CASE REPORT

Newborn with severe epidermolysis bullosa: to treat or not to treat?

Martin Lehmann Boesen,¹ Anette Bygum,² Jens Michael Hertz,³ Gitte Zachariassen⁴

¹Department of Paediatric, Hospital of Southern Denmark, Aabenraa, Aabenraa, Denmark
²Department of Dermatology and Allergy Center, University Hospital of Odense, Odense, Denmark

³Department of Clinical Genetics, University Hospital of Odense, Odense, Denmark
⁴Neonatal Intensive Care Unit, HC Andersen Child Hospital, Odense, Denmark

Correspondence to

Martin Lehmann Boesen,
 lehmannboesen@gmail.com

Accepted 11 April 2016

SUMMARY

Epidermolysis bullosa (EB) is an inherited skin disease with four main subtypes that cannot be distinguished clinically at birth. All subtypes may present with widespread life-threatening blisters and fragile skin, making treatment and handling of the newborn with EB challenging. The prognosis of EB depends on the subtype, and therefore maximum treatment is necessary until the final diagnosis is known. In this case, it took 2 weeks before a final diagnosis was reached. In the meantime, we had several ethical discussions on the treatment level. The most important issues were management of pain and nutrition. For immediate pain relief, intranasal fentanyl worked best and gabapentin was successfully used for chronic pain. The feeding difficulties were handled first by a nasogastric feeding tube. Later a normal feeding bottle proved to be adequate.

erosions evolved. Within 30 min, he was transferred to the neonatal intensive care unit (NICU) for pain and intravenous fluid treatment. A diagnosis of EB was suspected (figure 1).

At birth, the skin on the baby's chest and abdomen was erythrodermic with blisters. Around the joints on the extremities the skin was easily peeled off when touched, leaving moist erosions, which bled easily. Four natal teeth (two incisors and two molars) present were removed. The child's nails were long and dystrophic.

A local dermatologist performed a diagnostic skin biopsy for immunofluorescence mapping, and the staff from the department of dermatology took care of bathing the child and dressing his wounds.

BACKGROUND

Epidermolysis bullosa (EB) is a severe inherited skin disease with separation of the dermal epidermal component of the basal membrane.¹ There are four subgroups: Kindler syndrome, epidermolysis bullosa simplex (EBS), dystrophic epidermolysis bullosa and junctional epidermolysis bullosa.² The prognosis for each subtype is very different, ranging from a normal life span with only minor skin affection, to death in the neonatal period, with severe skin affection.³ The individual subtypes cannot be distinguished clinically at birth, and all subtypes may present with severe life-threatening blistering and variable mucosal involvement. The handling of the newborn, until a final diagnosis and prognosis is assured, is a challenging and difficult time with severe ethical dilemmas, both to the family and healthcare professionals.⁴ The ethical questions on life and 'quality of life' are difficult but important when dealing with these dilemmas. These questions and discussions are necessary in the management of the patient and the family.

We want to share this case for the benefit of future patients, as we gained useful experience on early EB management with a focus on pain therapy started immediately after birth, handling of the ethical dilemmas and addressing how to reduce blood transfusions.

CASE PRESENTATION

A baby boy was born at term after an uncomplicated pregnancy. He presented with severe skin blistering and was apparently in pain, crying more than normal. When handled, new blisters and

Figure 1 Clinical photo of the child shortly after birth.

To cite: Boesen ML, Bygum A, Hertz JM, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214727

Obtaining a final diagnosis was expected to take 3 weeks or more, which meant a lot of speculations about the diagnosis, prognosis and future. Ethical considerations on treatment and quality of life arose among the healthcare professionals and the mother, who was a single parent.

Handling was painful for the baby and the fragile skin became eroded with new blisters formed. Even normal hygiene procedures such as changing of diapers became a troublesome event, which made healthcare professionals reluctant to nurse the boy. Some of the healthcare workers also found the smell of his skin unpleasant. After starting wound dressings, some pain relief was seen, but further pain relief was necessary. Paracetamol and morphine worked insufficiently and increased dosing of morphine led to respiratory failure treated with naloxone. After this episode, new ethical discussions on the level of treatment were taken. The paediatricians discussed the ethical dilemmas with a paediatric ethical committee at another university hospital, and the involved persons agreed that the situation was very difficult. At the age of 1 week, the paediatricians assessed that treatment in this case was hopeless. The dermatologists, on the other hand, focused on possible improvement over years and referred to two former patients diagnosed with EB during the past 20 years. At the department of paediatrics, it was decided that a medical ventilator was not an option if respiratory failure should occur within the first months of life. This decision was taken following the guidelines from the National Board of Health.⁵

Similarly to the healthcare personnel, the mother had challenges in handling her child. She was encouraged to take as much care of her son as possible with a focus on his neuropsychological stimulation. Unfortunately, the mother was a single parent and also had to take care of another son, a 3-year-old, at home. Nurses on shifts resulted in constant changes in adult contact with the patient. Light and sound entertainment was brought to his room at the NICU to increase stimulation and for entertainment of the child. Gradually, the mother took more care of the boy, and began to accept the situation and provide as much care as she possibly could. Within 6 weeks, she was handling all the feeding and diaper changes during the daytime, and also assisted in his daily bathing procedures and changes of wound dressings.

INVESTIGATIONS

Indirect immunofluorescence staining was performed with 17 antibodies on a skin biopsy and the result was consistent with EBS. Two intraepidermal splits were found in the granular and basal layers. Diagnosing EBS can be made by histology on skin biopsies but at the time of investigation the clinical team chose to only take one biopsy due to the risk of infections, and this biopsy was used for immunofluorescence.

Molecular genetic analysis by direct sequencing of DNA extracted from peripheral blood lymphocytes from the proband identified a *KRT5* sequence variant: c.1429G>A; p.(Glu477Lys) in heterozygous form. This missense mutation has previously been reported in 2 (both sporadic) of 10 cases with generalised severe EBS.⁶ The parents of the proband were both clinically unaffected and, as most cases of EBS are autosomal dominant, this case was most probably sporadic. The sequence variant was not present in DNA from the mother, but a blood sample for molecular genetic analysis from the father for the familial *KRT5* mutation was not available.

EBS can be caused by mutation in either *KRT5* or *KRT14*, thereby disturbing the normal K5/K14 keratin filament assembly.⁷

TREATMENT

In the NICU, an umbilical catheter was placed in order to provide the child with intravenous saline to prevent dehydration from extended evaporation from the skin. The catheter lasted for 2 weeks, after which it was almost impossible to regain intravenous access.

Pain treatment

Initially, paracetamol and morphine were used but proved insufficient; phenobarbital was then introduced. As the child developed tolerance to morphine, he was changed to methadone and ketamine. Before bathing and skin care, which was apparently painful, he was treated additionally with midazolam and ketamine. Later, the preprocedure treatment was optimised with intranasal fentanyl.

At the age of 2 months, oral gabapentin was introduced in order to replace the phenobarbital and methadone, as this combination heavily sedated the child. For 7 weeks during this transition, he had to be treated with clonidine due to abstinences. At discharge (21 weeks old), gabapentin 4 mg/kg daily was the primary pain medication dosed in three divided doses. Paracetamol was administered before painful procedures. See table 1.

Nutrition and feeding

Initially, the baby was fed on his mother's milk, using a nasogastric tube, and he was orally stimulated by short time breastfeeding. In a 2-week period he also received intravenous glucose and saline through his umbilical catheter. During hospitalisation, when fed his mother's milk, he developed diarrhoea and did not gain weight. He was changed to Pregestimil (Mead Johnson) and later to Infatrini (Nutricia), which made him gain weight. At discharge, when he was 6 months old, he was bottle fed with

Table 1 Showing pain medication over time

Week	Medication on a daily basis	Medication for procedures
1	Morphine Paracetamol Methadone Phenobarbital	Morphine only used 1st week
2	Morphine phasing out and dc during 2nd week Ketamine (rp)	Fentanyl 1.5 µg (nasal) Midazolam Ketamine
3	Ketamine (dc)	
8	Gabapentin (rp) 2 mg/kg (one dose) Phenobarbital phasing out	
12	Methadone phasing out Phenobarbital (dc) Paracetamol (dc)	Paracetamol (rp)
13	Clonidin (rp) due to abstinences	
17		Ketamine (dc) Midazolam (dc)
20	Clonidine (dc)	
21 at discharge	Gabapentin 4 mg/kg (on 3 doses) Methadone 1.1 mg×2, phasing out	*Paracetamol 48 mg
28 at home	Methadone (dc)	Fentanyl 20 µg nasal (dc)
1 year	Gabapentin 4 mg/kg on 3 doses	*Paracetamol 48 mg
2 years	None	None

All medications orally/through nasogastric tube except fentanyl.

*Only at the dermatological department when bathing and dressing. dc, discontinued; rp, new.

Infatrini and water and the nasogastric tube could be removed. Two months after discharge he began on a normal diet for age.

Infections

When he was 3 days old, the child had an infection with elevated infection parameters and neutropenia. He was successfully treated with ciprofloxacin administered through an umbilical catheter. After this infection, amoxicillin was given orally for 3 days.

Blood samples

Only a few blood samples were taken during this patient's admission; these revealed anaemia and hypoalbuminaemia, which was accompanied by periorbital oedema. A single blood transfusion and two transfusions with human albumin 20% were performed through a scalp vein catheter. Intramuscular erythropoietin (EPO) was administered twice weekly until the age of 9 months, which made further blood transfusions unnecessary.

Skin therapy

During the first days of life, the child was treated with open exposure in a humid incubator. When moving his extremities the skin became eroded with blistering, requiring him to be wrapped with non-adhesive dressings (Mepilex) and tubular bandages. From the age of 2 weeks, he was bathed initially in physiological saline. As his skin became malodorous, this was changed to a weak solution of potassium permanganate (one-fourth of usual solution).

OUTCOME AND FOLLOW-UP

Two weeks after birth, the baby was diagnosed with EBS, generalised severe (formerly called Dowling Meara) based on the clinical picture and skin biopsy. He was discharged at the age of 6 months. Personal assistants, and counselling and training of the child by physiotherapists and ergo therapists, supported his mother in caring for the child. At the time of writing, the boy is 2-years-old and has no need for medical pain relief. According to his mother, he does have episodes of pain, especially when bathing and, at times, during play.

He is seen regularly in the outpatient clinic at the department of paediatrics and the department of dermatology. He has achieved normal weight, length and head circumference, and seems normal in his psychological development but delayed in his neuromotor development (figure 2). At the time of writing, he walks as expected of his age but in future he might experience motor difficulties due to contractions.

DISCUSSION

EB is a rare disease and, at our university hospital, with an uptake area of 1.2 million inhabitants, only 2 patients have been diagnosed with EBS generalised severe (Dowling Meara) during the past 20 years. The incidence in Denmark has earlier been estimated at 1/300 000.⁸

The uncertain outcome and crying of a child in pain is stressful for both the mother and healthcare professionals, calling for special handling and treatment. The collaboration between the department of dermatology—having special knowledge on diagnosing and skin management of EB—and the NICU, was essential in this case. International help was sought in the UK from 'Best Practice Guidelines for Skin and Wound care in EB',⁹ published in 2012, which provided good knowledge and ideas on the daily care for the child, including placement of the nasogastric tube. Many of these recommendations have been published as multicentre consensus recommendations by El Hachem *et al.*¹⁰

Figure 2 Clinical photo of the child at 6 months.

Pain management was difficult but important in this case. Inspiration was found in the literature where oral ketamine and midazolam was recommended, but also at a risk of long time consequences.^{11 12}

For immediate pain relief, intranasal fentanyl proved to be successful. It was easy to administer, had instant effect and was harmless to the skin. With this drug, the procedures became bearable to the child, mother and healthcare professionals at the department of paediatrics. However, the child seemed rather sedated, which compromised contact.

Learning points

- ▶ Pain relief and nutrition are essential in treating a newborn infant with generalised epidermolysis bullosa (EB).
- ▶ Keep encouraging the family to be the main caregiver for the child even if the child is severely sick.
- ▶ Use an interdisciplinary approach to these difficult-to-treat patients.
- ▶ Have ethical discussions and write down decisions.
- ▶ Use EPO to reduce the necessity of blood transfusion, which are very traumatic when dealing with generalised EB.

Taking care of the child's pain and nutrition also helped the mother to be more at ease with the situation, and she accepted the uncertainty of the prognosis. Also, morale improved among the healthcare professionals, and they were better able to support the mother—especially after gabapentin was initiated and the boy did not have pain. Even though she was a single parent with two children, the mother became the primary caregiver for this very sick child during his admittance to the hospital and certainly after hospital discharge.

Contributors MLB drafted the initial manuscript and has been in contact with the parent. GZ was the main contributor on the paediatric field. AB contributed mainly on the dermatological aspects and JMH on the genetic aspects. All four authors reviewed the entire case report in depth and contributed with their points of view on what the important aspects are in this case. The final manuscript was approved by all four authors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Sawamura D, Nakano H, Matsuzaki Y. Overview of epidermolysis bullosa. *J Dermatol* 2010;37:214–19.
- 2 Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the third international consensus meeting on diagnosis and classification of EB. *J Am Acad Dermatol* 2008;58:931–50.
- 3 Yuen WY, Duipmans JC, Molenbuur B, et al. Long-term follow-up of patients with Herlitz-type junctional epidermolysis bullosa. *Br J Dermatol* 2012;167:374–82.
- 4 Gonzalez ME. Evaluation and treatment of the newborn with epidermolysis bullosa. *Semin Perinatol* 2013;37:32–9.
- 5 The National Board of Health. <https://www.retsinformation.dk/Forms/R0710.aspx?id=141135> The complete Danish guidelines.
- 6 Stephens K, Ehrlich P, Weaver M, et al. Primers for exon-specific amplification of the KRT5 gene: identification of novel and recurrent mutations in epidermolysis bullosa simplex patients. *J Invest Dermatol* 1997;108:349–53.
- 7 Titeux M, Mazereeuw-Hautier J, Hadj-Rabia S, et al. Three severe cases of EBS Dowling-Meara caused by missense and frameshift mutations in the keratin 14 gene. *J Invest Dermatol* 2006;126:773–6.
- 8 Frangu M, Gedde-Dahl T Jr, Verder H. Epidermolysis bullosa simplex Dowling-Meara. *Ugeskr Laeg* 2006;168:4222–4.
- 9 Denyer J, Pillay E. Best practice guidelines for skin and wound care in Epidermolysis Bullosa. International Consensus. DEBRA, 2012.
- 10 El Hachem M, Zambruno G, Bourdon-Lanoy E, et al. Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. *Orphanet J Rare Dis* 2014;9:76.
- 11 Norambuene C, Yañez J, Flores V, et al. Oral ketamine and midazolam for pediatric burn patients: a prospective, randomized, double-blind study. *J Pediatr Surg* 2013;48:629–34.
- 12 Bredlau AL, McDermott MP, Adams HR, et al. Oral ketamine for children with chronic pain: a pilot phase 1 study. *J Pediatr* 2013;163:194–200.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow