9 Cruchaudet B, Eicher JC, Sgro C, *et al*. Reversible cardiomyopathy induced by psychotropic drugs: case report and literature overview. *Ann Cardiol Angeiol (Paris)* 2002;**51**:386–90.
- 10 Marti V, Ballester M, Obrador D, *et al*. Reversal of dilated cardiomyopathy after chronic tricyclic antidepressant drug withdrawal. *Int J Cardiol* 1995;**48**:192–4.
- 11 Marti V, Ballister M, Udina C, *et al*. Evaluation of myocardial cell damage by In-111-monoclonal anti-myosin antibodies in patients under chronic tricyclic antidepressant drug treatment. *Circulation* 1995;**91**:1619–23.
- 12 Medicines Control Agency/Committee on Safety of Medicines. Cisapride: risk of arrhythmias. *Curr Probl Pharmacovigilance* 1998;**24**:11.