Management of oesophageal stenosis in epidermolysis bullosa dystrophica

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SUMMARY Seven patients with epidermolysis bullosa dystrophica and chronic and recurrent oesophageal lesions such as spasm, strictures, and complete occlusion were studied. Dysphagia could be cured with drugs if it was caused by bullae formation or spasm. If oesophageal strictures were present, endoscopy and bouginage with corticosteroid prophylaxis during the quiescent phase of the disease was a safe and useful procedure. We have also given corticosteroids, which reduced the oedema caused by bullae formation and oral phenytoin, which reduced epithelial detachment by inhibiting collagenase activity. Verapamil counteracted oesophageal spasm and pureed food during periods of dysphagia reduced blistering of the upper oesophagus.

Epidermolysis bullosa dystrophica is a group of hereditary mechanobullous disorders affecting both the skin and gastrointestinal mucosa (table). In the recessive type, trauma is followed by a separation of skin at the dermoepidermal junction and at the lamina propria of the mucous membrane, probably because of an increase in mutant collagenase activity.¹ The recessive type can be further subdivided into two forms, localised and generalised, on the electron microscopic appearance of the dermoepidermal junction in non-blistered skin. In the localised form there are recognisable anchoring fibrils below the basement membrane, but they are attenuated in appearance and sparse. In the generalised form (which is clinically more severe) the anchoring fibrils are absent.²

In the recessive type the bullous lesions of the skin

are usually present at birth and they quickly spread to affect the skin and mouth. Healing is slow, with chronic scarring that leads to digital fusion (syndactyly) and flexion contractures of the fingers and toes. The mucosa of the mouth, pharynx, and oesophagus is often affected. Oesophageal problems develop insidiously and are caused by bullae formation, ulceration, and oedema, which ultimately lead to stricture formation that may in turn cause complete oesophageal obstruction with regurgitation of blood stained secretions.

In the dominant form of epidermolysis bullosa dystrophica the skin disease is milder, but patients may develop tight webs in the upper oesophagus. These develop several years later than in the recessive type.

In this paper we describe our experiences over a

Table Ultrastructural abnormalities in epidermolysis bullosa dystrophica with oesophageal disease

Disease	Specific structural defect	Clinical signs
Recessive epidermolysis bullosa dystrophica:		
Generalised	Separation below basal lamina	Oesophageal stricture always found
Localised	Absence of anchoring fibrils and collagenolysis	Oesophageal stricture and webs often seen
	Variable decrease of anchoring fibrils and collagenolysis	
Dominant epidermolysis bullosa dystrophica:		
Cockayne-Tauraine	Separation below basal lamina	
	Anchoring fibrils decreased and abnormal in skin that blisters easily	
Albopapular	Anchoring fibrils abnormal and decreased in all skin areas	Oesophageal webs

period of 17 years with the medical and surgical management of patients with epidermolysis bullosa dystrophica who also have serious oesophageal complications. We describe seven cases to illustrate the clinical course of the oesophageal lesions and the response to treatment. Six patients had the recessive type (four localised and two generalised), and one had the dominant type. Cineoesophagograms were carried out in all patients with particular attention to the posterior pharynx and upper oesophagus to avoid missing the oesophageal webs that indicate a more favourable prognosis. Radiological follow up studies provided new information with aetiological and therapeutic implications.

Case reports

LOCALISED RECESSIVE EPIDERMOLYSIS BULLOSA DYSTROPHICA

Case 1

A boy aged 17 was diagnosed as having the localised recessive type at birth. After the first week of life he had extensive oral ulceration requiring nasogastric feeding. At the age of 1 year he developed acute dysphagia, and a cineoesophagogram showed a thin web at the cricopharyngeal level. Endoscopy with steroid prophylaxis was carried out with great difficulty because of microstomia and oral ulceration though the stricture was easily dilated to 20 G with Chevalier Jackson rubber bougies.³ After seven months he again developed dysphagia and required further dilatation, which was performed in two stages. He was then given oral phenytoin, which he was still taking at the time of writing.

He required no further dilatations until the age of 11 when he developed acute obstruction secondary to impaction of food. Two similar episodes of acute obstruction occurred at the ages of 12 and 15 years, and both required oesophagoscopy and dilatation.

Case 2

A boy aged 14 was diagnosed as having the localised recessive type at 3 weeks of age; at the age of 10 months he was started on oral phenytoin. At the age of 2 years he had a haematemesis, and a barium swallow examination showed extensive mucosal ulceration in his mid oesophagus. His symptoms responded to a short course of steroids.

At the age of 6 he developed chronic dysphagia that worsened over a period of three months despite repeated courses of steroids. Barium studies showed a tight stricture in the mid oesophagus. He underwent dilatation to 27 G and was able to drink the same day. He required another dilatation two months later and remained free of symptoms for six

years. At the age of 12 he again developed dysphagia and required two dilatations one week apart.

Case 3

A girl aged 8 had the localised recessive type diagnosed at the age of 4 months, and was started on oral phenytoin at the age of 2. At the age of 3 she presented with episodes of distressing nocturnal dysphagia that lasted about 90 minutes each and ended with a haematemesis. On admission her haemoglobin concentration was 60 g/l and she required transfusion. A cineradiograph showed a tight stenosis in the upper third of the oesophagus (fig 1). This was dilated to 22 G after treatment with prednisone. She required another dilatation three months later.

At 4 years of age she again developed recurrent dysphagia, usually at night, which was not relieved by a course of steroids. Radiographically she had a tight stricture of the mid oesophagus (fig 2). This was fully dilated to 28 G in two stages four months apart; although this relieved the dysphagia during the day it did little to reduce the frequency of the nocturnal episodes. It was thought on clinical grounds that these were partly the result of disturbed oesophageal motility and spasm precipitated by nocturnal gastro-oesophageal reflux, although reflux could not be shown by scintigraphy. The reported ability of calcium channel blockers to inhibit the contractions in normal human oesophagus and relieve the symptoms of nutcracker oesophagus prompted us to use oral verapamil in our patient, beginning with a single nightly dose of 40 mg; her nocturnal dysphagia ceased immediately, confirming that her symptoms were the result of oesophageal spasm. She had two further episodes of acute obstruction when she was 6 and 8 years old, both of which needed endoscopy and dilatation.

Case 4

A 9 year old girl had the localised recessive type diagnosed when she was 2 days old. At the age of 4 months she developed dysphagia when fed semisolid food. In the next seven months she had two episodes when she vomited casts of oesophageal mucosa. These were followed by prolonged complete dysphagia that responded to treatment with prednisone.

She remained asymptomatic until she was 6 years old, when her dysphagia recurred. Radiological examination of the oesophagus showed a mid oesophageal stricture and she was admitted to hospital for treatment with corticosteroids and oesophageal dilatation. She was drinking and eating a soft diet one day after operation.

Fig 1 Long stricture of cervical oesophagus in a 3 year old girl with severe dysphagia.

Fig 2 Short stricture of mid oesophagus in a 4 year old patient with persistent bullous lesions of the oesophagus.

GENERALISED RECESSIVE EPIDERMOLYSIS BULLOSA
DYSTROPHICA

Case 5

A girl aged 4 years was first diagnosed as having the generalised recessive type at the age of 2½ years when she was first seen at this hospital. She spent 67

weeks in hospital during the first two years of life with recurrent skin infections, chest infections, chronic anaemia, and failure to thrive. At the age of 3½ years she had dysphagia, which was attributed to oropharangeal ulceration as barium studies had been reported as normal. One year later her dysphagia worsened so that she had to be main-

tained on a semiliquid diet. At the age of 4 years she was admitted to hospital because her general condition had deteriorated and there was radiological evidence of a tight oesophageal stricture just above the carina. Treatment with corticosteroids did not improve the dysphagia so oesophageal dilatation was carried out under general anaesthesia. The stricture was dilated to 18 G without any difficulties. Postoperatively she initially made a good recovery, her condition was stable, and she drank a small amount of water. Five hours later she drank 300 ml of milk, and nine hours later suddenly collapsed, became pulseless, apnoeic, and died in spite of attempts at resuscitation. At necropsy a perforation of the lower oesophagus was found with a large amount of gastric contents within the peritoneal cavity, and her heart was enlarged.

Case 6

A boy aged 5 was diagnosed as having the generalised recessive type at birth. He was started on treatment with oral phenytoin at the age of 4 years 10 months. He had severe oral ulceration and tongue tethering that caused chronic dysphagia. He was investigated at this hospital at the age of 4, and a subcricopharyngeal web was diagnosed on oesophagogram. Six months later his dysphagia increased for two weeks. A tight, long stricture in the upper oesophagus was dilated with difficulty to 20 G. After the experience with case 5 distal oesophagoscopy was not attempted. The stricture was electively dilated again six weeks later to 27 G.

DOMINANT EPIDERMOLYSIS BULLOSA DYSTROPHICA

Case 7

A girl aged 14 was born with bullous lesions affecting all four limbs but the dominant form of the disease was only diagnosed at the age of 18 months. From the age of 8 years she had dysphagia caused by solid food that increased over the next two years until she could only swallow pureed food. At the age of 10 years she had an episode of aspiration pneumonia. Radiological examination of the oesophagus showed a cricopharyngeal web.

At the age of 11 she had an acute obstruction at the level of C6 by a bolus of meat, which passed spontaneously. Because of these complications she was admitted to hospital for oesophageal dilatation. This was accomplished without difficulties but had to be repeated three times in the next three years.

Discussion

Oesophageal disease in recessive epidermolysis bul-

losa dystrophica is the most serious complication after the first year of life. Barium studies of the oesophagus in the early stages show non-specific inflammatory changes—mucosal oedema, superficial ulceration, and areas of inconstant spasm.⁴ As diffuse inflammatory changes progress to scarring, motility disturbances become more pronounced. Oesophageal trauma leads to stricture formation, which occurs most commonly in the upper third (50%) followed by the lower third (25%). Once strictures have formed they are permanent, and the patients are at risk of developing complete occlusion of the lumen of the oesophagus by a food bolus trapped at the site of the stricture. Oesophageal stenosis and obstruction may therefore eventually become the central problem for these patients, and lead to severe malnutrition, refractory anaemia, and (as in case 5) to aspiration pneumonitis.

In all our patients, when there were symptoms of severe obstruction, we often found it difficult to know whether the obstruction was caused by bullae, spasm, or stricture; radiological examination during the acute period did not always help to differentiate between them. Treatment at this stage was therefore symptomatic and aimed at decreasing the formation of oesophageal bullae and preventing aspiration of food and secretions. All our patients with the recessive type had moderate to severe malnutrition and case 3 had profound anaemia as a result of blood loss. High doses of corticosteroids (prednisone 2.5 mg/kg or the equivalent given intravenously as hydrocortisone) were effective in decreasing dysphagia, usually within 48 hours. Doses of steroids were gradually reduced over a two week period after the symptoms had subsided. Oesophageal dilatation was undertaken when the dysphagia failed to respond to medical treatment. In all our patients with chronic dysphagia, dilatation was carried out only when the skin disease was sufficiently quiescent.

We have performed 23 oesophageal dilatations in seven patients with epidermolysis bullosa dystrophica. Four were for acute obstructive symptoms (case 1), which required immediate intervention, and 19 were for increasingly incapacitating dysphagia caused by stricture formation. All the patients with the recessive type were taking phenytoin, which was maintained at a plasma concentration of 10 µg/ml. Clearly the drug has proved to be effective in the treatment of the skin lesions,⁵⁻⁷ and it seems to be most beneficial in young patients at the time of the onset of their oesophageal symptoms. It was clear from our results that phenytoin was less effective when given at the time of dilatation of strictures.

The dilatations were performed through a rigid

oesophagoscope using Chevalier Jackson rubber tipped dilators. The general anaesthetic technique has been described previously.^{8,9} Induction was by inhalation, either by mask or head box, and the endotracheal tube was held in place throughout the whole procedure. There were no tracheal problems postoperatively. The death of case 5 resulted from a cardiac arrest due to rupture of the weakened oesophagus. The incidence of perforation of the oesophagus during endoscopy is low, and this usually manifests itself by shock, dyspnoea, and chest or abdominal pain. The management is operative and usually successful.¹⁰ In this patient the cardiac arrest was caused by the added shock of peritonitis on a diseased myocardium. After this we modified our technique in patients with generalised disease, and only dilated the stricture, making no attempt to visualise the distal oesophagus. With the exception of that case there were no other complications. All patients were on full oral feeding by the next morning and were fit for discharge that day. Postoperatively as much normal solid diet as could be tolerated was encouraged to help maintain the dilatation.

One child experienced episodes of oesophageal spasm that were precipitated by gastro-oesophageal reflux and that responded immediately to oral verapamil.¹¹ This drug, a calcium channel blocker, is a potent inhibitor of oesophageal spasm and has brought relief to this patient for the past two years.

The natural history of oesophageal disease in our patients was stricture formation beginning at about the age of 2 years that required several dilatations over a period of months, followed by a few years of quiescence that was possibly due to treatment with phenytoin. Disturbances of oesophageal motility occurred in all patients, but in case 4 they were a serious problem and successfully managed with verapamil. This is the first report that we know of the use of this drug in the treatment of epidermolysis bullosa dystrophica.

A review of published reports shows that some authors were reluctant to recommend endoscopy and bouginage because of fear that tangential shearing forces could cause further mucosal damage.¹² Feurle *et al* report the use of inflatable dilator balloons that produce vertical pressure that seems to be less traumatic.¹³ The difficulty of using this technique in children is the need for the patient to swallow a bead fixed to a string that serves as a guide for the balloon. It may, however, be necessary to use a balloon dilator introduced over a guide wire to keep the area of stricture open once it has been dilated at endoscopy.¹⁴

Colonic interposition has been carried out in a limited number of patients for whom eating had

become a serious problem.¹⁵ Harmel used a reversed gastric tube constructed from the greater curvature of the stomach in one patient.¹⁶ These operations should be reserved for patients with extensive mucosal lesions or those in whom dilatation has caused mucosal injury and aggravated the dysphagia. Although colonic interposition has been used successfully to relieve dysphagia in these patients it is an operation with considerable morbidity—for example, anastomotic leaks and strictures that require further dilatation and cause inconvenience by lengthening the hospital stay. There is also a risk of cancer in the bypassed oesophagus that cannot be seen either radiologically or endoscopically.

The aim of this paper was to report our experience with the medical management of oesophageal lesions in patients with epidermolysis bullosa dystrophica. Treatment in the acute stage was aimed at decreasing bullae formation by treatment with high doses of prednisone. Motility disturbances were effectively managed with verapamil. Our report clearly showed that dilatation of acute and chronic strictures was successful and rewarding for our patients with incapacitating dysphagia. We feel that this procedure has an important role in the management of such children, and compares favourably with colonic interposition.

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