Neonate with polyuria and hydrocephalus

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Flow of presentation

Antenatal  Genitourinary

CNS        Sepsis
Introduction

- Very preterm (31+4 wks) AGA male baby delivered by forceps assisted vaginal delivery (spontaneous onset of preterm labor with poor bearing down efforts) to primigravida mother

- Birth weight 1700 grams (around 50th centile)
Antenatal history

- Maternal age: 30 years
- Primipara, spontaneous conception
- Polyhydramnios diagnosed at 20 weeks (Level 2 scan)
Pre-drainage deepest vertical pool (DVP): 10.2, AFI 32.7
4.7 litres AF drained under LA,
Post-drainage DVP: 5.8
Refilling of amniotic fluid with persistently full fetal bladder after 2 weeks (28 weeks), amnioreduction repeated at 29 weeks
<table>
<thead>
<tr>
<th>Impaired Swallowing</th>
<th>Excess Urine Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Obstruction</td>
<td>Neuro-Muscular</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>TE Fistula</td>
<td>Arthrogryposis</td>
</tr>
<tr>
<td>Thoracic mass</td>
<td>Intracranial anomaly</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td></td>
</tr>
</tbody>
</table>
Antenatal history contd.

- Developed Intrahepatic cholestasis of pregnancy (IHCP) at 28 wks
- Had Gestational diabetes
- Received full course of steroid at 26 weeks of gestation in view of polyhydramnios and anticipated preterm labor
- Rescue dose of dexamethasone started at 31+4 weeks on initiation of preterm labor
Resuscitation Details

- Baby was born limp, with no spontaneous respiratory efforts
- Following initial steps, positive pressure ventilation started with T piece resuscitator
- After 60 seconds of effective PPV baby had spontaneous respiratory efforts with heart rate >100/min
- Delivery room CPAP started in view of respiratory distress
- Transferred to NICU in incubator on CPAP support
- Apgars were 6/7/7
Course in NICU: Respiratory system

- Started on CPAP support (7cm H₂O)
- FiO₂ requirements were persistently in range of 40%
- Surfactant given
- Through Less invasive route (LISA)
- CPAP continued
Respiratory system continued..

- At around 48 hours of life baby was intubated and put on mechanical ventilation due to recurrent apnea episodes.
- Extubated to nasal intermittent mandatory ventilation (nasal IMV) on day 7 of life.
- Weaned to CPAP and to room air on day 9 of life.
- Again put on mechanical ventilation on day 14 due to clinical deterioration.
- Weaned off gradually and was off respiratory support by day 25 of life.
Genito-urinary system

- Unexplained polyhydramnios requiring amnioreduction twice
- Possibility of Renal tubulopathy (Antenatal Bartter syndrome)
- Microarray in amniocentesis was normal
- Started on high fluids from day 1 of life
- Whole exome sequencing was sent
- Weight and urine output was closely monitored
Daily fluid intake and output

IV fluids were stopped on D17 of life
Electrolyte levels

<table>
<thead>
<tr>
<th>Day of life =&gt;</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Sodium (mmol/L)</td>
<td>139</td>
<td>135/138</td>
<td>133/128</td>
<td>133/143</td>
<td>143/138</td>
<td>128</td>
</tr>
<tr>
<td>S. Chloride (mmol/L)</td>
<td>97</td>
<td>89/88</td>
<td>89/85</td>
<td>91/105</td>
<td>103/90</td>
<td>76</td>
</tr>
<tr>
<td>S. Potassium (mmol/L)</td>
<td>4.7</td>
<td>4.7/3.1</td>
<td>5.4/4.8</td>
<td>4.7/4.8</td>
<td>5.1/4.3</td>
<td>3.9</td>
</tr>
<tr>
<td>S. Calcium (mg/dL)</td>
<td>8.7</td>
<td>6.3/9.8</td>
<td>10.3/8.1</td>
<td>8.4/9.2</td>
<td>9.6/11.3</td>
<td>10.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.22</td>
<td>7.39</td>
<td>7.41</td>
<td>7.37</td>
<td>7.45</td>
<td></td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>26.1</td>
<td>26.6</td>
<td>21.3</td>
<td>25.9</td>
<td>32.7</td>
<td></td>
</tr>
</tbody>
</table>

- Sodium, Potassium and Calcium were supplemented as per the daily blood reports
- Initially they were given intravenously as infusion along with iv fluids
- Later oral supplementation was continued as per the serum electrolytes
Management continued…

- Ultrasound KUB on day 2 of life - Structurally normal kidneys
- Spot Urine Calcium: Urine Creatinine Ratio: 2.7 (raised)
- Nephrocalcinosis started at D31 of life
- For polyuria
  - Indomethacin was started at D70 of life
**RESULTS**

**LIKELY COMPOUND HETEROZYGOUS VARIANTS TO BE CAUSATIVE OF THE REPORTED PHENOTYPE WERE IDENTIFIED**

<table>
<thead>
<tr>
<th>Gene (Transcript)</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Disease (OMIM)</th>
<th>Inheritance</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC12A1 (+)</td>
<td>Intron 7</td>
<td>c.975+1G&gt;A (5’ Splice site)</td>
<td>Heterozygous</td>
<td>Bartter syndrome type 1</td>
<td>Autosomal recessive</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>(ENST00000647546.1)</td>
<td>Exon 9</td>
<td>c.1215G&gt;A (p.Glu405(=))</td>
<td>Heterozygous</td>
<td></td>
<td></td>
<td>Uncertain Significance</td>
</tr>
</tbody>
</table>

"Reclassification of these variants could be considered based on parental testing."

Impression – Bartter syndrome type 1
Follow up Electrolytes post discharge

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (meq/L)</td>
<td>136</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (meq/l)</td>
<td>3.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Chloride (meq/L)</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.6</td>
<td>10.9</td>
</tr>
</tbody>
</table>
Central Nervous System
Central Nervous System

- Screening neurosonogram done on D3 of life
- No Intraventricular hemorrhage
- Minimally dilated lateral ventricles (Anterior horn width 6 mm)
CNS: progression of ventricular dilatation

Ventricular index progressively increased to 12 mm on DOL 7 and 19 mm on DOL 15 with dilatation of third ventricle.
Case Contd.

- Progressively increasing ventricular dilatation

- Reasons
  - Post hemorrhagic hydrocephalus (IVH missed)
  - Infections (Sepsis work up so far negative)
  - Some channelopathy (as part of bartter syndrome)
Monitoring hydrocephalus

Red line – Ventricular index
White – Anterior horn width
## VI: Summary

<table>
<thead>
<tr>
<th>DOL</th>
<th>PMA (wks)</th>
<th>Ventricular index</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>35+3</td>
<td>29.4</td>
<td>Lumbar puncture (alternate day)</td>
</tr>
<tr>
<td>32</td>
<td>36+3</td>
<td>26.2</td>
<td>Ventricular tap (continued), candida meningitis</td>
</tr>
<tr>
<td>45</td>
<td>38</td>
<td>28.9</td>
<td>VT</td>
</tr>
<tr>
<td>59</td>
<td>40</td>
<td>33.9</td>
<td>VT</td>
</tr>
<tr>
<td>65</td>
<td>27.6</td>
<td>VT</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>28.8</td>
<td>VT</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>31</td>
<td>VT</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>30.6</td>
<td>Subcutaneous reservoir placed</td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>35.6</td>
<td>2-3 times weekly drainage done during this period</td>
<td></td>
</tr>
<tr>
<td>144 days</td>
<td>29.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5 months</td>
<td></td>
<td>Venticulo peritoneal shunt placed</td>
<td></td>
</tr>
</tbody>
</table>
MRI Brain
CNS Part: Summary

- Antenatal ultrasound normal
- Postnatal D3 – ventricular width – 6mm
- Progressively increasing hydrocephalus
- Therapeutic drainage started on D25 – first lumbar puncture followed by ventricular tap
- Complicated by candida ventriculitis
- Omaya reservoir (External ventricular drainage) placed on D88
- Serial drainage continued (Head circumference, fontanelle fullness, ventricular index)
- VP shunt placed at age of 6.5 months
Sepsis
Infection

- On D1, antibiotics were started in view of prematurity with respiratory distress
- Work up normal
- Antibiotics stopped after 3 days
Deterioration D14 of life

- Clinical deterioration in form of apneas requiring intubation
- Antibiotics restarted (Meropenem, Amikacin)
- Blood culture showed growth of Klebsiella sp., CRP 28
- CSF examination showed 50 cells, culture sterile
- Antibiotics (Mero/ Amika) planned for 21 days
Day 25 of life

- Baby had fever spike
- Work up repeated
- Blood culture grew Candida albicans
- Started on Liposomal amphotericin B
- CSF cultures negative, cell count 10
Further course

- Fever spikes got better initially
- Started again having spikes around D35
- Same time Ventricular taps were being done in view of rapidly increasing hydrocephalus
- Blood and CSF (ventricular fluid) were sent on D36
- CSF culture grew Candida albicans (same sensitivity pattern as blood)
DOL 17
BC – Kleb
AB – Mero, Amika

DOL 25
BC – Candida
Liposomal Ampho B added

DOL 38
CSF – Candida
Caspofungin

DOL 50
Flucytosine, fluconazole added
Caspofungin stopped after total 14 days

Diagrammtitel

Liposomal AMB – 42 days
Caspofungin – 14 days
Flucytosine – 28 days
Fluconazole – 28 days

Intraventricular AMB started
Course

- Omaya reservoir was placed on 88th day of life
- Baby was discharged from hospital on D95 of life
- **Diagnosis** – *Type 1 Bartter syndrome with candida ventriculitis with hydrocephalus*
- Regularly followed up
- VP shunt done at age of 6.5 months of life
Child is now 1 years old (Corrected age 10 month)
Still receiving Potchlor and 3% saline
Indomethacin 5mg, thrice a day
Last electrolytes have been normal

Milestones - Stand with support, cruises well along furniture
Interacts well
Growth Monitoring

![Growth Monitoring Chart](image-url)
Discussion
Bartter’s Syndrome

- Group of rare renal tubulopathies, first described by Frederic Bartter in 1962
- Defective transepithelial chloride reabsorption in thick ascending limb of loop of Henle
- Hypokalemia, metabolic alkalosis, and secondary hyperaldosteronism
- Normal to low blood pressure due to renal loss of sodium
Bartter’s Syndrome continued..

- Fetal polyuria
- Early onset maternal polyhydramnios
- Intrauterine growth restriction
- Preterm birth
- Postnatal polyuria
- Episodes of dehydration
- Recurrent vomiting
- Failure to thrive

- Types I, II, and III have severe antenatal symptoms
  - Usually delivered prematurely
  - Poor postnatal weight gain and failure to thrive
- IV is a mild salt losing nephropathy with mild antenatal symptoms
### Bartter’s Syndrome continued..

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
<th>Gene affected</th>
<th>Ion channel affected</th>
<th>Site of Renal Tubule</th>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Antenatal</td>
<td>KCNJ1/11q24</td>
<td>Kir1.1 potassium channel</td>
<td>Thick Ascending limb</td>
<td>Thiazide type</td>
</tr>
<tr>
<td>III</td>
<td>Classic</td>
<td>CLCNKB/1p36</td>
<td>ClC-Kb chloride channel</td>
<td>Distal convoluted tubule (DCT)</td>
<td>Thiazide type</td>
</tr>
<tr>
<td>IV</td>
<td>Bartter Syndrome with Sensorineural Deafness</td>
<td>BSND/1p31 or CLCNKA/CLCNKB/1p36</td>
<td>Barttin, ClC-Ka and ClC-Kb chloride channels</td>
<td>Both TAL and DCT</td>
<td>Thiazide-Furosemide type</td>
</tr>
</tbody>
</table>
Bartter’s Syndrome pathophysiology..

Defective gene (NKCC2/ ROMK/ ClC-Kb)

Defect in NaCl absorption in thick ascending limb of loop of Henle

Increased NaCl delivery to distal nephron

Volume contraction

Increased Renin

Increased Angiotensin II

Increased Aldosterone

Increased H+ and K+ secretion

Metabolic alkalosis and hypokalemia

Impaired vasopressin mediated urinary concentration

Hyponatremia

Normotension- blunted vascular response to Angiotensin II

Increased Urinary prostaglandins

Bone reabsorption

Fever

Increased PGE2

Decreased reabsorption of paracelluar Ca²⁺ and Mg²⁺

Hypercalciuria & Hypermagnesuria

Hyposthenuria
Investigations

- **Antenatal:**
  - Ultrasonography: to confirm structurally normal fetus and placenta
  - Amniocentesis: High chloride in amniotic fluid
  - Other electrolytes in the amniotic fluid will be normal

- **Post-natal:**
  - Hypokalemia
  - Metabolic alkalosis
  - Increased urinary sodium, potassium, and chloride levels
  - Plasma renin is usually high
  - Ultrasonography of the kidneys: bilateral medullary nephrocalcinosis; after several weeks of severe hypercalciuria
  - Mutational analysis of the genomic DNA
Complications…

- Growth restriction
- Hypercalciuria: leading to nephrocalcinosis
- Type IV disease associated with sensorineural deafness
- Rare complications:
  - Progressive renal disease
  - Renal failure
  - Interstitial nephritis can occur
Treatment

- Post-natal:
  - Dehydration correction
  - Correction of electrolyte imbalance
  - Potassium supplements are usually needed by 2-3 weeks
  - Indomethacin
Prognosis

- Untreated: death due to
  i. Dehydration ii. Dyselectrolytemia iii. Infections
- Timely and appropriate therapy:
  i. Clinical improvement
  ii. Catch up growth in majority of children
  iii. Long-term outcome including mental development and puberty is usually normal
- Spontaneous recovery following a period of treatment has been recognized
Hydrocephalus

- Clinical diagnosis of CSF accumulation in the ventricles and brain spaces accompanied by an increase in ICP
- Neonatal hydrocephalus is broadly categorized as congenital or acquired
- Congenital hydrocephalus is further categorized as
  - Syndromic
  - Isolated/ non-syndromic
Hydrocephalous management

- Treatment options
  - Ventricular access devices
  - External ventricular drains
  - Ventriculo- subgaleal/peritoneal shunts
  - Lumbar punctures

- Routine use of serial LP
  - not recommended to reduce the need for shunt placement or to avoid the progression of hydrocephalus in premature infants

Tracy M. Flanders et al. Neonatal Hydrocephalus; Neoreviews; 2018; 19(8); e467-e477
Pubmed search with keywords “Bartter syndrome” and “Hydrocephalus” and we could find only 2 reported cases of Bartter syndrome with Hydrocephalus

Artemis Simopolus in 1979 studied the growth and development pattern of 9 patients of Bartter syndrome

Among these 1 patient was reported to have severe motor and cognitive retardation with a communicating hydrocephalus

Ozmert OM et al in 2016 reported a case of neonatal Bartter syndrome with cholelithiasis and hydrocephalus.

- Preterm 28 weeks with polyhydramnios detected at 25 weeks
- Dehydration with 15% weight loss by day 6 of life
- Cranial sonogram was normal on day 3 and 7 of life
- On day 22, grossly dilated lateral and third ventricles without any evidence of hemorrhage
- Managed by VP shunt placement
- Sonography also revealed gall bladder stones, operated for gallstones on day 57 of life

Ozdemir OM et al. Neonatal Bartter syndrome with cholelithiasis and hydrocephalus: Rare association. Pediatr Int; 2016; 912-915
Plausible Hypothesis

- The Na-K-2Cl co-transporter is expressed on membranes of the choroid plexus and plays an important role in CSF production.

- Ozdemir OM et al hypothesized that genetic mutations causing defective Na-K-2Cl channel in the thick ascending limb, might be associated with similar channelopathy in the choroid plexus, thus causing hydrocephalus due to excessive CSF production.

- Kim and Jung reported that the choroid plexus aquaporin-1 (AQP1) channel and the Na-K-2Cl co-transporter 1 play an important role in the disruption of the blood–CSF barrier in acute rat models.

1) Ozdemir OM et al. Neonatal Bartter syndrome with cholelithiasis and hydrocephalus: Rare association. Pediatr Int; 2016; 912-915

**Take home Message**

- Therapeutic amnio drainage has its role in management of polyhydramnios
- Early optimum fluid and electrolyte therapy can help preventing complications in babies with antenatal bartter syndrome
- There may be a link between antenatal bartter syndrome type 1 and hydrocephalus
- Early and protocolized intervention for neonatal hydrocephalus may improve neurodevelopment outcomes
- Team work plays an important role in managing such babies
Team involved

- Fetal Medicine – Dr Chanchal Singh
- Obstetrics – Dr Jayasree Sunder
- Neonatology – Dr Naveen Gupta, Dr Anil Batra, Dr Kirti Gupta, Dr Gajendra, Dr Sandeep, Dr Devendra
- Pediatric Neurosurgeon – Dr Anurag
- Pediatric Nephrologist – Dr Amit Aggarwal
- Infectious Disease Specialist – Dr Arvind Taneja, Dr Aparna
- PICU team – Dr Praveen Khilnani, Dr Chandrasekhar Singha
THANK YOU