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## Case Report

# Clinical Case of Pregnancy and Follow-Up of Bartter Syndrome (Type II) with a Novel Mutation

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#### Abbreviation:

BMI: Body mass index

AFI: Amniotic fluid index

PCR- RT: Polymerase chain reaction

real time

DNA: Deoxyribonucleic acid

CAS: Chorioamniotic separation

NICU: Neonatal Intensive Care Unit

ROMK: Renal outer medullary

potassium channel

### ABSTRACT

**Background:** Bartter syndrome is a rare autosomal recessive inherited salt wasting tubulopathy, its incidence proportion is 1.2 cases per 1.000.000 live births. The present case - report discusses a clinical case of an antenatal Bartter syndrome (type II) with a novel mutation and its course from antenatal presentation to 6 months postpartum.

**Case Presentation:** The case-report discusses a clinical case of an antenatal Bartter syndrome (type II) with a novel homozygous missense variant mutation in KCNJ1 gene: c.554C>T (p. Pro185Leu). Symptoms presented from 24 weeks of pregnancy as premature labour threats, maternal dyspnoea and severe polyhydramnios (amniotic fluid index 36 cm). Therapeutic interventions included use of indomethacin, dexamethasone, micronized progesterone and three consequent amnioreductions. Pregnancy was prolonged until 32 weeks and induced due to severe reoccurring polyhydramnios, progressing maternal dyspnoea and inability to perform next amnioreduction. Labour was complicated by severe placental abruption and new born – boy was referred to neonatal intensive care unit. Neonatal period was complicated by electrolyte abnormalities: hyponatremia, hypochloremic metabolic alkalosis, transient hyperkalaemia that gradually developed into hypokalaemia, hypercalcemia and elevated rennin and aldosterone levels characteristic to type II Bartter syndrome. At 6 months (corrected age 4 months) he is gaining weight within normal ranges and his psychomotor development is ahead of his corrected age, without any need for daily medications.

**Conclusion:** The present case report describes the clinical course of a Bartter syndrome is of high importance, due to the reason that it shows clinical course of patient with novel mutation and offers one of the ways how to manage the disease. The described novel mutation may have favourable prognosis for neonate. The pregnancy should be managed as high-risk pregnancy with expertise in perinatal diagnostics and interventions. Early recognition, and interventions, are and essential to prolong a pregnancy and lessen prematurity complications.

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## Case Study

### I Pregnancy

29 years old pregnant woman, obese with body mass index (BMI) 46 kg/m<sup>2</sup>, was referred to second opinion ultrasound to perinatal center

because of severe *polyhydramnion* at 26+4 weeks of gestation . Previously the patient underwent standard regular antenatal care in outpatient care services. Her pregnancy was spontaneous; she was expecting a baby of non-consanguineous marriage. As to the ethnic origin, woman and her husband were Latvians. The pregnancy was complicated by a subchorionic hematoma with bleeding at early 10/11

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weeks, respiratory virus infection at 17 weeks and flu infection at 24 weeks of gestation. All other standard follow-ups were unremarkable.

Patient's complaints on admission included shortness of breath, increased vaginal discharge and lower abdominal pain. Accelerated abdominal growth and increased vaginal discharge during the last two-week period were reported. A detailed ultrasound examination revealed anatomically normal foetus. The fetal biometric data of the patient was consistent with 27/28 gestational weeks (weight 1007g) and amniotic fluid index, appeared to be 36.4 cm, showing severe polyhydramnios, ultrasound also demonstrated a shortened cervix (7 mm). A normal oral glucose tolerance test helped the researchers to rule out gestational diabetes mellitus. A magnetic resonance examination allowed to exclude severe malformations including tracheal agenesis (Table 1).

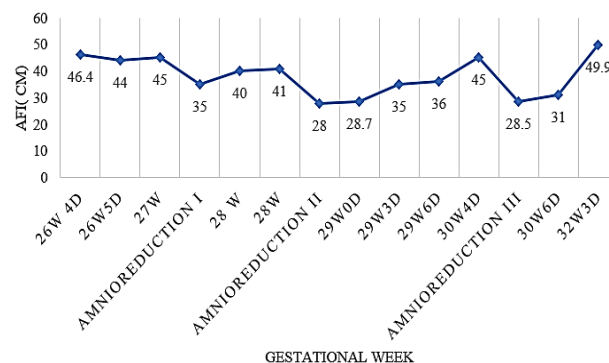
**Table 1:** Common causes for polyhydramnios [1, 2].

Structural abnormalities (Impaired Swallowing)
Gastrointestinal obstruction:
Digestive tract atresia;
Diaphragmatic hernia;
Tracheal atresia;
Trachea oesophageal fistula;
Thoracic mass;
Neuro-muscular :
Myotonic dystrophy
Arthroriposis
Intracranial anomaly
Fetal akinesia/hypokinesia sequence
Caniofacial :
Cleft lip/palate
Micrognathia
Neck mass
Structural abnormalities (Excess Urine Production)
Ureteropelvic obstruction
Mesoblastic nephroma
Cardiac structural anomaly
Tachyarrhythmias
Sacroccocygeal teratoma
Hydrops
Maternal-fetal infection
Cytomegalovirus
Toxoplasmosis
Herpes simplex infection
Parvovirus infection
Aneuploidies, sex chromosome aneuploidies
Maternal diabetes
Placental tumours
Bartter syndrome

Dexamethasone 6 mg i/m every 12 h for 48 h (for respiratory distress prophylaxis) and micronized progesterone vaginally (for a short cervix) 200 mg once a day were administered. Later, diagnostic amniocentesis and amnioreduction were carried out to facilitate maternal dyspnoea and exclude chromosomal abnormalities and TORCH infections. Herpes simplex, toxoplasmosis, cytomegalovirus, ebstein barr virus infections

were excluded using real time polymerase chain reactions (PCR-RT). The results are shown in (Table 2).

The amniotic fluid analysis results showed low protein level (1.96 g/l); elevated sodium (144 mmol/l) and chlorides in upper reference limit (108 mmol/l). Results of severe polyhydramnios with low protein and without presence of infections or severe malformations enabled the researchers to suggest that there is a presence of antenatal Bartter syndrome. For this reason, a therapy with indomethacin 50 mg p/r 4x day at 28 weeks of gestation was prescribed (for a week). However, severe polyhydramnios was reoccurring and two more amnioreductions were needed (Graph 1) at 28 and at 30 weeks of gestation.



**Graph 1:** Amniotic fluid index through amnioreductions.

At 31 weeks of gestation a wide chorioamniotic separation (CAS) on the anterior uterine wall was detected on the image taken (Figure 1). At 32+2 weeks of gestation a decision to induce labour was made because maternal dyspnoea and inability to preform fourth amnioreduction due to wide chorioamniotic separation. Amniotomy was used for induction and 3.5 l of clear amniotic fluid was drained. Regular uterine activity developed, and the patient progressed normally during the labour until a cervical dilatation reached 8-9 cm, when a severe placental abruption occurred. An emergency Caesarean section was performed, and massive postoperative atonic haemorrhage developed during the surgery. The total blood loss was 3.5 litres. Bleeding was managed with oxytocin, misoprostol, Bacri balloon tamponade, fluid resuscitation and haemotransfusion. The postoperative period was uneventful. Furthermore, a neonate was delivered, using podalic extraction method. The new-born was transferred to the Neonatal Intensive Care Unit (NICU) with Apgar score 7/7.



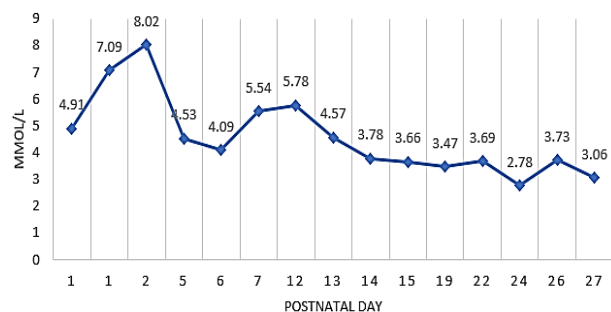
**Figure 1:** Chorioamniotic separation.

## II Newborn

The neonate weighed 1840 g (50 percentile) and had Apgar scores of 7-7. A clinical evaluation of the new-born showed subcutaneous tissue oedema, respiratory difficulties, hypotonia and hyporeflexia. Due to this condition he received an initial stabilization, tactile stimulation and airway clearance and respiratory support with peak inspiratory pressure of 5 cm H<sub>2</sub>O. Moreover, NaCl 0.9% 20 ml was administered (as a bolus) in order to maintain circulation. At the NICU, where the infant was transferred to, further examination revealed hematoma on the right foot and leg. Active bleeding, however, was not detected. His blood pressure was 52/26 mmHg; the respiratory rate was 60 x/min. According to the Silverman-Andersen Retraction scoring system, the infant's score was 3-4 points. Therefore, respiratory support with continuous positive airway pressure was started.

From the first days of his life electrolyte abnormalities developed: hyperkalemia up to 8.1 mmol/l (3.6-6.1 mmol/l) which gradually decreased and later developed into hypokalemia 2.78 mmol/L (Graph 2). From the 5<sup>th</sup> day of the now-borns life hypochloremia 91.8mmol/L (95-116 mmol/l) and hypercalcemia 2.7 mmol/l (1.9-2.6 mmol/l) developed. In addition, ionized calcium levels arose on the 2<sup>nd</sup> week of his life. At the age of two weeks transient hyponatraemia 120.2 mmol/l (132-147 mmol/l) developed. After the discharge from the Maternity Hospital, serum calcium levels remain elevated: at corrected age 4 months the level is 2.72 mmol/L, two months later 2.90 mmol/L.

Simultaneously there was metabolic alkalosis pH 7.424 (7.2-7.4), hCO<sub>3</sub>-act 29.0 mmol/L (18.6-22.6 mmol/l) and an increased anion gap 33.9 mmol/L (10-20 mmol/l), thought to be due to hypochloremia. Severe polyuria with dehydration was not seen and neonates condition gradually improved. Next diagnostic steps included renin and aldosterone analysis, it showed hyperreninemia (>500 µU/ml) and hyperaldosteronism (>1000 pg/ml). From the 5<sup>th</sup> day renal ultrasound suggested early nephrocalcinosis.



**Graph 2:** Neonate potassium level.

As on the 2<sup>nd</sup> day of his life the infant developed neonatal apnoea of prematurity, oral caffeine was added to the therapy. The infant was in an incubator; parenteral feeding from the first day was carried out. Mother's breast milk of 17 ml every 3 hours was given. K vitamin of 1 mg was administrated i/v on the 1<sup>st</sup> and 4<sup>th</sup> day of life. From the first day of infant's life, antibacterial, including Ampicillin 92 mg together with Bifidobacterium was prescribed as per protocol in NICU.

In addition, electrolyte supplementation therapy which implied the use of NaCl 0.9%, Calcium gluconate 8.9 mg/ml and NaCl 5.85% administered twice a day, was performed. Also, the infant underwent phototherapy as a treatment of hyperbilirubinemia. On the 5<sup>th</sup> day the infant's condition improved. From that point breastfeeding was successfully started, periodically supplemented with formula. The genetic evaluation revealed homozygous mutation in KCNJ1 gene, c.554C>T(Pro185Leu) confirming Bartter syndrome (type II). In 39 days, he was discharged from Children's hospital. At the time he weighed 2660 g; his length was 48 cm.

## III Follow-Up

At 6 months (corrected age: 4 months) the baby weighs 5.6 kg and is 68 cm tall. His motor development is ahead of his corrected age. As concerns the baby's motor skills, they are symmetric. He can roll on his both sides and stomach, hold his head and chest upright, lying on his stomach, differentiate people and make hand-hand and hand-mouth contact. There's no need for daily medication and he is observed by paediatrician and nephrologist. Renal ultrasound shows bilateral nephrocalcinosis without negative dynamic.

## Discussion and Conclusion

The present case deals with novel homozygous missense mutation detected by Bartter syndrome gene in KCNJ1 gene: c.554C>T (p. Pro185Leu). Both parents of the infant appeared to be sequencing the carriers for the above-mentioned type of mutation. No genetic disorders or infant deaths were noted in family tree. After the conduction of literature review it was concluded that the present case of Barter syndrome (type II) is the first one illustrated in medical literature, described with this specific mutation. The value of this report lies in that it can give insights into a clinical course for parents and doctors who may encounter this genotype in future.

In this specific case the severe manifestation of the disease occurred during pregnancy. Notable that its manifestation in the neonatal period was milder than expected, which means there was no severe dehydration and need to take medication on the daily basis. The infant's development was normal up to 6 months of age. Bartter syndrome (type II), defined also as antenatal syndrome, is caused by a mutation in gene KCNJ1 located in 11q24, leading to dysfunction in renal outer medullary potassium channel (ROMK) in thick ascending Henles loop [3]. As it was stated in other research articles, the clinical evidences of the disease may be electrolyte disbalance (hyponatraemia, hypochloremia, transient hyperkalemia, hypokalaemia that develops during time span and hypomagnesemia), metabolic alkalosis, polyuria, hyperreninaemic hyperaldosteronism, nephrocalcinosis and failure to thrive in infancy [4]. Prenatally Bartter syndrome (type II) manifests with severe polyhydramnion from 23-26 gestational weeks and premature delivery [5].

The neonates with Bartter syndrome (type II) are typically born from 31 up to 35 weeks, with a vast majority being premature at approximately 33 weeks [6]. Hypercalcemia, as seen in this case, is not a typical finding in antenatal Bartter syndrome. Atypical presentation with hypercalcemia due to hyperparathyroidism in type I Bartter syndrome have been

previously reported in literature [7]. Unfortunately, we have no data of parathyroid hormone tests in this case. In the present case Bartter syndrome was preliminary diagnosed by excluding the common causes of severe *polyhydramnion* (Table 2) with fetal karyotype, magnetic resonance imaging and by determining low protein in amniotic fluid. Low protein is thought to be due to the dilution, but not the excess of fetal proteinuria [8]. Amniotic fluid sodium was slightly elevated, and the level of chlorides appeared to be in the upper reference limit.

**Table 2:** Amniotic fluid analysis.

Tested infection	Results	Reference values	
Herpes simplex DNA PCR-RT	negative		
Toxoplasma gondii DNA PCR-RT	Negative		
Cytomegalovirus DNA PCR-RT	Negative		
Ebstein Barr virus DNA PCR-RT	negative		
<b>Amniotic fluid biochemistry</b>		(Garnier et. al 2010, Nature)	(Bernie et al. Am J Obstet Gynecol 1974)
Protein	1.96 g/l	5.2 (2.3–9.9) g/l	
Potassium (K <sup>+</sup> )	3.6 mmol/l	3.8 (3.1–4.6) mmol/l	4.0 ±0.2 mmol/l
Sodium (Na <sup>+</sup> )	144 mmol/l	136 (129–141) mmol/l	136.0 ± 6.8 mmol/l
Chloride (Cl <sup>-</sup> )	108 mmol/l	111 (105–118) mol/l	108.8 ±3.2 mmol/l
Calcium (Ca <sup>2+</sup> )	1.41 mmol/l	1.47 (0.67–1.93) mmol/l	7.4 ±2.2 (mg/dl)
Karyotype	46, XY		

During the pregnancy indomethacin treatment was started from 28-29 weeks. It is thought that indomethacin stimulates fetal secretion of arginine vasopressin and inhibits prostaglandin synthetase leading to decreased diuresis, renal salt wasting and polyhydramnios [1]. The suggested maximal dose is 2-3mg kg/day [3]. There are several reports of indomethacin use in neonatal period, but less during pregnancy. There are no randomised trials for its use due to the rarity of the syndrome. And Society for Maternal-Fetal Medicine advices against its use in the cases if it is needed to decrease AFI. Caution should be taken against early ductus arteriosus construction and it should be used until 32 weeks of gestation [3].

Amnioreduction, which is considered to be a safe procedure in singleton pregnancies, was performed to reduce severe *polyhydramnion*, defined as AFI  $\geq 35$  cm, and maternal dyspnoea [1, 10]. Other similar case reports claim that it is commonly used regimen for antenatal Bartter syndrome management [3, 11-13]. Diagnostic problems were encountered in the present case as the patient had the 3<sup>rd</sup> stage of obesity. Punctures were technically difficult due to problems visualising the needle tips precise location. According to literature, obesity with BMI > 40 kg/m<sup>2</sup> is linked to multiple needle insertions and more frequent fetal losses after amniocentesis [14]. Chorioamniotic separation formation (CAS) is linked to amniocentesis, amnioreduction and fetal surgery [10, 15]. Forth amnioreduction weren't carried out due to case reports of complete CAS and *fetal demise in utero* after amniocentesis performed on pre-existing chorioamniotic separation [15].

However, in the present case the difficulties with diagnosing were not the only ones. The delivery of the infant was technically challenging as well, as first category caesarean section was performed due to a placental abruption. As a result, the neonate was delivered by a podalic extraction, resulting in a small hematoma on the right foot and leg. The infant had persistent hypochloremia metabolic alkalosis, hyperkalemia, which

According to Garnier (2010), electrolytes should not be used in diagnosis. In previous researches Bartter index has been proposed for diagnostics, but it should be taken into account that it has low sensitivity and specificity, which approximately 85.7% and 84.2% [9]. The diagnosis of the disease should be considered when there is a presence of severe reoccurring polyhydramnios with no morphological anomalies from the second trimester with low protein in amniotic fluid biochemistry.

gradually developed into hypokalaemia, hypercalcemia, one-time hyponatraemia, hyperreninemia and hyperaldosteronism. Neonatal complications may arise from untreated severe dehydration, which may lead to severe electrolyte imbalances and arrhythmias. Gallstones, growth retardation and decrease in bone mineral density have been described in other types of Bartter syndrome [16, 17].

Coming to the conclusions it should be stated that if to manage Bartter syndrome (type II) adequately, it has a positive prognosis. Typically, infant's somatic, neurodevelopmental growth is normal and renal failure is uncommon [17]. For this reason, it is important to avoid associated complications to improve an outcome. In the case of prenatal Bartter syndrome, early recognition, and interventions, such as amnioreductions, is safe and essential to prolong a pregnancy and lessen prematurity complications. At the same time, it should be balanced, as mother's wellbeing should be taken into consideration.

To summarise, the suggestion of the authors of this paper are the following:

- i. Type II Bartter syndrome with described novel mutation may have favourable prognosis for neonate. The pregnancy should be managed as high-risk pregnancy with expertise in perinatal diagnostics and interventions. If a woman with risk factors such as severe polyhydramnios, high body mass index and serial amnioreductions is in labour, cross matched blood must be available due to the high risk of placental abruption and postpartum haemorrhage.
- ii. From women's perspective she is thankful for all doctors who took care for her and is thankful that her son is thriving well.

### Consent and Ethical Approval

Written informed consent for case study publication was obtained from the women. Riga Stradins university ethics approval was granted.

### Competing Interest

None.

### Funding

None.

### Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author LL. The data are not publicly available due to that could compromise research participant privacy and consent.

### Author Contributions

LL and SK were involved in manuscript preparation and literature review. DR, NV, AM and GJ were involved in patient care in obstetric unit. KR is involved in ongoing neonate postnatal follow up. The authors have read and approved final manuscript.

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