CASE REPORT

Pregnancy in a patient with congenital analbuminaemia

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SUMMARY

Congenital analbuminaemia is a rare autosomal recessive disorder that is characterised by a severe reduction or total absence of serum albumin. This condition has implications for therapeutics as a large proportion of commonly used drugs are plasma protein bound where albumin is the primary component of plasma protein. This is the first case report of pregnancy in a patient with congenital analbuminaemia in the medical literature. In the absence of drug dosage guidelines for patients with congenital analbuminaemia, a list of drugs which may be required for this patient during pregnancy, delivery and/or emergency situations were compiled by a multidisciplinary team. Our patient suffered from polyhydramnios during her pregnancy which was successfully managed with albumin transfusions and had a normal vaginal delivery with no complications in the intrapartum or postpartum period. The management and unique challenges of pregnancy in a patient with congenital analbuminaemia are discussed.

BACKGROUND

We report the management and outcome of a pregnancy in an Australian patient with congenital analbuminaemia, whose condition was first reported in 2015.¹ Congenital analbuminaemia is extremely rare, with about 70 cases described worldwide, and an estimated prevalence of less than one in a million.¹ Despite its rarity, lessons from managing this disorder in pregnancy may also apply to management of individuals with severe hypoalbuminaemia due to other causes.

Analbuminaemia is suspected when there is very low serum albumin combined with normal liver function and absence of protein loss from other sources.² The diagnosis is confirmed by plasma protein electrophoresis and the identification of mutations in the gene encoding albumin on chromosome 4.³ Heterozygotes exhibit a mildly reduced serum albumin (33–34 g/L).¹ Twenty-two different mutations of the albumin gene have been identified so far¹ including mutations that cause non-sense mutations or splicing defects^{4–5} with about one-third of individuals affected estimated to have the Kayseri mutation.⁶

Congenital analbuminaemia is usually asymptomatic in adults although they may suffer from fatigue, lower limb oedema, hypotension and disfiguring lipodystrophy affecting the lower limbs.⁷ Management, if required, includes statins, liposuction and albumin transfusion in some circumstances.^{7–9} Whether these individuals are at risk of premature atherosclerosis and cardiovascular

disease is controversial due to the lack of long-term follow-up.⁷ Increased serum coagulation factors may theoretically increase risk of thrombotic events.² Of ~70 documented cases, only 4 have recorded cause of death: 2 cases of cancer, 1 of pneumonia and 1 of cardiac failure.⁵ Clinical manifestations in children have included respiratory distress in a newborn, tetany crisis, oedema, diarrhoea and increased infections.^{4 10–12}

Albumin is the primary component of plasma protein and contributes to 80% of plasma colloid osmotic pressure, which prevents systemic oedema.² In the absence of albumin, the human body compensates through the synthesis of immunoglobulins and other serum proteins including globulins, transferrin, coagulation factors and apolipoprotein-B.^{2 13 14} Patients subsequently have hypercholesterolaemia, with elevated plasma low-density lipoprotein (LDL) cholesterol levels and normal or reduced high-density lipoprotein cholesterol levels.

Changes in maternal physiology during pregnancy include increased maternal fat and total body water and decreased plasma protein concentrations, especially albumin. This is due to increased maternal blood volume, cardiac output and blood flow to the renal system, leading to increased urinary excretion of plasma proteins. The physiological hypoalbuminaemic state combined with congenital analbuminaemia has implications for therapeutics, as a large proportion of commonly used drugs are highly protein bound. Frohlich *et al*¹⁵ have reported in analbuminaemic children, a 10-fold increase in the unbound fraction of warfarin and diazepam. Demirsoy *et al*⁸ reported no observed changes in pharmacokinetics of perioperative drugs; however, their patient was given perioperative albumin.

Ions and hormones also show altered protein binding in analbuminaemia.^{2 16 17} The level of protein-bound calcium is low while free active ionised calcium levels are normal. Conversely the protein-bound portion of thyroxine usually increases due to high thyroxine binding globulin and patients develop increased total thyroxine levels with a normal free fraction.¹² Vitamin D is also usually increased due to an increase in the level of vitamin D-binding globulin. It has been suggested that there is an increased risk of osteoporosis associated with the condition¹⁷ although this has not been found in subsequent cases.

Analbuminaemia may significantly impact antenatal development, which could explain the low incidence of pregnancy reports for patients with

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Table 1 Medications which may be required in obstetric patients and their possible risk in patients with congenital analbuminaemia*

Drug	Protein binding	Acid/base†	Possible risk if normal dosage is used
Analgesia			
Bupivacaine	95% ²⁰	Weak base	Low
Fentanyl	80–85% ²¹	Weak base, but protein-binding behaviour different to basic drugs	Unknown
Lignocaine	Concentration dependent	Basic	Low
Morphine	20–36% ²¹	Basic	Low
NSAIDs (sulindac, diclofenac, ibuprofen)	>90%	Acidic	High
Oxycodone	45% ²²	Basic	Low
Paracetamol	~20% ²³	Unionised	Low
Antibiotics			
Ampicillin	20% ²¹	Acidic	Low
Cefazolin	Up to 85% ²⁴	Acidic	Unknown
Doxycycline	80–93%	Can act as acid or base	High
Gentamicin	0–30%	Basic	Low
Metronidazole	10–20%	Unionised	Low
Anticoagulation			
Enoxaparin	80% ²⁵	Acidic	Moderate/high
Heparin	More protein bound than low molecular weight heparin	Acidic	High
Antiemetics			
Metoclopramide	Primarily bound to α -1-acid glycoprotein ²¹	Basic	Low
Ondansetron	70–76% ²⁶	Acidic ²⁷	Moderate
Antihypertensives			
Hydralazine	88–90% ²⁹	Basic ³⁰	Unknown, possibly low
Labetalol	52%	Can act as acid or base	Unknown
Magnesium sulfate	25–30%	Weak base	Low
Methyldopa	Negligible	Acidic	Low
Nifedipine	95%	Unionised	Unknown
Emergency medications			
Epinephrine	Unknown	Acidic	Unknown
Amiodarone	96% ²¹	Basic	Unknown
<i>N</i> -acetylcysteine	83% ²¹	–	Unknown
Naloxone	50% ²⁸	–	Unknown
Postpartum haemorrhage medications			
Carboprost	Unknown	Acidic	Unknown
Ergometrine	Unknown	Basic	Unknown
Misoprostol	81–88%	Unionised, then converted to free acid	Unknown
Oxytocin	Very low	–	Low
Prostaglandin F2 α	~50–60% bound to albumin in studies	–	Unknown

General guidance—

concern about drug dosage and requirements for dosage reduction is greatest for drugs that are:

I. highly protein bound and

II. acidic or neutral.

*The assessed risks in this table are based on theoretical predictions due to lack of clinical experience in humans.

†Based on the parent molecule.

NSAID, non-steroidal anti-inflammatory drug.

analbuminaemia. Neonates with analbuminaemia are often born ‘small-for-gestational-age’ and there is a significantly increased prevalence of neonatal death and maternal miscarriage.^{2 12 16 18 19}

CASE PRESENTATION

A 24-year-old primigravida was referred to the Westmead Hospital High Risk Antenatal clinic by her immunologist for management of her pregnancy. The patient had been diagnosed with congenital analbuminaemia ~18 months prior to her pregnancy. She initially presented with several years history of oedema and lipodystrophy of her lower limbs. She was found to have a very low serum albumin but elevated serum cholesterol, LDL cholesterol, triglycerides, globulins, transferrin and fibrinogen.

Diagnosis was confirmed via protein electrophoresis and genetic evaluation where she was found to have the Kayseri mutation—homozygous AT deletion at the 91st and 92nd bases of exon 3 on chromosome 4.¹ Investigations of her close family members revealed that they were heterozygous for the mutation in that region of the molecule and also had elevated serum proteins similar to the patient.

The patient had one previous miscarriage but had an unremarkable obstetric and medical history. She was overweight with a body mass index of 33 kg/m² but otherwise in good health. She was in a non-consanguineous relationship and given that her partner had normal serum albumin levels (heterozygous individuals would have mildly reduced serum albumin levels) her children could be predicted to be heterozygous carriers.¹

She was first reviewed in the high-risk antenatal clinic in her 11th week of pregnancy where an antenatal care plan was established for her. This included deep vein thrombosis (DVT) prophylaxis (compression stockings and enoxaparin) during any hospital admissions and postpartum, and formal growth scans at 28 and 34 weeks gestation. The patient had normal antenatal serology as well as a low-risk first trimester screening test at 13+1 weeks and a normal morphology scan at 19+5 weeks. Her early and repeat fasting glucose tolerance tests were negative for gestational diabetes. Her thyroid function and vitamin D levels were within normal limits.

TREATMENT

The patient underwent her first growth scan in her 27th week where she was found to have polyhydramnios (amniotic fluid index (AFI) 27) with a shortened cervix of 9 mm. The estimated fetal weight (EFW) was just over 1 kg (just below 50th centile) with a normal umbilical artery Doppler ratio. She was asymptomatic for her shortened cervix and denied any tightenings or contractions. There was no abnormal vaginal discharge with good fetal movements.

She was admitted for monitoring and started on sulindac 200 mg twice daily, 25 mg glyceryl trinitrate (GTN) patch daily, progesterone 200 mg pessary nightly, a course of steroids (two intramuscular doses of betamethasone 11.4 mg, 24 hours apart to stimulate fetal lung growth), DVT prophylaxis as well as albumin infusions. Sulindac is a prostaglandin synthetase inhibitor that was given to reduce the amniotic fluid volume by reducing fetal urine production thereby potentially reducing the risk of rupture of membranes and preterm labour. The GTN patch was given as a tocolytic and the progesterone was given as a management for the shortened cervix.

The polyhydramnios was postulated to be secondary to her low oncotic pressure as a result of her condition and therefore there may have been a theoretical benefit of giving albumin to manage this. She was given twice daily albumin infusions and received a total of 11×100 mL concentrated albumin 20% during her admission. Her serum albumin improved from <6 to 18 g/L after receiving the albumin. A growth scan was repeated just over a week later and her polyhydramnios had resolved with her AFI decreasing to 21.

After receiving two doses of 200 mg sulindac 12 hours apart the patient reported a burning sensation and flushing of the face. Sulindac was ceased and the facial burning sensation and flushing resolved spontaneously within 1 day.

In the absence of drug dosage guidelines for patients with congenital analbuminaemia a list of drugs which may be required for this patient during pregnancy, delivery (vaginally or caesarean section) and/or emergency medications were compiled by a multidisciplinary team. These medications were researched with respect to protein binding and acid/base properties in order to assess potential drug administration risks for this patient and to consider alternatives (see [table 1](#)).

During her 34th week she underwent another growth scan which redemonstrated polyhydramnios (AFI 30). Again she had normal umbilical artery Doppler ratio with an EFW just below the 50th centile. She was transfused with albumin—a total of 4×100 mL concentrated albumin 20%. An informal bedside ultrasound scan performed a week later showed an AFI of 16. The progesterone pessaries were ceased in her 34th week.

In her 35th week she presented to hospital with constant backache and intermittent uterine tightenings. On speculum examination her cervix was closed and there was no pooling of liquor. The cardiotocography tracing remained reassuring

throughout. She was monitored and given simple analgesia (paracetamol only). The cervical activity and back pain settled after a few hours and she was discharged home.

OUTCOME AND FOLLOW-UP

The patient presented to the birth unit at 36+5 weeks gestation with spontaneous rupture of membranes and delivered a healthy live male infant vaginally, weighing 2.58 kg, after 3 hours of labour. It was an uncomplicated delivery with minimal blood loss and the patient only required paracetamol and 10 units of oxytocin (active third stage management). She suffered a very small second-degree tear in the posterior vaginal wall and this was repaired under local anaesthetic (15 mL of 1% lidocaine).

Postpartum she was given paracetamol and ispaghula husk as well as 1 week of prophylactic 40 mg enoxaparin daily. She was discharged day 2 post normal vaginal delivery with routine postpartum midwifery follow-up as well as review with her immunologist at 6 weeks postpartum.

DISCUSSION

For highly protein-bound drugs, changes in plasma protein concentration affects the concentration of free drug available for pharmacological action.³¹ Acidic or neutral drugs primarily bind to albumin, while basic drugs tend to bind to α -1-acid glycoprotein. Therefore, the highest risk of adverse reactions exists for medications that are highly protein bound and acidic when used in normal dosage in patients with analbuminaemia. Caution should be taken with drugs such as non-steroidal anti-inflammatory drugs and unfractionated heparin which are both acidic and protein bound.

In the absence of published guidance for pregnant patients with congenital analbuminaemia and knowing that changes in plasma protein concentration affects the concentration of free drug available for pharmacological action of highly protein-bound drugs, a literature review was conducted using MEDLINE, EMBASE, Journals at Ovid Full Text and internet searches. Search terms used (as Emtree or MEDLINE terms where appropriate, or as mapping or textword terms) included 'hypoalbuminemia', 'hypoalbuminaemia', 'analbuminemia' or 'analbuminaemia'. This very general search enabled a broad view of the literature. The available literature from this search was scanned specifically for drug dosage recommendations. Articles about pregnant patients with this condition were not located; however, a number of articles about protein-bound drugs were located including studies in mutant Nagase analbuminaemic rats (an animal model for human familial analbuminaemia).

This is the 71st case of congenital analbuminaemia reported in the literature since the first case was identified in 1954.⁵ The reported patients are diverse in age and geographical location, ranging from birth to 61 years old from Africa, Europe, Asia and North America.⁵ Fourteen patients were asymptomatic for the condition, 45 patients suffered from oedema to varying degrees, 11 patients suffered from lipodystrophy and 3 patients suffered from fatigue.⁵

Decreased oncotic pressure exerted by the lower levels of serum albumin is postulated to cause oedema and perhaps polyhydramnios in pregnancy. Albumin transfusions have been used successfully in patients in perioperative settings and in this patient with congenital analbuminaemia, during pregnancy.

The primary concern for patients with this condition in clinical practice is the unpredictable drug pharmacokinetics as a result of the reduced albumin and subsequent increase in other lipoproteins. Care should be taken when administering

medications that are highly protein bound and/or acidic in nature. An assessment of the patient's risk versus benefit with consideration of each drug's safety margin is required.

Learning points

- ▶ Congenital analbuminaemia is a rare, congenital disorder characterised by very low or absent serum albumin.
- ▶ The primary concern for patients with this condition in clinical practice is possible unpredictable drug pharmacokinetics as a result of the reduced albumin.
- ▶ Care should be taken when administering medications that are highly protein bound and/or acidic in nature to this patient group.
- ▶ Decreased oncotic pressure in congenital analbuminaemia exerted by the lower levels of serum albumin is postulated to cause oedema and perhaps polyhydramnios in pregnancy. Albumin transfusions have been used successfully in patients in perioperative settings and in pregnancy.
- ▶ Specialist multidisciplinary care is recommended for management of rare conditions such as described here.

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