Case Report

The medical and ethical challenges of extremely low birth weight infants with severe comorbidity: a case report of a 26 weeks old neonate with Maple Syrup Urine Disease

Phebe Debouver [a], Lara Garabedian [b], Patrick Verloo [c], Annelies Keymeulen [b]

[a] Department of Pediatrics, Ghent University Hospital, Ghent, Belgium
[b] Department of Neonatology, Ghent University Hospital, Ghent, Belgium
[c] Department of Pediatric Neurology and Metabolic Disorders, Ghent University Hospital, Ghent, Belgium

phebe.debouver@uzgent.be

Keywords

Case Report; Ethics; Extremely Low Birth Weight; Maple Syrup Urine Disease; Prematurity

Abstract

Infants born extremely preterm or with extremely low birth weight (ELBW) are at high risk of death and severe morbidity. We present a patient born at 26 weeks' gestation with severe intrauterine growth restriction (IUGR) and Maple Syrup Urine Disease (MSUD). The need for enteral feeding in MSUD patients and the practical and medical infeasibility of performing hemodialysis in our ELBW neonate substantially decreased therapeutic options. If severe comorbidity further complicates the care for ELBW infants, therapeutic options might be limited. Ethical considerations need to be taken into account when deciding on the best outcome for the individual neonate.

Introduction

Despite technological advances and efforts of child health experts over the last decades, extremely preterm infants (i.e., those with gestational age less than 28 weeks) and extremely low birth weight infants (ELBW; birth weight less than 1000 grams) remain at high risk for death and disability with 30–50% mortality and, in survivors, at least 20–50% risk of morbidity (1). Currently, some extremely preterm infants survive from 22 weeks' gestation. However, the risk for longer-term neuro-disability including cerebral palsy and severe cognitive impairment is significant (2). When infants born extremely preterm or with ELBW are diagnosed with a co-existing congenital anomaly, this has an enormous impact on their already compromised prognosis. In these situations, caregivers are confronted with supplementary therapeutic challenges, ethical problems and a difficult counseling of the parents. To our knowledge, we present the first case of an ELBW infant with Maple Syrup Urine Disease (MSUD). Below, we will discuss the medical and ethical difficulties encountered in this case.

Case presentation

At 26 weeks' gestation, an urgent caesarean section was performed in a 23-year old woman with sudden vaginal blood loss due to retroplacental hematoma. Ultrasound monitoring revealed severe intrauterine growth restriction (IUGR) with end-diastolic block and suboptimal cardiotocogram. No previous ultrasounds were available since the pregnancy was unmonitored. Because of the prognostic impact of IUGR accompanying severe prematurity, urgent prenatal counseling was performed. During counseling, both parents expressed their wish for maximal beneficial intervention.

Prenatal lung maturation was initiated but incomplete. Birth weight of the female infant was 475 grams (third percentile). Heart activity at birth was sufficient but intubation and invasive ventilation were needed due to severe respiratory distress syndrome. Clinical Risk Index for Babies II score (CRIB II) was 12, which corresponds to a predicted death rate of 25.4%. Hemodynamic support with dobutamine, dopamine and norepinephrine was initiated. A single dose of dexamethasone was given with short, refractory result. Antibiotic treatment was commenced on day seven after a rise of infection parameters. Brain ultrasound performed on a daily basis from the first until the fifth day of life revealed severe immaturity with bilateral intraventricular hemorrhage. Hypoglycemia up to 33 mg/dL on the first day of life urged an increase in carbohydrate intake via total parenteral nutrition (TPN). Hyperbilirubinemia required phototherapy and the initial hypernatremia as seen in extreme prematurity was followed by the need for sodium, potassium and phosphorus supplementation. Minimal enteral feeding was initiated on day two, supplemented with TPN as the main caloric source. On day 14, while still receiving invasive ventilation and hemodynamic support, our patient's blood spot screening test revealed elevated leucine and valine levels. Plasma analysis in our laboratory confirmed a leucine level of 3482 mcmol/L (45-263 mcmol/L) and a valine level of 384 mcmol/L (92-326 mcmol/L), suggestive of MSUD. Therefore, dietary measures were commenced and oral feeding was provided through amino acid supplementations free of branched-chain amino acids (BCAAs) with strict carbohydrate index calculation (10-12 mg/kg/min). To promote an anabolic state, glucose and insulin infusions were administered guided by frequent screening for ketonuria. Thiamine supplementation was started. Since our patient was not diagnosed on clinical grounds, no urinary organic acid analysis was performed. Lactate levels were mildly elevated (maximal value of 3.45 mmol/L). From day seven onwards, brain ultrasound showed increasing hyperintensity of the deep nuclei, presumably due to brain edema caused by MSUD. On day 17, increasing brain edema and refractory hypotension with anuria emerged. In absence of any curative perspective, the option of palliative care was discussed with the parents. Because they firmly expressed their wish for continued maximal support, the team of neonatologists decided to continue but not to further expand life-sustaining treatment and not to perform reanimation (DNR 2). On day 18, our patient deceased as a result of bradycardia and increasing hypotension resulting in asystole. Gene panel analysis of our patient and both consanguineous parents later revealed a homozygous nonsense variant in the *DBT* (dihydrolipoamide branched chain transacylase E2) gene, which is seen in MSUD (type II).

Discussion

The well-known inverse relationship between gestational age at birth and morbidity among survivors has been well established (1,2). In 2009, a national framework was published by the British Association of Perinatal Medicine (BAPM) to support extremely preterm birth perinatal care decision-making.

The framework indicated active treatment should not normally be attempted below 23 weeks' gestation and should be attempted from 24 weeks onwards unless severe infant compromise was anticipated. A revised 2019 BAPM Framework for Practice recommends that Active Treatment from 22 weeks' gestation may be appropriate after risk assessment and consideration of parental views. It emphasises that decision-making must be led by senior obstetric and neonatal staff and in full consultation with parents (2). To guide the decision whether to initiate intensive care or not, different prognostic models were designed, of which the National Institute of Child Health and Human Development Neonatal Research Network (NICHD-NRN) estimator is one of the more well-known tools (via https://www.nichd.nih.gov/research/supported/EPBO/use) (3). Predictor variables are gestational age, birth weight, gender, singleton birth and antenatal steroid treatment. Prognostic models are helpful tools in prenatal counseling (4). A NICHD-NRN score was not calculated for our ELBW patient with IUGR since gestational age exceeded 25 weeks. In our center, initiation of intensive care is considered starting from 24 weeks' gestation and prenatal counseling is provided at multiple occasions when early or extreme prematurity is expected or in the case of congenital conditions. In this case, the serious medical and ethical concerns regarding the combination of extreme prematurity and IUGR were communicated to the parents.

As a part of postnatal risk assessment, CRIB II score (via https://sfar.org/espace-professionel-anesthesiste-reanimateur/outils-professionnels/scores-sfar/) (5) in our patient was 12, which corresponds to a predicted death rate of 25.4%. Our patient's prognosis was further compromised by an inborn error of metabolism. Since the rarity of extreme prematurity and complex diseases limits extensive study, literature on extremely preterm or ELBW neonates with inborn errors of metabolism is scarce. MSUD is an autosomal recessive organic aciduria that affects the body's ability to metabolize BCAAs: leucine, isoleucine and valine. Acute elevations of leucine and alpha-ketoisocaproic acid can cause life-threatening metabolic encephalopathy and critical brain edema (6). Treatment consists of high caloric supplementation to suppress catabolism, stopping protein intake, strict monitoring of BCAA levels, correction of metabolic abnormalities (hypoglycemia, metabolic acidosis, hyperammonemia) and monitoring sodium level to prevent cerebral edema (6,7). Keeping in mind the increased risk for false-positive results on blood spot screening test in preterm infants due to immaturity of enzymes involved in metabolic pathways or clinical interventions such as TPN (7), urgent plasma amino acid testing was performed. By the time of confirmation of diagnosis, there was already hyperintensity of the deep nuclei on brain ultrasound. A leucine-free diet was initiated on day 14 but enteral feeding was not well tolerated. In the absence of suitable alternatives for enteral feeding, this imposed serious treatment difficulties. Hemodialysis could be a suitable treatment option to remove the BCAAs rapidly, but was not considered possible in our ELBW patient. In literature, despite advancing techniques, reports about successful hemodialysis in the ELBW and VLBW population are scarce as a result of difficult blood access and large extracorporeal circuits relative to an infant's blood volume (8). Peritoneal dialysis (PD) is technically feasible and effective in extremely immature infants (9). To our knowledge, however, no cases of successful PD in neonates with birth weights less than 500 grams have been described.

As a result of the combination of feeding difficulties in the absence of a leucine-free parenteral feeding mix with the infeasibility to perform dialysis in our ELBW neonate, further treatment was no longer feasible or meaningful. Despite advances in life-saving technology for critically ill neonates, challenges continue to rise for infants delivered with extreme prematurity or congenital conditions that exceed the limits of currently available interventions. In these situations, parents face extremely difficult decisions. Parents are reported wishing to save their infant at all costs, regardless of the projected outcome, more frequently than physicians do. Hope, spirituality and compassion tend to outweigh clinical data in some cases and parents and former patients are less likely to rate disability as worse than death compared to their physicians. Furthermore, input from family members and religious beliefs are among the most highly influential factors when making these decisions (10). A helpful practical tool for ethical decision-making in neonatology is the I-P-O (impermissible-permissible-obligatory) framework (11). When applied to our patient, ethically permissible options ranging from maximal beneficial intervention through palliative care were proposed and discussed at multiple occasions. As a result of lack of therapeutic perspective despite (near) maximal intensive care, the obligatory decision was made not to further expand therapy and not to reanimate.

Our case is an extreme example of therapeutic limitations in ELBW infants with severe metabolic disorders. Even though there were no curative options, the question could be raised how far we are willing to go in other extremely preterm or ELBW infants with severe comorbidity. Even in the absence of treatment impossibility, (future) quality of life needs to be taken into account when deciding on whether to continue active treatment or not. Especially with rapidly advancing techniques, we must be careful to guard the meaningfulness of foregoing life-sustaining treatment. It is clear that more research is needed regarding outcomes of extreme prematurity with severe comorbidity in order to correctly address these ethical concerns.

Take-home message

If severe comorbidity further complicates the care for extremely preterm or ELBW infants, therapeutic options can be limited. The rarity of extreme prematurity and severe congenital conditions limits extensive study, which causes prognostic uncertainty and results in difficult prenatal counseling. Ethical considerations need to be taken into account when deciding on the best outcome for the neonate.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

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