CASE REPORT

HELLP syndrome preceded by intrahepatic cholestasis of pregnancy: one serious itch

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SUMMARY

We present four women with seven ongoing pregnancies. Five pregnancies were complicated by intrahepatic cholestasis of pregnancy (ICP) and severe haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome with uncommon maternal morbidity. The combination of ICP and HELLP syndrome has not previously been reported. Awareness is warranted to accurately identify this combination of pregnancy-specific diseases with severe maternal morbidity.

BACKGROUND

Haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and intrahepatic cholestasis of pregnancy (ICP) are pregnancy-specific disorders both resolving usually 1 week¹ and 2–3 weeks² after pregnancy, respectively.

The incidence of HELLP syndrome is 0.1–0.6%. It is usually considered a complication of pre-eclampsia,³ but may also occur during normotensive pregnancy.⁴ In about 30% of HELLP cases the syndrome develops within 48 h after delivery.⁵ HELLP syndrome is associated with maternal and neonatal morbidity and mortality. The maternal consequences are mainly due to disseminated intravascular coagulation (DIC) occurring in 5–56% of cases and the maternal mortality rate is 1%.⁶ Neonatal complications are due to placental abruption,⁷ growth retardation and iatrogenic premature delivery.^{8–9} The recurrence rate after experiencing HELLP syndrome in first pregnancy in a subsequent pregnancy is about 3%.¹⁰

ICP is characterised by maternal pruritus with onset usually in the third trimester, raised fastened total serum bile acid levels and increased rates of adverse fetal outcomes.¹¹ Although quality of life is greatly diminished for women with ICP, it is not regarded as a disorder with substantial maternal morbidity.¹² Cholestatic effects of reproductive hormones and their metabolites in genetically susceptible women are considered to be causal.¹¹

Obligate female carriers of mutations in families with progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC) suffer from ICP more frequently compared to the general population,^{13–14} although not during all of their pregnancies indicating that beside genetic factors additional factors must be involved. PFIC and BRIC are caused by homozygous or compound heterozygous inactivating mutations in *ABCB4*, *ABCB11* and *ATP8B1* genes encoding biliary transport proteins.¹⁵ HELLP syndrome has no well-defined

genetic background.¹⁶ We present a case series of four women with HELLP syndrome preceded by ICP with extreme maternal complications.

CASE PRESENTATION

Patient 1 was a multiparous woman referred to a secondary care hospital because of abdominal pain, nausea and vomiting at 36⁺⁵ weeks of gestation. Her first pregnancy was uneventful.

Patient 2 was referred to a secondary care hospital by the midwife at 33⁺¹ weeks of gestation because of premature contractions. Cardiotocography (CTG) indicated fetal distress and emergency caesarean section was performed. No reason for the fetal distress was documented. She complained of dyspnoea and oliguria 2 days postdelivery.

Patient 3 conceived by in vitro fertilisation (IVF) because of secondary unexplained subfertility and was under antenatal care at our hospital because of a previous pre-eclamptic pregnancy. She experienced pruritus combined with raised levels of alanine transaminase (ALT), γ -glutamyl transferase (GGT) and total serum bile salt levels (85 μ mol/L) during her (spontaneously conceived) first pregnancy (figure 1).

She presented at 30⁺² weeks of gestation with pre-eclampsia, nocturnal pruritus and elevated ALT, aspartate aminotransferase (AST) and GGT (table 1). Ultrasonic evaluation showed a decline in estimated fetal weight from the 90th centile at 28 weeks to the 20th centile at 34 weeks with an increase of the pulsatility index of the umbilical artery less than 2 SDs of the mean.

Patient 4 experienced Kawasaki's disease at the age of 1.5 years and was treated during the first trimester of pregnancy with calcium carbasalate 100 mg daily followed by enoxaparin 60 mg twice daily because of several coronary aneurysms (maximum diameter 10 mm). She started experiencing pruritus of feet, hands and chest at 26⁺⁰ weeks of gestation. Total fastened serum bile acid levels were raised (48 μ mol/L).

INVESTIGATIONS

HELLP syndrome was classified according to the Tennessee classification.¹⁷ ICP was diagnosed based on raised total fastened serum bile acids (>10 μ mol/L), pruritus¹¹ or positive family history with a causative mutation. Hepatitis and Epstein-Barr virus/cytomegalovirus serology was negative for active infections in all patients. DNA analyses of genes encoding biliary transport

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Figure 1 Graphical depiction of relation between ICP/HELLP pregnancies and obstetric history of the four cases including genotype. Mutations in *ABCB4*, *ABCB11* and *ATP8B1* were investigated in the index patients. In case of a mutation, the relatives were tested for that specific mutation. Triangles represent first-trimester fetal loss. Circles represent women and squares represent men. Arrow points at affected pregnancies by HELLP preceded by ICP. Question mark represents unknown genotype. GA, gestational age at delivery; HELLP, haemolysis, elevated liver enzymes and low platelets; ICP, intrahepatic cholestasis of pregnancy.

proteins (*ABCB4*, *ABCB11* and *ATP8B1*) were performed as part of routine clinical care.

Mutation analysis of family members was performed on DNA collected by buccal swab (eSwab, Copan Diagnostics Inc, California, USA) according to the manufacturers' protocol. For the sibling from case 4, placental tissue was investigated; collection of placental tissue was performed as previously described.¹⁸ Experimental details of DNA analysis are provided on request.

DIFFERENTIAL DIAGNOSIS

Patient 1 was diagnosed with normotensive HELLP syndrome with renal impairment (table 1). The differential diagnosis included acute fatty liver of pregnancy (AFLP) based on raised ammonium levels with decreased glucose levels and prolonged prothrombin time (PT)/activated partial thromboplastin time (APTT), thrombotic microangiopathy (TMA) based on thrombocytopenia and renal impairment and DIC based on thrombocytopenia and coagulation abnormalities.

Patient 2's blood testing showed anaemia, thrombocytopenia, coagulation abnormalities, imminent respiratory insufficiency (oxygen saturation 92%, 24 respirations/min) and renal failure and she required intensive care. The differential diagnosis at that time was severe HELLP or TMA because of thrombocytopenia and renal impairment. ADAMTS-13 activity was determined and was decreased (table 1).

Patient 3 was started on β -methasone treatment at 30⁺⁶ weeks of gestation because a possible iatrogenic premature delivery was anticipated. ICP was diagnosed based on elevated total bile acid levels.

Patient 4 was diagnosed with ICP at 33 weeks of gestation. At 34⁺² weeks she developed pre-eclampsia with elevated serum creatinine (table 1).

TREATMENT

Patient 1 was transferred to our tertiary care centre and received 1 g of fibrinogen, 10 mg of vitamin K and 5 units of fresh frozen plasma. PT decreased from 28.7 s to 19.5 s, APTT from 69 to 49 s with thrombocytes stable at $70 \times 10^9/L$. She delivered by caesarean section on maternal indication. Massive blood loss during surgery, treated with 24 packed cells, 18 units of fresh frozen plasma and 7 units of thrombocyte suspension, required embolisation of the uterine arteries. She was admitted to the intensive care unit (ICU). Day 6 postpartum she deteriorated again with increasing liver enzymes, amylase and lipase.

Patient 2 received 4 units of fresh frozen plasma at day 3 to treat coagulation abnormalities. Owing to elevated creatinine and phosphate she underwent a single renal dialysis. The patient was transferred to our ICU on day 4 for possible treatment with plasmapheresis.

Patient 3 was started on ursodeoxycholic acid (UDCA) at 31⁺³ weeks of gestation. Methyldopa was started at 32⁺⁴ weeks of gestation and at 34⁺¹ weeks she showed signs of haemolysis, elevated liver enzymes and thrombocytopenia (table 1). That day during routine CTG evaluation she developed abdominal pain with abdominal guarding in combination with bright red vaginal blood loss and fetal tachycardia indicating a possible placental abruption with fetal distress. An emergency caesarean section confirmed the diagnosis of placental abruption.

Patient 4 received UDCA two times 300 mg daily.

Table 1 Pregnancy and laboratory parameters at the time of complicated pregnancy

	Parameter	Case 1	Case 2	Case 3	Case 4	Reference values
Pregnancy parameters						
Maternal	Maternal age (years)	32	28	34	20	n.a.
	Highest diastolic BP (mm Hg)	85	80	105	90	n.a.
	Gravidity & parity	G4P1	G1P0	G2P1	G1P0	n.a.
	GA delivery (weeks ^{+days})	36 ⁺⁶	33 ⁺¹	34 ⁺¹	34 ⁺⁴	n.a.
	Mode of delivery	Caesarean	Caesarean	Caesarean	Vaginal	n.a.
	GA onset pruritus (weeks ^{+days})	35 ⁺⁶	28 ⁺⁰	30 ⁺²	26 ⁺⁰	n.a.
Neonatal	GA HELLP criteria (weeks ^{+days})	36 ⁺⁵	post partum	34 ⁺¹ *	34 ⁺³ *	n.a.
	Weight (grams)	2540	2100	1860	1990	n.a.
	Birth percentile	20–50	50–80	16–20	20–50	n.a.
	Gender	Male	Male	Male	Female	n.a.
	Apgar scores 1' and 5'	2/6	2/7	4/7	8/9	n.a.
Laboratory parameters						
HELLP	Hemoglobin (mmol/L)	4.4	3.8	4.5	8.1	7.5–9.8
	LDH (U/L 37°C)	886	850	632	305	0–247
	Haptoglobin (g/L)	<0.2	<0.2	<0.2	<0.2	0.3–2.00
	Thrombocytes (*10 ⁹ /L)	34	53	114*	105*	150–350
	AST (U/L 37°C)	143	132	457	73	0–40
	ALT (U/L 37°C)	106	101	490	52	0–34
	GGT (U/L 37°C)	362	106	170	97	0–40
Liver	Bilirubin total/direct (μmol/L)	255/208	352/291	9 / <2	7/n.d.	0–17/0–7
	Total Bile acids (μmol/L)	88 [†]	n.d.	110	67	<10
	Ammonia (μmol/L)	67	37	n.d.	43	0–40
	Glucose (mmol/L)	3.0/13.9	7.2	6.7	3.5	4.1–5.6
	PT / APTT (sec)	28.7/ 93	23.2/57	15.5/46	10.1/41	0–14.7 / 28–42
Renal	Albumin (g/L)	15	23	19	26	35–50
	Creatinine (μmol/L)	217	252	139	113	65–95
	Urea (mmol/L)	14	25	8.8	5	2.1–7.1
	Sodium (mmol/L)	128	137	130	136	135–145
	Potassium (mmol/L)	4.2	2.4	7.3	4.9	3.5–4.5
	ADAMTS13 activity (%)	n.d.	25	n.d.	n.d.	54–160
	Other					
Other	Urinary protein (grams/day)	n.d.	0.16	0.66	0.36	<0.3
	Mutation analysis <i>ABCB4</i>	p. Arg652Gly	–	–	p. Arg652Gly	n.a.
	Mutation analysis <i>ABCB11</i>	–	p. Arg575X	–	–	n.a.
	Mutation analysis <i>ATP8B1</i>	–	–	–	–	n.a.

None of the neonates suffered long-term sequelae. The most abnormal value recorded during hospitalisation is shown. Birth weight percentiles were determined using the Dutch birth weight percentiles (<http://www.perinatreg.nl>). Hepatitis and EBV/CMV serology was negative for active infections in all patients. Laboratory abnormalities resolved in the postpartum period and returned to normal 6 weeks postpartum.

*Thrombocyte levels were declining, clinical situation warranted immediate delivery.

[†]Determined in referring hospital.

–, no mutation; ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GA, gestational age; GGT, γ-glutamyl transferase; HELLP, haemolysis, elevated liver enzymes and low platelets; LDH, lactate dehydrogenase; NA, not applicable; ND, not determined; PT, prothrombin time.

OUTCOME AND FOLLOW-UP

Patient 1 was treated with a lipid-low diet under the assumption of AFLP in combination with pancreatitis. A liver biopsy taken 9 days postpartum showed small, mid-sized and a few larger vacuoles (indicative of microvesicular and some macrovesicular steatosis) as well as canalicular and hepatocellular bilirubinostasis (figure 2). She spontaneously recovered and was discharged with her son on the 18th day postdelivery. Review of her medical charts on hindsight showed symptoms of pruritus and jaundice at 35⁺⁵ weeks and elevated fasted total bile acids determined at the secondary care hospital, indicating ICP as the most likely diagnosis. This information was not noticed at referral. DNA-analysis showed a heterozygous *ABCB4*-change c.1954 A>G p.Arg652Gly (human gene mutation database (HGMD) accession number CM072 814). The neonate was homozygous for the A allele. An elder sibling born after an uneventful pregnancy at 41⁺⁴ weeks of gestation has the maternal genotype (figure 1).

Patient 2's liver and kidney functions spontaneously improved at day 6 postdelivery rendering TMA the less likely diagnosis. The patient was discharged at day 14 postdelivery. Inquiries after delivery revealed on hindsight that she had had symptoms

of pruritus, right-upper quadrant abdominal pain and oedema during the third trimester of pregnancy but she did not see a physician. Review of the family history revealed that her mother and her mother's sister had experienced pruritus and jaundice during pregnancy and while using the contraceptive pill. DNA analysis showed a heterozygous *ABCB11*-mutation (c.1723 C>T p.Arg575X), reported previously in association with PFIC¹⁹ (HGMD accession number CM980 248) of maternal origin. The diagnosis was set at (familial) ICP, complicated by HELLP syndrome. Both children are unaffected (figure 1).

Patient 3 was discharged from hospital on day 5 postdelivery. Six weeks after delivery, laboratory parameters had returned to baseline and she no longer required antihypertensive medication. Total serum bile salt levels had returned to normal levels (6.6 μmol/L). DNA analysis of the coding sequences of the *ABCB4*, *ABCB11* and *ATP8B1* genes was performed but was negative for any known mutations.

Patient 4 deteriorated at 34⁺² weeks with signs of nausea, vomiting and fatigue and was referred to our centre. ALT and AST and total fastened bile salt levels (68 μmol/L) had increased despite good adherence to UDCA therapy. Hours after admittance she developed preeclampsia with elevated serum

Figure 2 Liver biopsy from case 1 taken 9 days postdelivery (H&E staining, magnification $\times 400$). Small, mid-sized and a few larger intracellular fat vacuoles, without displacement of the nucleus (arrow). Canalicular (closed arrow head) and hepatocellular bilirubinostasis (open arrow head).

creatinine. At 34⁺³ weeks ammonium increased with clotting abnormalities and low glucose levels, indicating possible liver failure (table 1). Fetal condition was normal. Thrombocytes were declining indicating a threatening HELLP syndrome; it was decided to induce labour with oxytocin and 5 h later the patient delivered uneventfully. DNA analysis also revealed heterozygosity for the c.1954 A>G p.Arg652Gly change in *ABCB4* (HGMD accession number CM072 814). The neonate is homozygous for the G allele (figure 1). The patient's family history was positive for gallstones (father and paternal aunt).

DISCUSSION

The combination of HELLP syndrome and ICP in the four cases we present resulted in severe maternal disease. Physicians and even obstetricians frequently regard pruritus, the main clinical symptom of ICP, as a natural association of pregnancy thereby possibly delaying proper diagnosis in up to 25% of cases.²⁰ In all four cases pruritus was the first presenting symptom, indicating that cholestasis was present before the onset of full-blown HELLP syndrome. Patient 3 conceived by IVF treatment, a known risk factor for ICP with an incidence of 2.7% compared with 0.7% in naturally conceived pregnancies.¹¹ However, she also experienced preeclampsia in combination with ICP in her first naturally conceived pregnancy. The missense change c.1954A>G p.Arg652Gly in patients 1 and 4 was considered a possible disease-associated single nucleotide polymorphism (SNP) (dbSNP # rs2 230 028)^{13 21} with a mean allele frequency in European Americans of 0.079 and 0.343 in African Americans (NHLBI Exome Sequencing Project, accessed 24 February 2013). Other studies did not show a significant difference in frequency of this variation in patients with ICP.^{22 23}

Since not all pregnancies of our index patients were complicated by ICP/HELLP, we explored whether the fetal/placental genotype could be an additional triggering factor. The mechanism of interaction between fetal and maternal genotype responsible for a maternal phenotype during pregnancy has been well described in literature for long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency (LCHAD deficiency). Heterozygous mothers of LCHAD-deficient fetus are at increased risk for AFLP and HELPP syndrome.^{24 25} We investigated whether there was a relation between the fetal genotype and the co-occurrence of ICP

and HELLP but saw no evidence of this in our four cases and their five affected and two unaffected pregnancies (figure 1).

In order to establish if female carriers of an *ABCB11* or *ABCB4* mutation in families with PFIC in general have pregnancies complicated by ICP and/or HELLP, we contacted four known families with PFIC under care in our hospital. We questioned four obligate heterozygous mothers of both homozygous *ABCB11* (n=1), compound heterozygous *ABCB11* (n=2) and compound heterozygous *ABCB4* (n=1) patients with PFIC. They had 11 pregnancies with 13 live born neonates of which 6 were diagnosed with PFIC. ICP occurred in one of the six pregnancies of a PFIC neonate and in none of the five pregnancies of unaffected neonates. Within these families there were no pregnancies complicated by HELLP syndrome.

In conclusion, we have discussed four patients with ICP that was complicated by HELLP syndrome during pregnancy, a combination not previously reported. Our case series demonstrates that awareness of pruritus in women with HELLP syndrome is essential because of possible severe complications.

Learning points

- Take itch in pregnancy seriously.
- In all pregnant women with pruritus total bile acids should be determined.
- Awareness of pruritus in women with haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is essential because of possible severe complications.

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Contributors JJ wrote the first draft of the manuscript. MT inquired pregnancy outcome in families with progressive familial intrahepatic cholestasis families as attending paediatric hepatologist and critically revised the manuscript. GA determined placental genotype from cases 3 and 4 and critically revised the manuscript. UB and ROE provided clinical input and critically revised the manuscript. CR-S assisted with the design of the study, supervised the data collection and analysis, and contributed to writing and editing of the paper. JvdP made clinical observation for all four cases as attending obstetrician and supervised the research and critically revised the manuscript.

Competing interests None.

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