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Role of early management of hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome in pregnancy

Matthew James Billingham,[1] Rania Rizk[2]

[1]Department of Anaesthesia, Birmingham Heartlands Hospital, Birmingham, UK
[2]Department of Obstetrics and Gynaecology, Birmingham Heartlands Hospital, Birmingham, UK

Correspondence to
Dr Matthew James Billingham; mbillingham@doctors.org.uk

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SUMMARY

Hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome is a rare inherited metabolic disorder of the urea cycle. Few reports exist to guide practices during pregnancy and fetal delivery. Yet, with affected patients often surviving into reproductive age, appropriate management of the peripartum phase is essential to ensure positive maternal and fetal outcomes.

Reassuringly, the vast majority of offspring of parturients with HHH syndrome have normal developmental outcomes; yet as seen here, fetal growth restriction does appear more frequently. Furthermore, in addition to the absent fetal corpus callosum observed in this case, other fetal cerebral abnormalities, including speech delay and intellectual impairment, have been recognised.

Unregulated dietary intake is one proposed factor for the observed disruption in fetal growth and early cerebral development. These stipulations not only reinforce the importance of extensive planning and teamwork, but also demonstrate the importance of timely intervention by a metabolic dietician and dietary compliance in the early organogenesis stage of pregnancy.

BACKGROUND

Hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome is a rare inherited metabolic disorder of the urea cycle (UCD).[1] First identified in 1969, it is characterised by a unique metabolic triad of hyperammonaemia, hyperornithinaemia and urinary excretion of homocitrulline.[2]

The syndrome is caused by a homozygous pathogenic variant in the *SLC25A15* gene,[3] which encodes the 301-amino acid mitochondrial ornithine carrier protein.[4] The defective transport of ornithine from the cytosol into the mitochondria results in a dysfunctional urea cycle, with consequent hyperammonaemia and the accumulation of cytosolic ornithine (hyperornithinaemia). The intramitochondrial ornithine deficiency also results in condensation of carbamoylphosphate with lysine rather than ornithine and the production of homocitrulline (figure 1).[5]

Encephalopathy, liver disease and coagulopathy are common acute features, whereas pyramidal dysfunction and cognitive impairment often depict the chronic course.[1] Although age and severity of presentation are extremely variable, women with HHH syndrome usually survive into their reproductive years, where various pregnancy-related issues have become well-established potential precipitants of irreversible neurological disability and even fatal metabolic crises.[6–8]

Once complicated by nausea and vomiting, pregnancy may lead to acute decompensation at any stage due to reduced calorie intake, dehydration and the inability to ingest essential supplements and medications. In addition, adequacy of consumption may be further complicated by food aversion and non-compliance.[6] Insufficient energy intake may also occur during labour, which if prolonged and physically intense, or complicated by surgical intervention or general anaesthesia, may also trigger a catabolic state.[9 10]

Alarmingly, previously asymptomatic and undiagnosed women with UCDs have suffered severe postpartum hyperammonaemic encephalopathy following normal pregnancies.[8 11] This has been attributed to the release of large nitrogen loads as the uterus involutes[12 13] and further exemplifies the prodigious challenge to ensure favourable maternal and fetal outcomes for parturients with such conditions.

Within this case report, a novel HHH syndrome genetic variant, alongside the peripartum management pathway, will be reviewed, with the aim of enhancing the care of maternal HHH syndrome in conjunction with former initiatives, which have streamlined the care of mothers with similar UCDs.[8 9 14–18]

CASE PRESENTATION

A 28-year-old Asian primigravida with no significant medical history was referred to the fetal medicine team at 7 weeks and 2 days' gestation, due to the presence of metabolic disorder in her family. Her younger sister was diagnosed with HHH syndrome at the age of 5 years after presenting with intermittent episodes of vomiting, confusion, lethargy and hepatitis-like attacks, but has since responded well to treatment without relapse or disease progression.

A clinical genetics referral was completed and molecular genetic sequence analysis scheduled, with a novel intronic homozygous variant c.623–1G>A detected in the *SLC25A15* gene. This variant has not been reported in the medical literature to date and with a minor allele frequency of 0.000008 in the genome aggregation database, is a very rare allele. The variant affects a canonical acceptor splice site (IVS5-1G>A), with similar splice site variants being reported as pathogenic in association with HHH syndrome.[19–21]

With confirmation of the diagnosis of HHH syndrome at 17 weeks and 4 days' gestation, a low-protein diet of 0.8 g protein/kg/day (approximately

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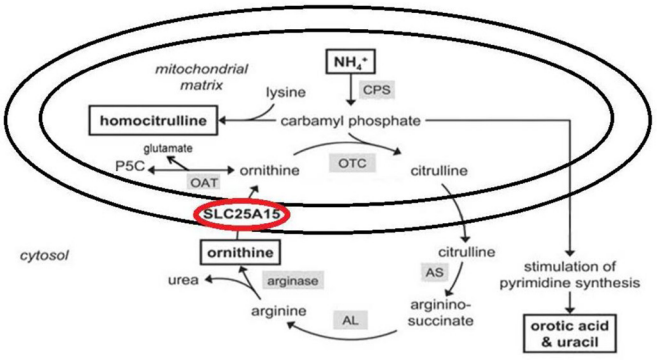

Figure 1 Metabolic basis of the HHH syndrome. AL, argininosuccinic acid lyase; AS, argininosuccinic acid synthase; CPS, carbamyl phosphate synthase; HHH, hyperornithinaemia-hyperammonaemia-homocitrullinuria; OAT, ornithine aminotransferase; OTC, ornithine transcarbamylase; P5C, pyrroline-5-carboxylate. Adapted from Korman *et al*.[5] Copyright 2004, with permission from Elsevier.

50 g/day with pre-pregnancy weight of 65 kg) and citrulline were commenced and a referral was also made to the regional British Inherited Metabolic Disease Group (BIMDG). Here it was noted that she was generally well, without any preceding decompensation. Although it was anticipated that she would have an uncomplicated pregnancy, delivery and postpartum period, a comprehensive management protocol was formulated for the unlikely scenario of clinical destabilisation.

Given the autosomal recessive inheritance pattern,[1] her partner was also referred for molecular genetic analysis to assess the risk of HHH syndrome affecting their children. The analysis did not reveal a pathogenic variant, conferring no strongly elevated fetal risk.

During the second trimester she remained well, with close follow-up by a metabolic dietician and monthly plasma amino acids and ammonia measurements. She was able to meet her target protein levels and caloric intake despite reports that this may represent a significant challenge for many.[6 22]

However, despite maintaining adequate dietary compliance, her 19 weeks' gestation fetal ultrasound detected an absent corpus callosum (ACC), borderline ventriculomegaly and severe (<5% centile) fetal growth restriction (FGR). A follow-up fetal MRI scan confirmed the finding of ACC but revealed no other distinct major structural brain abnormalities. Amniocentesis at 20 weeks and 4 days' gestation permitted detailed karyotype and microarray chromosomal analysis, with no imbalance detected. These findings were presented to our patient and her partner alongside the possible health, developmental and learning implications for their child, and together the decision was made to continue with their pregnancy.

At 28 weeks' gestation, she presented to the Early Pregnancy Assessment Unit with decreased fetal movements. Transabdominal ultrasound reaffirmed early onset severe FGR, with new absent end diastolic flow in the umbilical artery and absent ductus venosus 'a' wave on Doppler studies (figure 2). The coexistence of uteroplacental insufficiency and FGR mandated urgent admission to the delivery suite, and although not universally endorsed worldwide,[23] also led to the sanctioning of an expedited surgical fetal delivery in accordance with Royal College of Obstetrics and Gynaecology recommendations.[24]

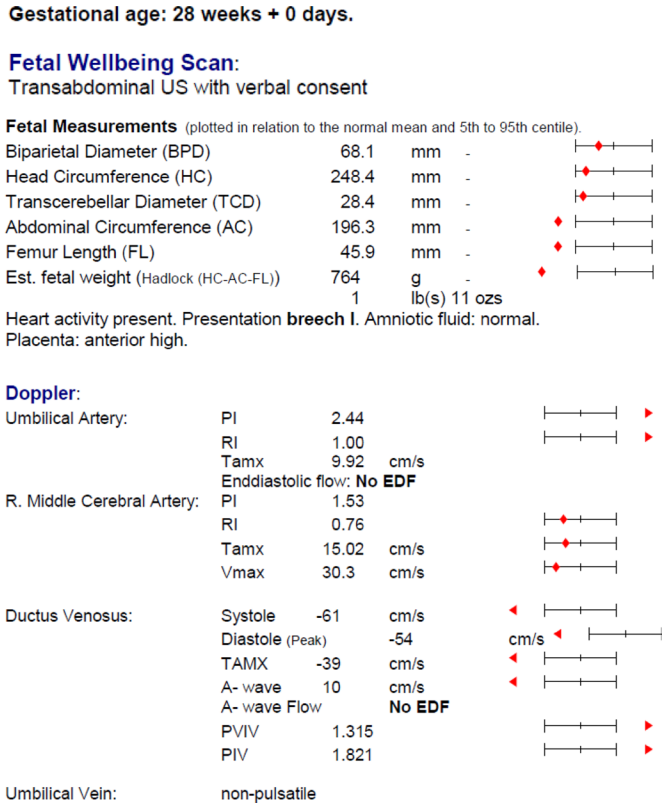

Figure 2 Fetal well-being ultrasound (US) scan and Doppler at 28 weeks' gestation. PI, pulsatility index; PIV, pulsatility index in ductus venosus; PVIV, peak velocity index in ductus venosus; RI, resistive index; Tamx, time-average maximal velocity.

TREATMENT

Preoperative management

Within the delivery suite, our patient was admitted to the obstetric high dependency unit (HDU): 'an interim level of care for women requiring interventions over and above the obstetric care that will be carried out routinely on a consultant led labour ward', in line with her BIMDG protocol and national guidelines.[25 26]

Regular 30-minute neuro-observations were initiated for early detection of metabolic decompensation (lethargy, loss of appetite, change in behaviour, confusion, irritability and seizures), in order to prevent established and irreversible cerebral oedema. If any clinical signs of decompensation were observed, ammonia-scavenging medications were to be commenced immediately, according to the emergency regimen (figure 3).

Continuous cardiotocography monitoring was initiated, magnesium sulfate was provided for fetal neuroprotection, and arterial cannulation was performed to facilitate frequent blood monitoring and collect the initial blood investigation set: full blood count, urea and electrolytes, glucose, blood pH and gases, coagulation screen (coagulopathy has previously been reported[19 27–33]), ammonia and an ABO and Rhesus group and antibody screen.

Review of the initial ammonia levels was then used to guide the subsequent preoperative management (figure 4). Our patient's initial ammonia level was 34 μmol/L and thus pathway 1 was followed, with a 10% dextrose intravenous infusion provided from the planned 6-hour preoperative time point.

L-Arginine 100 mg/kg/day = 6.5 g for a 65 kg individual over 24 hours
Sodium benzoate 250 mg/kg/day = 15 g for a 65 kg individual over 24 hours
Sodium phenylbutyrate 250 mg/kg/day = 15 g for a 65 kg individual over 24 hours

How to make up the infusion*:

In a 500 ml bag of 10% dextrose, due to the maximum concentration allowed, make up the following doses:

- L-Arginine: 2.1 g
- Sodium benzoate: 5 g
- Sodium phenylbutyrate: 5 g

Remove the dextrose volume equivalent of the drug doses from the bag and add the drugs
Run each 500 ml bag continuously over 8 hours – total three bags (1.5 L) over 24 hours

Simultaneously give an ADDITIONAL one litre (2 x 500 ml) of 10% dextrose over 24 hours (run at 40 ml/hr)

Figure 3 Acute metabolic decompensation emergency management regimen.

Intraoperative management

On arrival into theatre, spinal anaesthesia was performed. The lower catabolic effect of regional anaesthesia established this as our preferred anaesthetic technique,[10 11] with the 10% dextrose infusion continued to minimise protein breakdown.

A 700-gram boy was successfully delivered via lower segment caesarean section (LSCS) 5 min following knife-to-skin. Venous cord pH was noted at 7.27 with steadily improving post-delivery Apgar scores with the neonatology team (5 at 1 min, 8 at 5 min and 9 at 10 min), who subsequently transferred the baby to the neonatal unit (NNU).

Neurological features of metabolic decompensation were continuously monitored throughout the procedure and similarly to the preoperative stage; if any clinical signs of decompensation were noted intraoperatively (or an ammonia level >80 μmol/L), emergency regimen ammonia-scavenging medications were to be commenced.

Fortunately, our patient remained stable throughout the procedure, with an estimated blood loss of 500 mL and no clinical signs of decompensation.

Postoperative management

Given that the greatest risk of hyperammonaemic encephalopathy is in the first 48 hours postpartum,[16] HDU care was continued postoperatively according to the BIMDG protocol (figure 5).

Serial blood monitoring levels remained acceptable, with peak postoperative ammonia levels only becoming mildly elevated at 119 μmol/L on day 2 (figures 6 and 7). However, since no features of metabolic decompensation were observed, ammonia-scavenging medications were not required after discussion with the inherited metabolic disease (IMD) team.

Indeed, the postpartum period was only complicated by nausea (likely opiate induced) and mild hyponatraemia (likely intravenous glucose induced) on postoperative day 1. Once feeding was well established on postoperative day 2 and her nausea subsided, the dextrose infusion was discontinued and a routine low-protein diet and citrulline recommenced.

Pathway 1: Ammonia <60 µmol/L: no further action required. If well monitor 12 hourly prior to delivery. Whilst not eating for four hours or more, a 10% dextrose intravenous infusion must be commenced (2 ml/kg/hr)

Pathway 2: Ammonia 60 – 80 µmol/L: if patient is well with no vomiting or neurological symptoms or signs repeat ammonia within 2-4 hours. Neuro-observations half hourly. Whilst not eating for four hours or more, a 10% dextrose intravenous infusion must be commenced (2 ml/kg/hr)

Pathway 3: Ammonia >80 µmol/L or evidence of metabolic decompensation: commence intravenous dextrose, ammonia-scavenging medication and arginine (according to the emergency regimen)

Given that prolonged fasting may cause breakdown of muscle protein, leading to hyperammonaemia, excessive starvation should be avoided.
Regular (two hourly) snacks should be provided up to 6 hours pre-operatively with high carbohydrate 'clear' drinks up to 2 hours pre-operatively.
For all patients, whilst not eating for four hours or more, a 10% dextrose intravenous infusion must be commenced at 2 ml/kg/hr (130 ml/hr for this patient) regardless of the ammonia level
(This includes from the planned 6 hour pre-operative timepoint (from which point the patient will subsequently not be eating)).

Figure 4 Preoperative management pathway.

Monitor ammonia, potassium and blood gases 4 hourly for 48 hours, or more frequently if condition deteriorates
Monitor neurological observations every 15 minutes, or less frequently if stable.

Respiratory alkalosis (pH >7.46) can be an early sign of hyperammonaemia
Sodium benzoate may cause hypokalaemia – supplement if hypokalaemic
Continue the main (maintenance) 10% dextrose infusion (2 ml/kg/hr). Monitor glucose hourly and if hyperglycaemia develops commence IV variable rate insulin infusion. DO NOT stop or slow the dextrose infusion
Arginine causes hypotension – monitor blood pressure
An anti-emetic can be given safely (e.g.: ondansetron). Do NOT use steroids for anti-emetic purposes (these are potential triggers of hyperammonemic crises in UCD patients)

If ammonia is >80 µmol/L without signs of decompensation
Inform IMD Consultant
Regular (four hourly) blood ammonia trend assessments are required until a negative trend is observed
Regular monitoring of neurological observations (every 15 minutes) must also continue until ammonia levels show a negative trend
Escalation of care required (see below) if evidence of metabolic decompensation (change in behaviour, confusion, irritability and seizures)

If ammonia is >80 µmol/L AND she is showing signs of decompensation
Inform IMD Consultant
Loading doses of sodium benzoate and phenylbutyrate will become necessary: 15 g (= 75 ml) of each drug in 500 ml 10% dextrose over 90 minutes. If smaller fluid volumes are indicated, give 2.5 g in 50 ml 10% dextrose 'piggy-backed' (Y-connector) to the maintenance (2 ml/kg/hr) dextrose infusion

Normal food should be re-introduced as soon as possible. Protein intake should not exceed 50 g/day

If tolerating food at 48 hours, the IV dextrose maintenance fluid can be stopped and if necessary calories supplemented with 200 ml of 25% carbohydrate solution e.g.: Maxijul or SOS 25 every 2 hours (available from IMD Dieticians)

Postpartum oral medication after 48 hours AND patient eating and drinking
Nil if no sodium benzoate or phenylbutyrate has been required
If she has required IV ammonia-scavenging medication discuss with IMD Consultant whether she requires oral medication.
If required, dosing is as follows:

L-Arginine: 2 g TDS
Sodium benzoate: 5 g TDS
Sodium phenylbutyrate: 5 g TDS

Continue for 8 days

Figure 5 Postpartum management protocol. IMD, inherited metabolic disease; IV, intravenous; TDS, three times a day; UCD, urea cycle disorder.

OUTCOME AND FOLLOW-UP

Four days post-LSCS, our patient was discharged home, with routine obstetric and IMD follow-ups arranged and instructions provided to seek urgent medical support if clinical deterioration occurred. Through careful planning and close liaison with the IMD team, at no point was it felt necessary to commence ammonia-scavenging medications and no evidence of hyperammonaemic metabolic decompensation was ever observed.

On admission to NNU, the baby was treated for respiratory distress syndrome. He required mechanical ventilation for 3 days, 15 days of continuous positive airway pressure and further oxygen support for 52 days. Weighing 2200 g, he was discharged home after 82 days from the NNU.

Both the mother and the baby have remained well since returning home.

DISCUSSION

Approximately 100 patients with HHH syndrome have been reported,[1] with even fewer reports available to date to guide clinical practices during pregnancy.[6] Yet, with patients with HHH syndrome often surviving into reproductive age, appropriate management of the peripartum phase remains essential to ensure positive maternal and fetal outcomes.

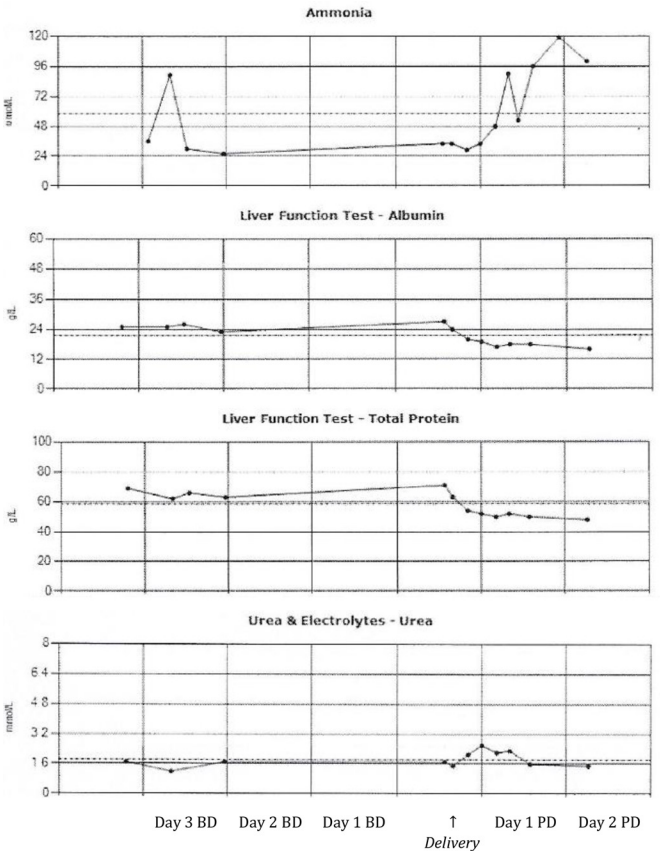

Figure 6 Serial laboratory venous blood analysis (ammonia, albumin, total protein and urea). BD, before delivery; PD, post-delivery.

Test	Range	Units								
FiO2			0.21	0.21	0.21	0.21	0.21	0.21	0.21	0.21	0.21
pH	7.40-7.46		7.47	7.45	7.42	7.41	7.41	7.39	7.44	7.43	7.42
pCO2	3.7-4.2	kPa	3.42	3.87	4.14	4.20	4.09	4.29	4.01	4.26	4.20
pO2	10-16	kPa	14.6	15.7	13.1	14.6	13.9	15.7	15.4	15.9	15.3
AG	10-20	mmol/L	22.2	18.4	14.6	18.9	19.4	15.9	17.3	16.4	16.5
BE(act)	-2-2	mmol/L	-3.5	-2.6	-2.5	-4.0	-4.3	-4.8	-2.7	-2.5	-3.0
cHCO3st	18-21	mmol/L	21.0	21.7	19.4	20.7	20.5	20.2	21.7	21.9	21.5
Ca++	1.15-1.35	mmol/L	1.22	1.15	1.13	1.15	1.15	1.14	1.19	1.20	1.17
Cl-	98-107	mmol/L	102	102	101	101	100	100	99	103	104
K+	3.5-5.1	mmol/L	3.8	3.7	4.3	3.2	3.3	3.1	4.0	4.0	3.6
Na+	136-145	mmol/L	139	136	130	136	135	132	133	136	137
COHb	0.5-1.5	%	1.0	0.9	1.4	1.0	1.0	1.1	1.1	1.2	1.1
Hct	36-53	%	39.1	38.0	36.2	33.2	32.9	31.7	31.5	30.9	27.4
MetHb	0.5-1.5	%	0.5	0.5	1.1	0.5	0.5	0.6	0.5	0.5	0.5
O2Hb	94-98	%	97.0	97.2	96.6	96.8	96.6	96.9	96.9	96.9	96.9
SO2	94-98	%	97.4	97.6	97.2	97.2	98.0	97.3	97.5	97.6	97.4
tHb	120-160	g/L	122	118	123	103	98	94	96	98	99
Glu	3.5-5.3	mmol/L	4.6	7.1	4.7	6.3	6.4	10.2	6.1	5.9	7.0
Lac	0.36-0.75	mmol/L	1.11	1.11	1.02	0.91	1.11	1.40	0.72	0.81	0.69
Timeline in relation to fetal delivery (hours):			-5	-3	+1	+3	+7	+11	+15	+20	+36

Figure 7 Cumulative view: point-of-care testing/blood gas analysis. AG, anion gap; BE(act), actual base excess; Ca++, blood ionised calcium concentration; $cHCO_3st$, standard bicarbonate; Cl–, blood chloride concentration; COHb, carboxyhaemoglobin level; FiO_2, inspired oxygen fraction; Glu, blood glucose concentration; Hct, haematocrit; K+, blood potassium concentration; Lac, blood lactate concentration; MetHb, methaemoglobin level; Na+, blood sodium concentration; O_2Hb, oxygen-carrying haemoglobin; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SO_2, oxygen saturation; tHb, total haemoglobin.

As outlined in this case report, management of HHH syndrome during the peripartum phase necessitated extensive planning and multidisciplinary teamwork. Collaboration between fetal medicine specialists, clinical geneticists, IMD specialists, medical endocrinologists, obstetricians, anaesthetists, paediatricians and neonatologists, metabolic dieticians and the midwifery and obstetric theatre teams was integral to achieving efficacious patient care.

Given that most deliveries have been performed by LSCS in the past,[1 6] an elective surgical delivery was originally planned for our patient. This approach is thought to offer the best option for metabolic control before, during and after delivery,[6] and is congruent with previous recommendations.[10] However, given the early FGR findings and evidence of uteroplacental insufficiency, it was deemed necessary to expedite delivery at 28 weeks' gestation.

Of note, previous studies have identified five of seven infants as being of normal weight, while the remaining two (29%) had growth restriction.[6 22] This proportion is much higher than the general population, which is estimated at 3%–7%.[6 34] Sadly, the underlying mechanism for FGR in relation to maternal HHH syndrome is not yet known. The complex picture of dietary compliance is one proposed factor, with inadequate protein and calorie intake considered contributory. This postulation not only reveals the importance of the metabolic dietician in the early stages of pregnancy, but also suggests that additional ultrasound monitoring should be considered as part of the management pathway to identify FGR in a timely fashion.

Of course, FGR may not only be caused by inadequate maternal dietary intake but also by placental insufficiency and/or genetic abnormalities. While the observed agenesis of the corpus callosum in this case may well indicate a genetic basis, no chromosomal abnormalities or copy variants were detected (although genetic sequencing was not performed) at amniocentesis. However, fetal cerebral abnormalities appear frequently in maternal HHH syndrome cases described previously, with speech delay,[6] intellectually impaired offspring[35] and even neonatal death reported,[36] often where dietary compliance was considered inadequate and the potential for hyperammonaemia was present. Since our patient was only commenced on a low-protein diet from 17 weeks and 4 days' gestation, the possible

Learning points

- Hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome is a rare inherited metabolic disorder of the urea cycle.
- Very few reports exist to guide clinical approaches during pregnancy and fetal delivery.
- Fetal growth restriction and fetal cerebral abnormalities, as seen here, seem to arise more frequently in mothers with HHH syndrome compared with those without the condition.
- Dietary optimisation, compliance and resultant maternal blood ammonia levels may play a critical role in fetal cerebral development in the early first trimester of pregnancy.
- Early multidisciplinary input seems vital to achieve positive maternal and fetal outcomes.

presence and effects of hyperammonaemia during the early pregnancy stages may well be implicated here.

Yet, the effect of maternal hyperammonaemia on fetal cerebral development is not well understood.[37 38] Currently, data are limited to animal literature, with a study of pregnant mares suggesting that elevated maternal ammonia levels could lead to fetal encephalopathy.[39] Again, this finding not only demonstrates the importance of the metabolic dietician and dietary compliance in early pregnancy, but may also suggest a role for regular maternal blood ammonia sampling in the organogenesis phase, especially where poor dietary compliance is suspected.

While these findings may raise questions over management of patients with HHH syndrome in the early stages of pregnancy, management of the latter peripartum phase is now thoroughly described. This case serves to highlight the importance of early multidisciplinary input to achieve timely, safe, and effective management of such rare, complex metabolic disorders before, during and after pregnancy.

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Contributors MJB—first (corresponding) author (Summary, Background, Case presentation, Treatment, Outcome and follow-up, and Discussion sections). RR—second (co)author (Case presentation, Treatment, Outcome and follow-up sections). MJB was responsible for the conceptualisation, design and construction of the paper and produced the draft version and revisions. RR was involved in the preparation of the draft version of the paper.

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