Neonate with polyuria and hydrocephalus

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Flow of presentation

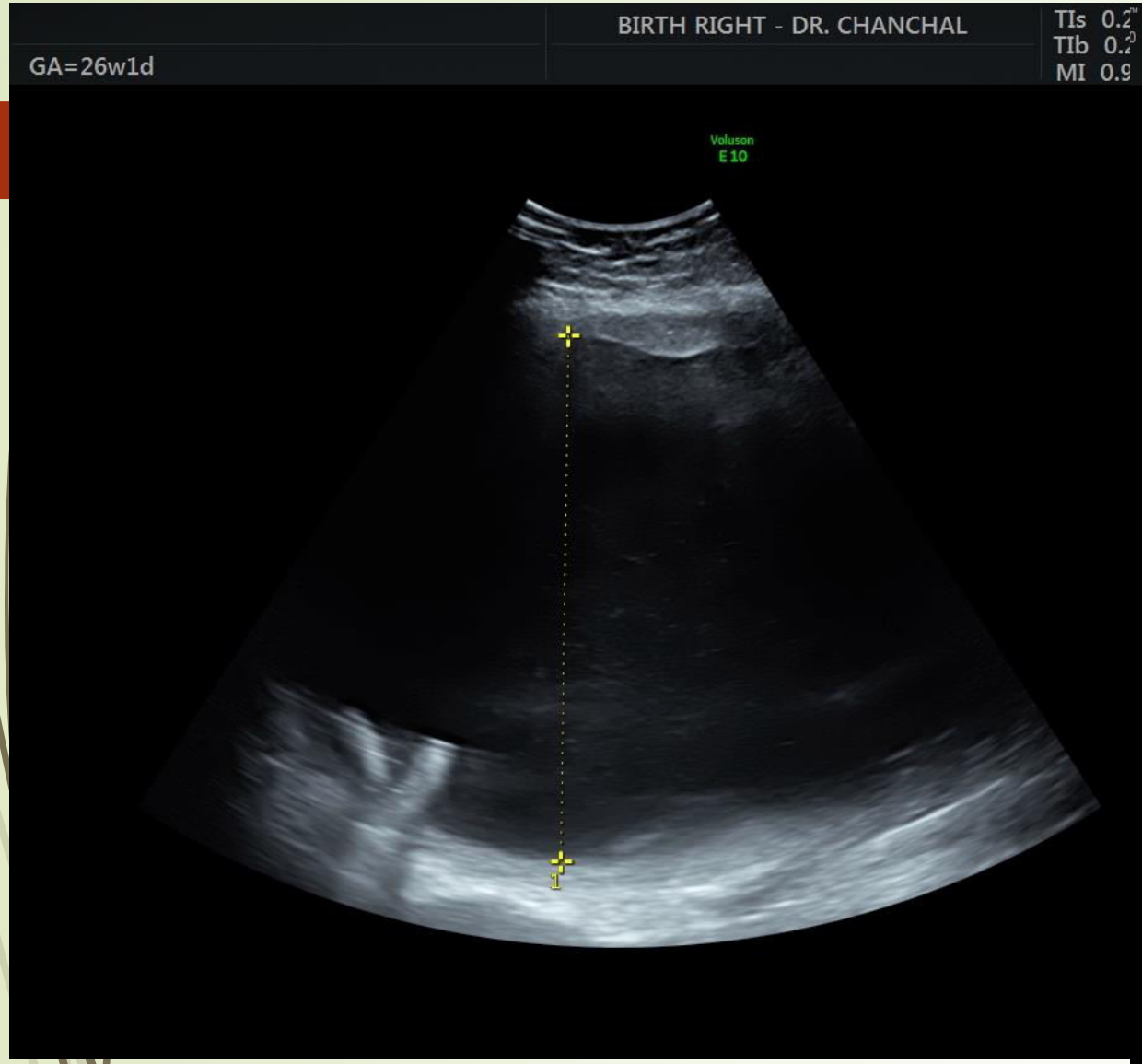
- Antenatal
- Genitourinary
- CNS
- Sepsis

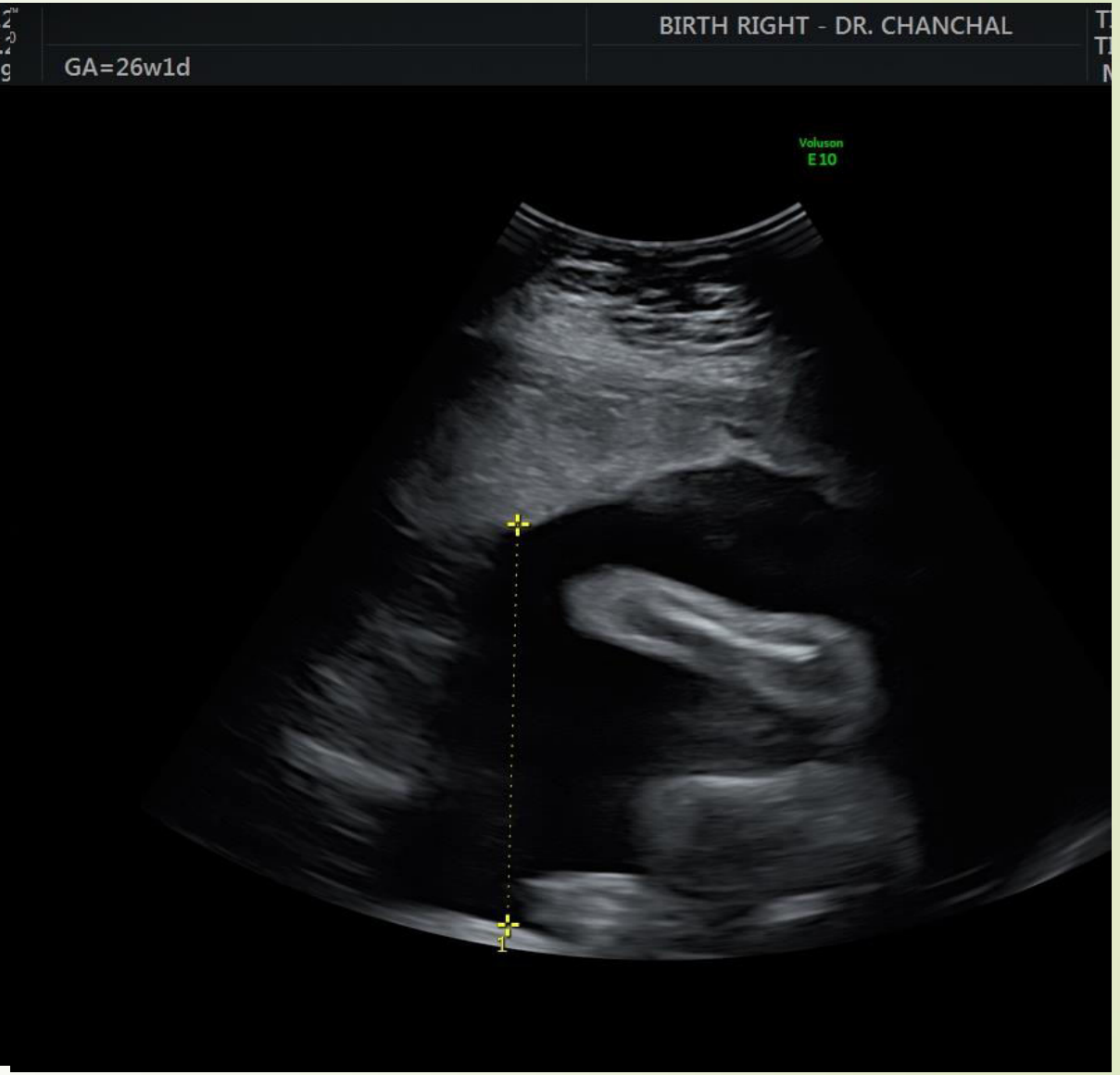
Introduction

- 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

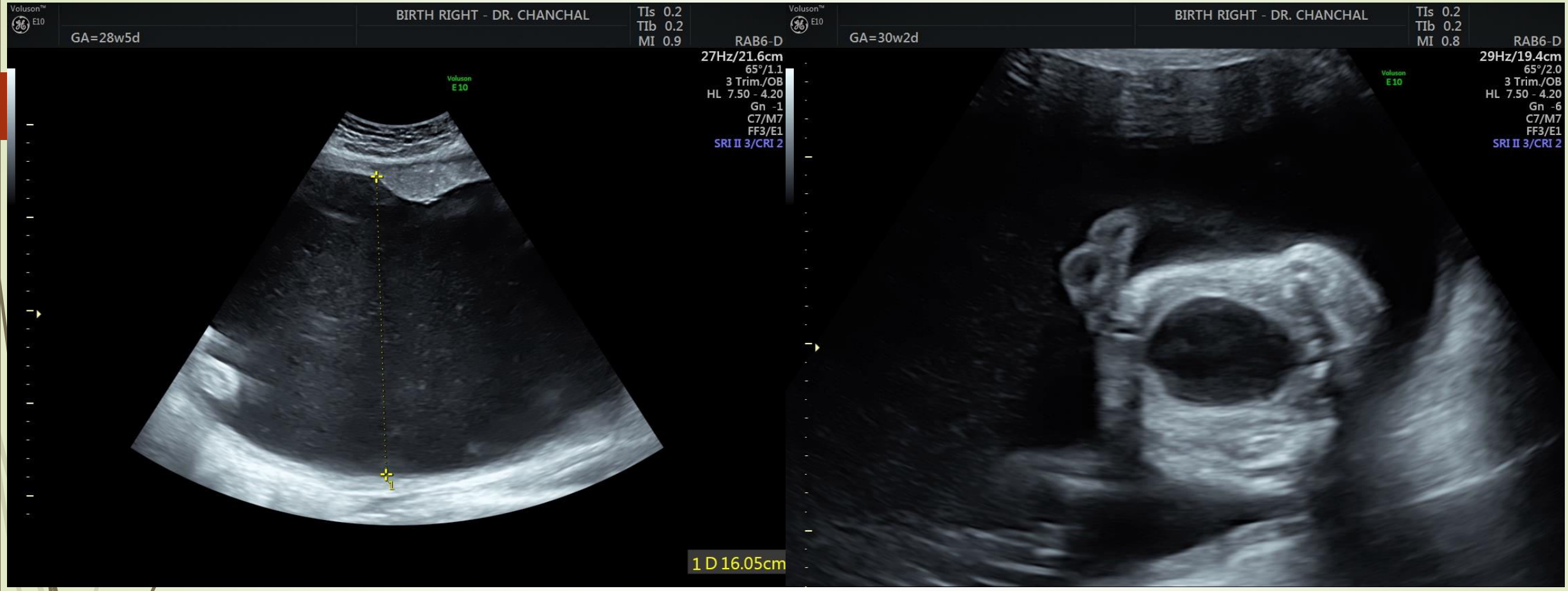
- Maternal age: 30 years
- Primipara, spontaneous conception
- Polyhydramnios diagnosed at 20 weeks (Level 2 scan)





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

Polyhydramnios

Impaired Swallowing			Excess Urine Production		
GI Obstruction	**Neuro-Muscular**	**Craniofacial**	**Renal**	**Cardiac**	**Osmotic diuresis**
Duodenal atresia	Myotonic dystrophy	Cleft lip/palate	UPJ obstruction	Cardiac structural anomaly	Diabetes
TE Fistula	Arthrogryposis	Micrognathia	Mesoblastic nephroma	Tachyarrhythmia	Hydrops
Thoracic mass	Intracranial anomaly	Neck mass	Bartter syndrome	Sacrococcygeal teratoma	Idiopathic
Diaphragmatic hernia				Chorioangioma	

Antenatal history contd.

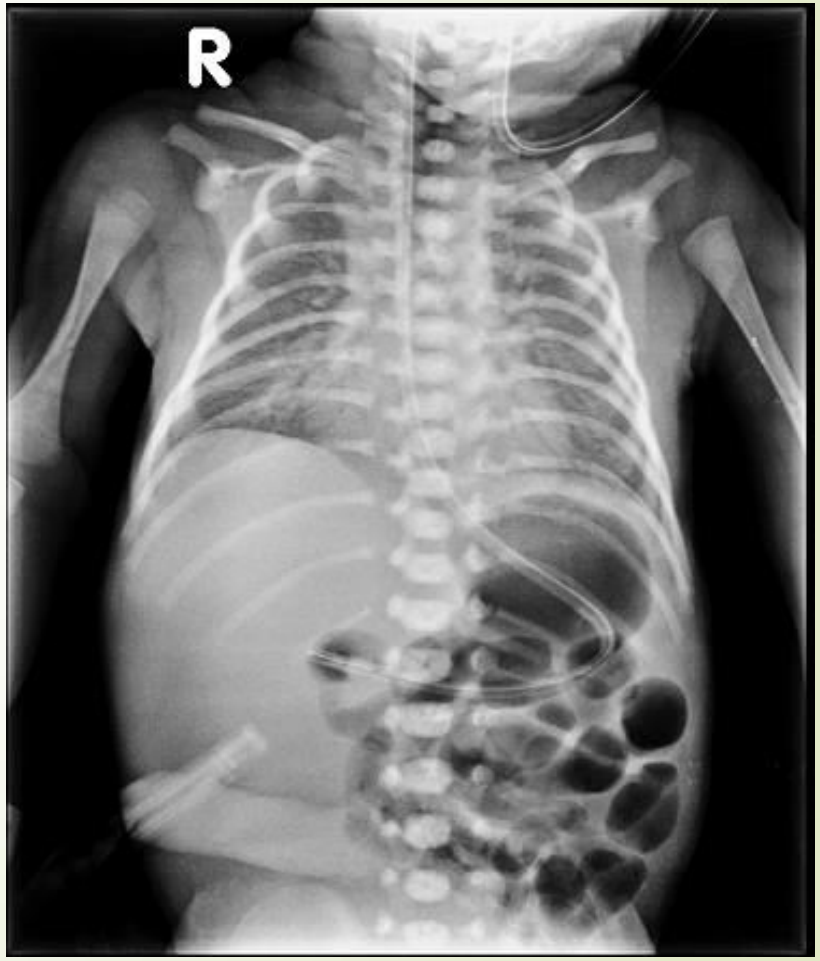
- Developed Intrahepatic cholestasis of pregnancy (IHCP) at 28 wks
- Had Gestational diabetes
- Received full course of steroid at 26 weeks of gestation in view of polyhydramnios and anticipated preterm labor
- Rescue dose of dexamethasone started at 31+4 weeks on initiation of preterm labor

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 ($7cm\ H_2O$)
- FiO_2 requirements were persistently in range of 40%
- Surfactant given
- Through Less invasive route (LISA)
- CPAP continued



Respiratory system continued..

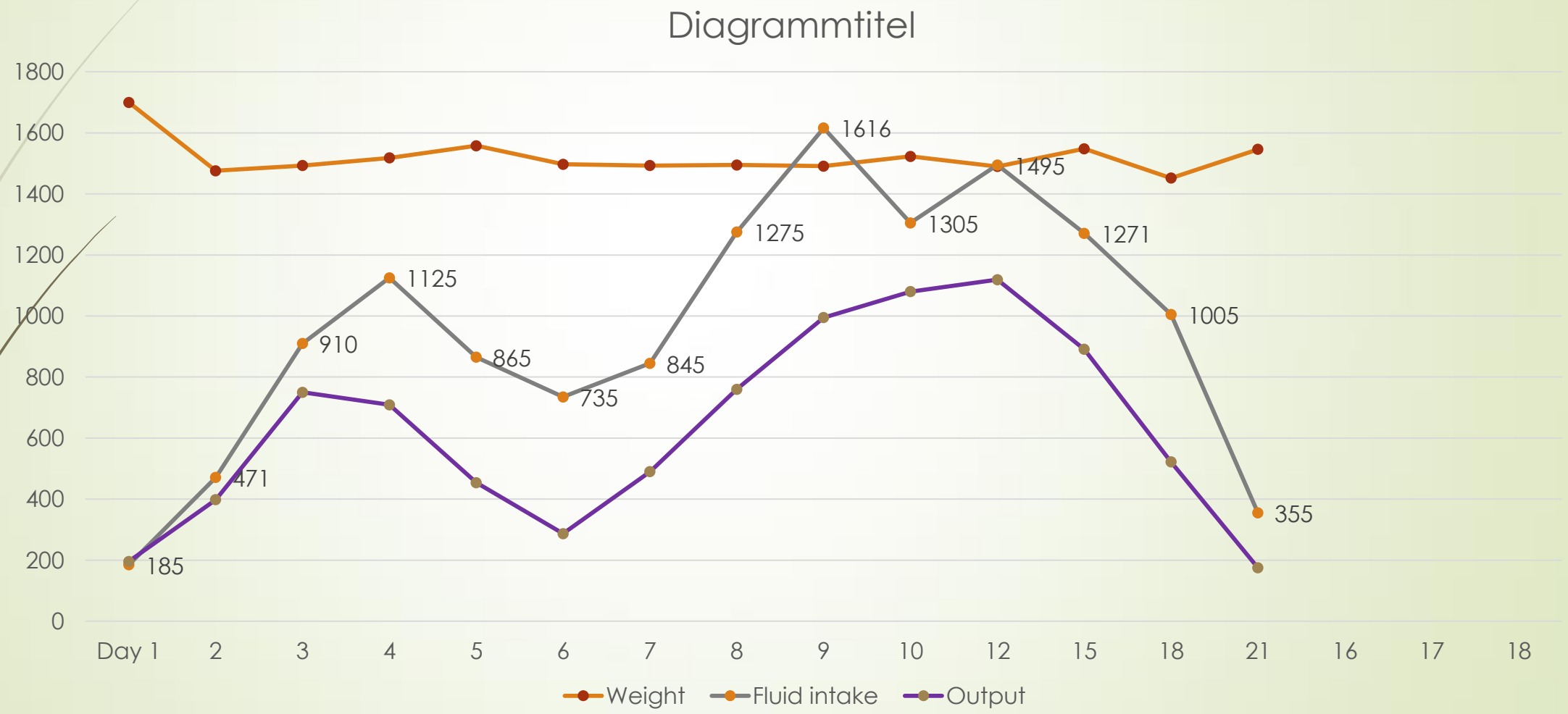
- At around 48 hours of life baby was intubated and put on mechanical ventilation due to recurrent apnea episodes
- Extubated to nasal intermittent mandatory ventilation (nasal IMV) on day 7 of life,
- Weaned to CPAP and to room air on day 9 of life
- Again put on mechanical ventilation on day 14 due 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

Day of life =>	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7
S. Sodium (mmol/L)	139	135/ 138	133/ 128	133/ 143	143/ 138	128
S. Chloride (mmol/L)	97	89/ 88	89/ 85	91/ 105	103/ 90	76
S. Potassium (mmol/L)	4.7	4.7/ 3.1	5.4/ 4.8	4.7/ 4.8	5.1/ 4.3	3.9
S. Calcium (mg/dL)	8.7	6.3/ 9.8	10.3/ 8.1	8.4/ 9.2	9.6/ 11.3	10.1
pH	7.22	7.39	7.41	7.37		7.45
HCO_3^-(mmol/L)	26.1	26.6	21.3	25.9		32.7

- 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

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***SLC12A1* (+)** (ENST00000647546.1)	Intron 7	c.975+1G>A **(5' Splice site)**	Heterozygous	Bartter syndrome type 1	Autosomal recessive	Pathogenic
	Exon 9	c.1215G>A **(p.Glu405(=))**	Heterozygous			Uncertain Significance

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

Impression – Bartter syndrome type 1

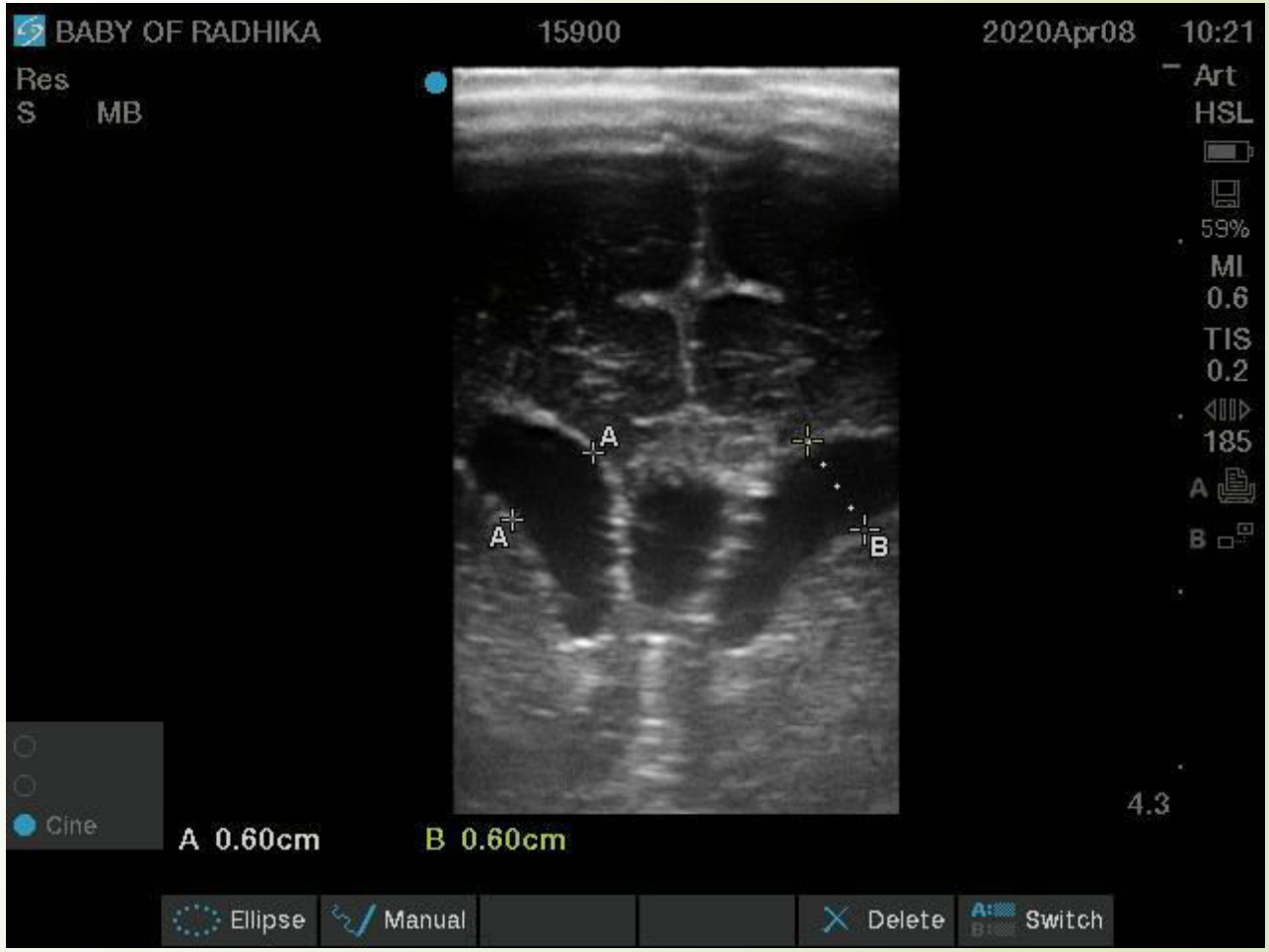
Follow up Electrolytes post discharge

	6 months	9 months
Sodium (meq/L)	136	140
Potassium (meq/l)	3.5	4.9
Chloride (meq/L)	92	96
Calcium (mg/dl)	10.6	10.9

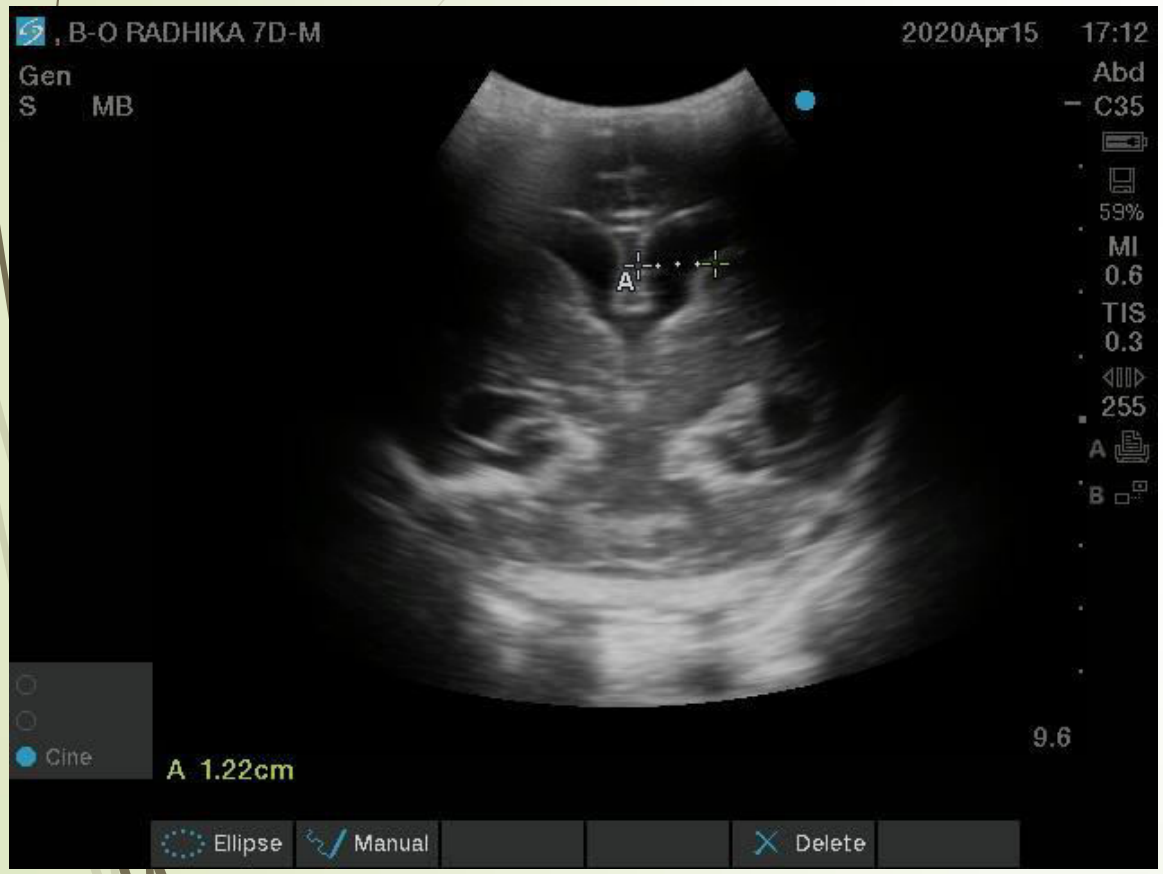
Central Nervous System

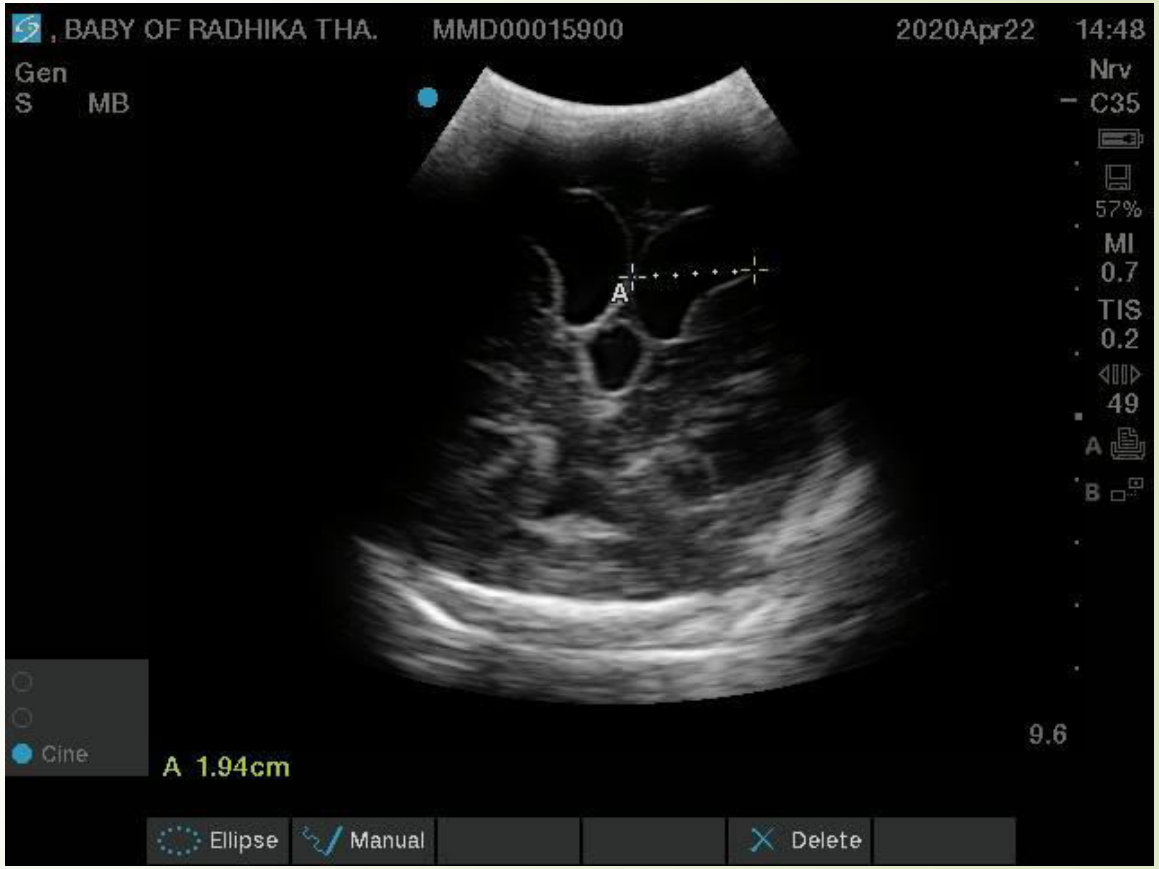
Central Nervous System

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



CNS: progression of ventricular dilatation



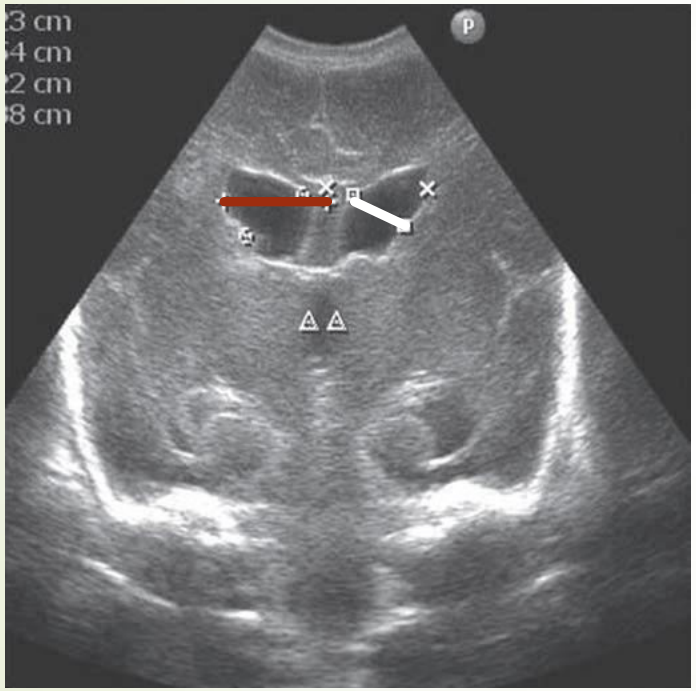


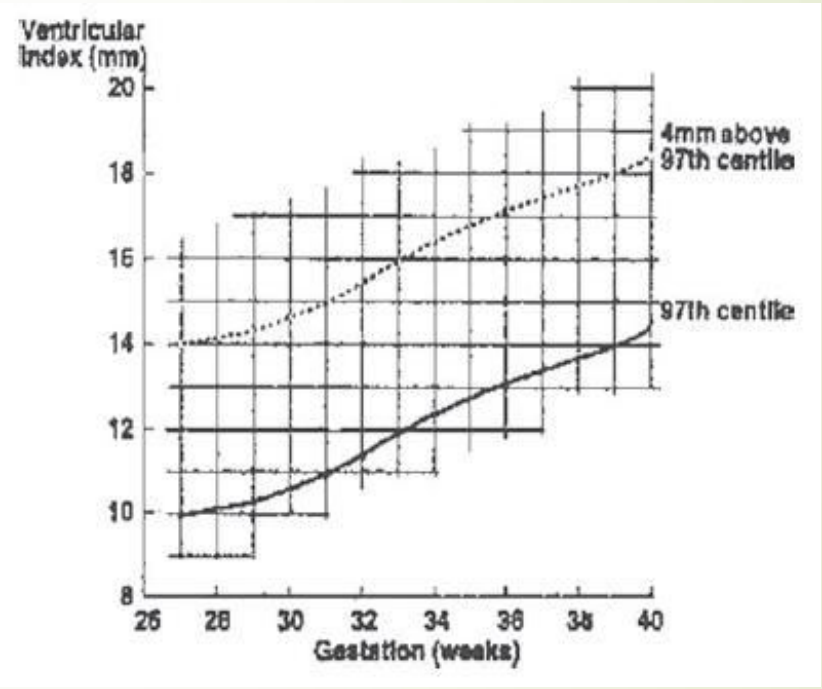
Ventricular index progressively increased to 12 mm on DOL7 and 19 mm on DOL 15 with dilatation of third ventricle

Case Contd.

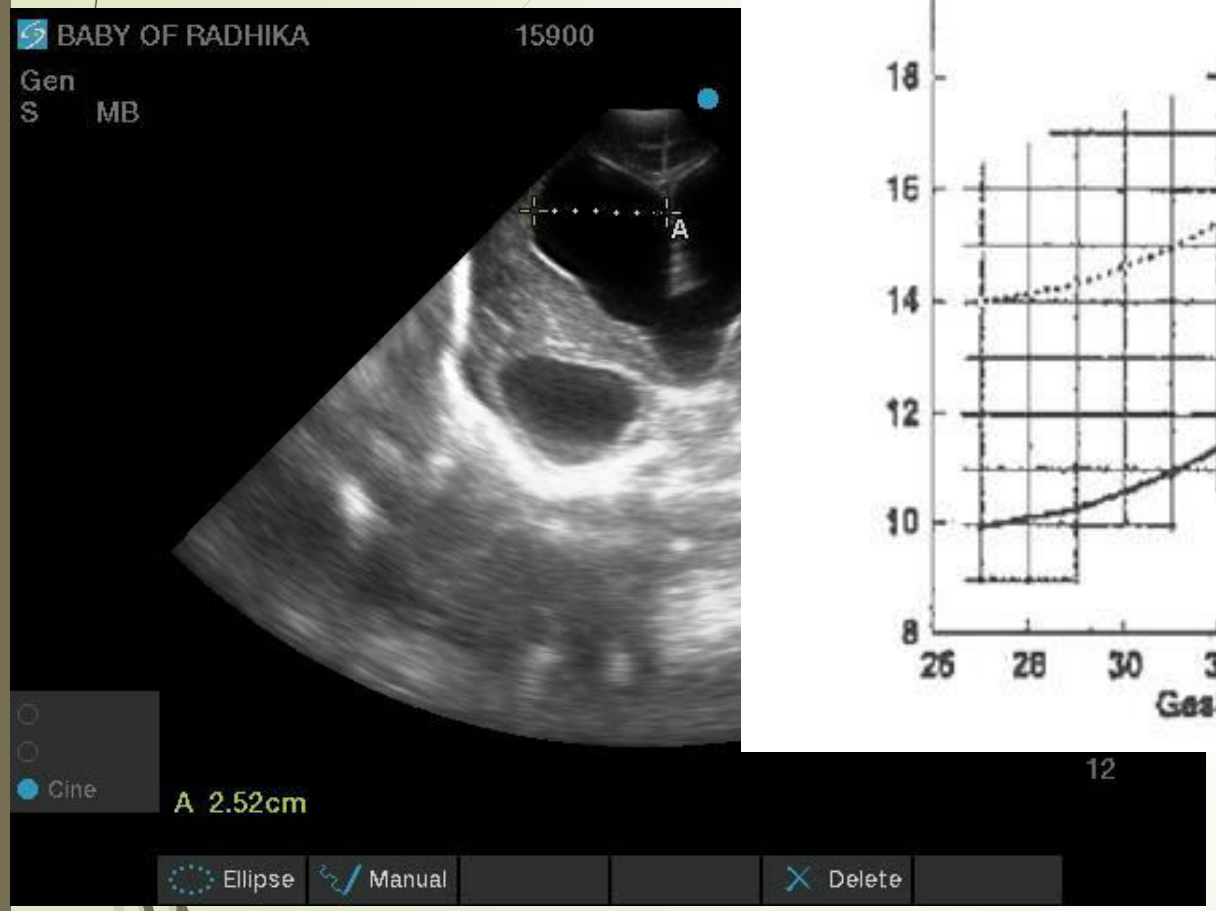
- Progressively increasing ventricular dilatation
- Reasons
  - Post hemorrhagic hydrocephalus (IVH missed)
  - Infections (Sepsis work up so far negative)
  - Some channelopathy (as part of bartter syndrome)

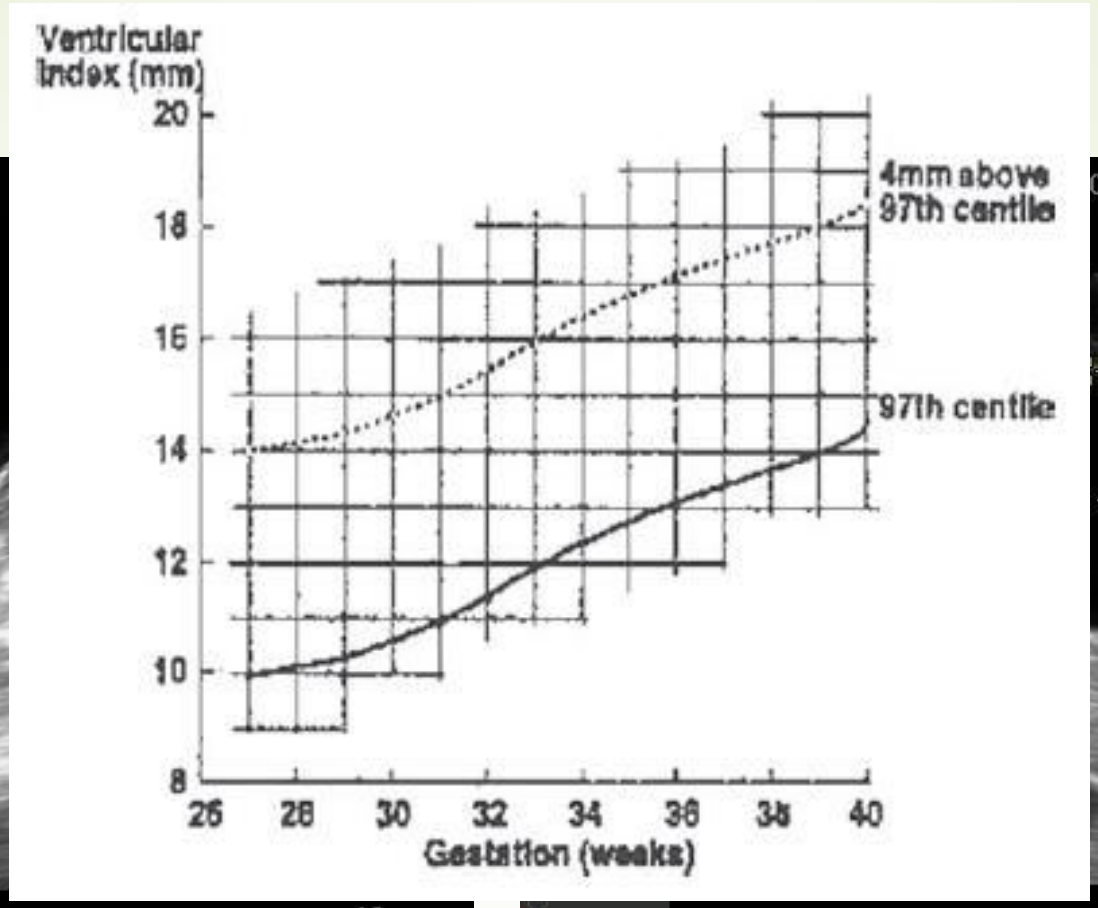
Monitoring hydrocephalus

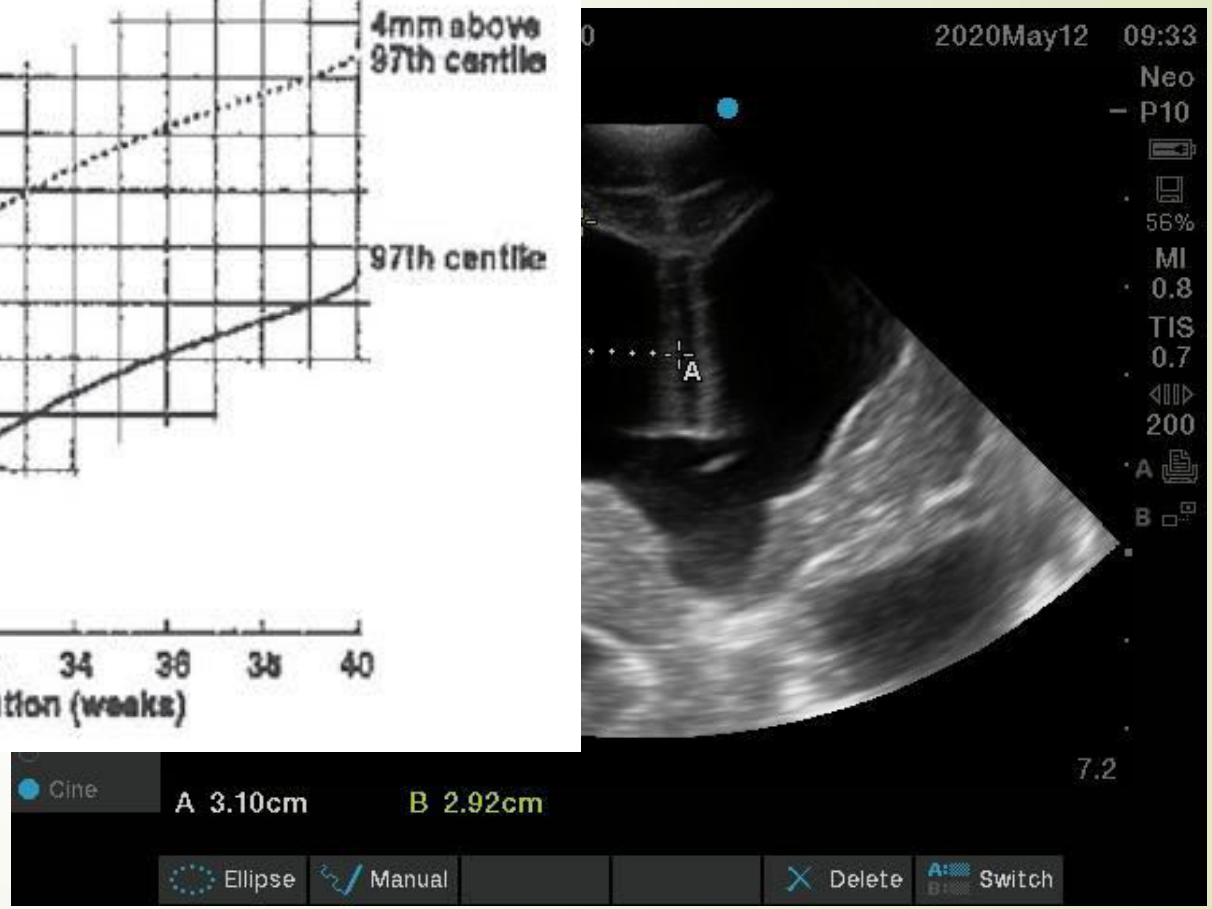




Red line – Ventricular index
White – Anterior horn width







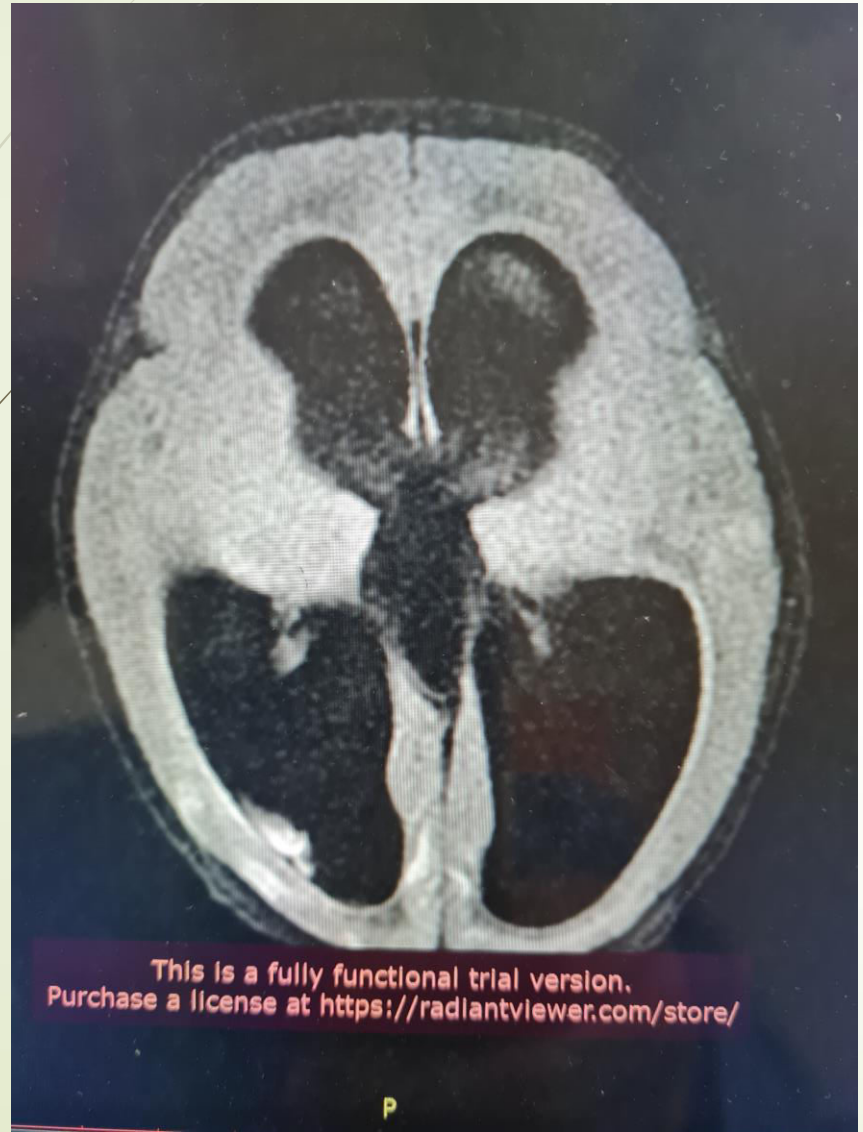
DOL 25
VI – 25.2 mm

DOL 37
VI 31 mm

VI: Summary

DOL	PMA (wks)	Ventricular index	Intervention
25	35+3	29.4	Lumbar puncture (alternate day)
32	36+3	26.2	Ventricular tap (continued), candida meningitis
45	38	28.9	VT
59	40	33.9	VT
65		27.6	VT
75		28.8	VT
81		31	VT
87		30.6	Subcutaneous reservoir placed
116		35.6	2-3 times weekly drainage done during this period
144 days		29.8	
7.5 months			Ventriculo peritoneal shunt placed

MRI Brain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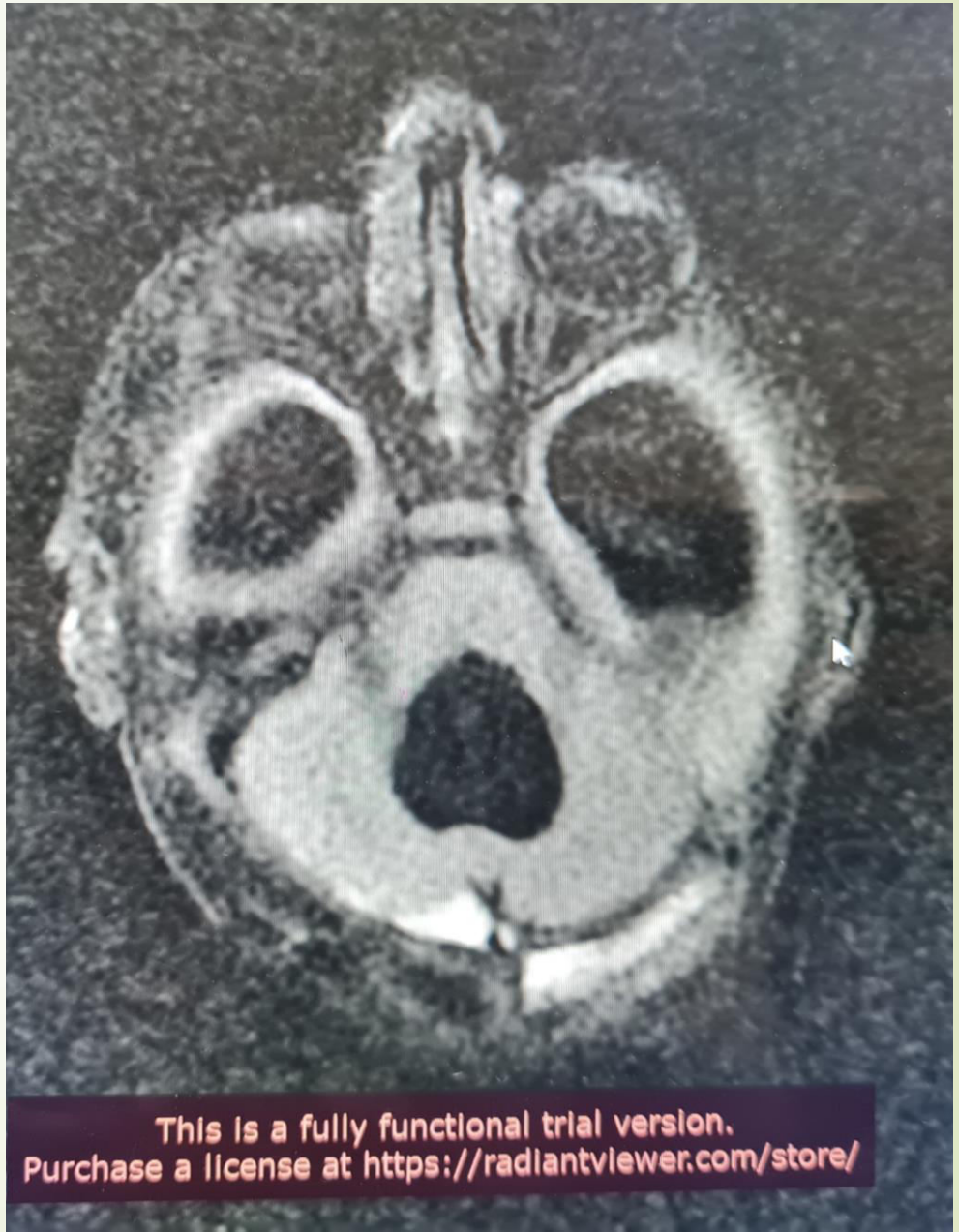
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CNS Part: Summary

- 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 21days

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)

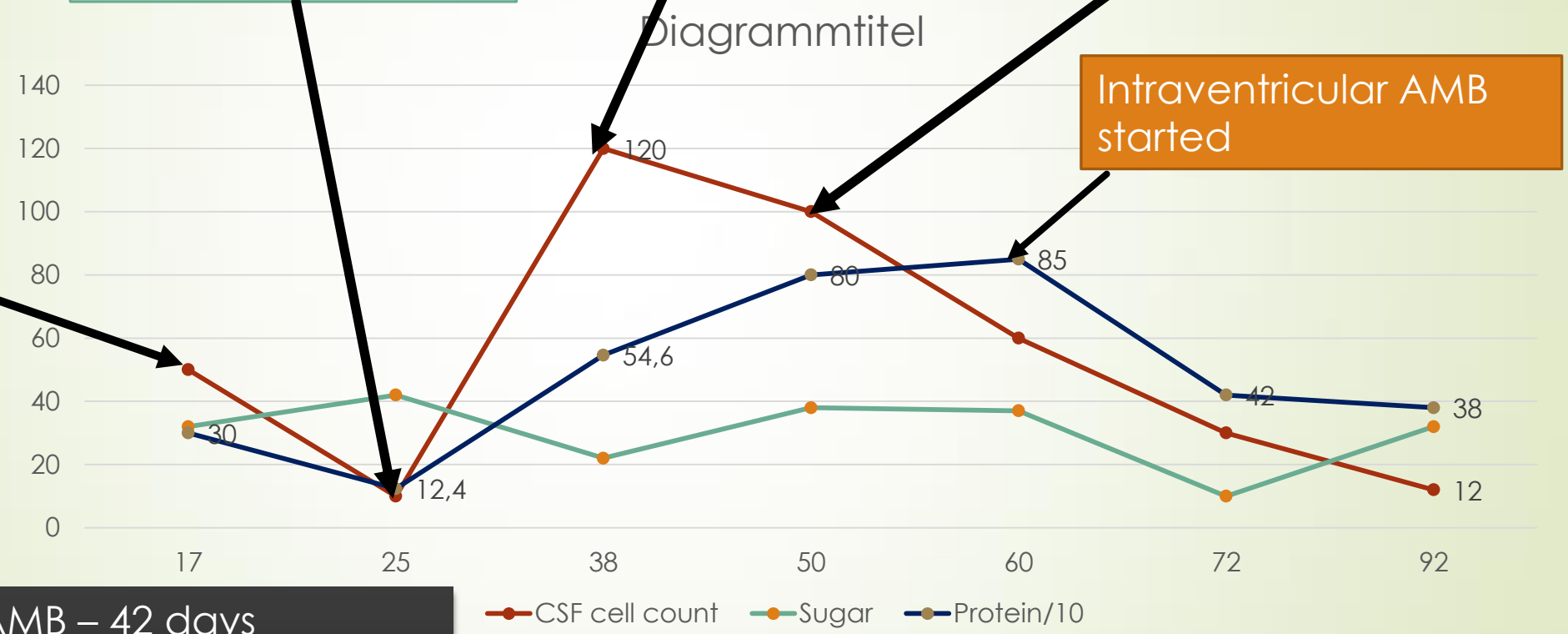
DOL 38
CSF – Candida
Caspofungin

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

DOL 25
BC – Candida
Liposomal Ampho B
added

Intraventricular AMB
started

DOL 17
BC – Kleb
AB– Mero, Amika



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

Course

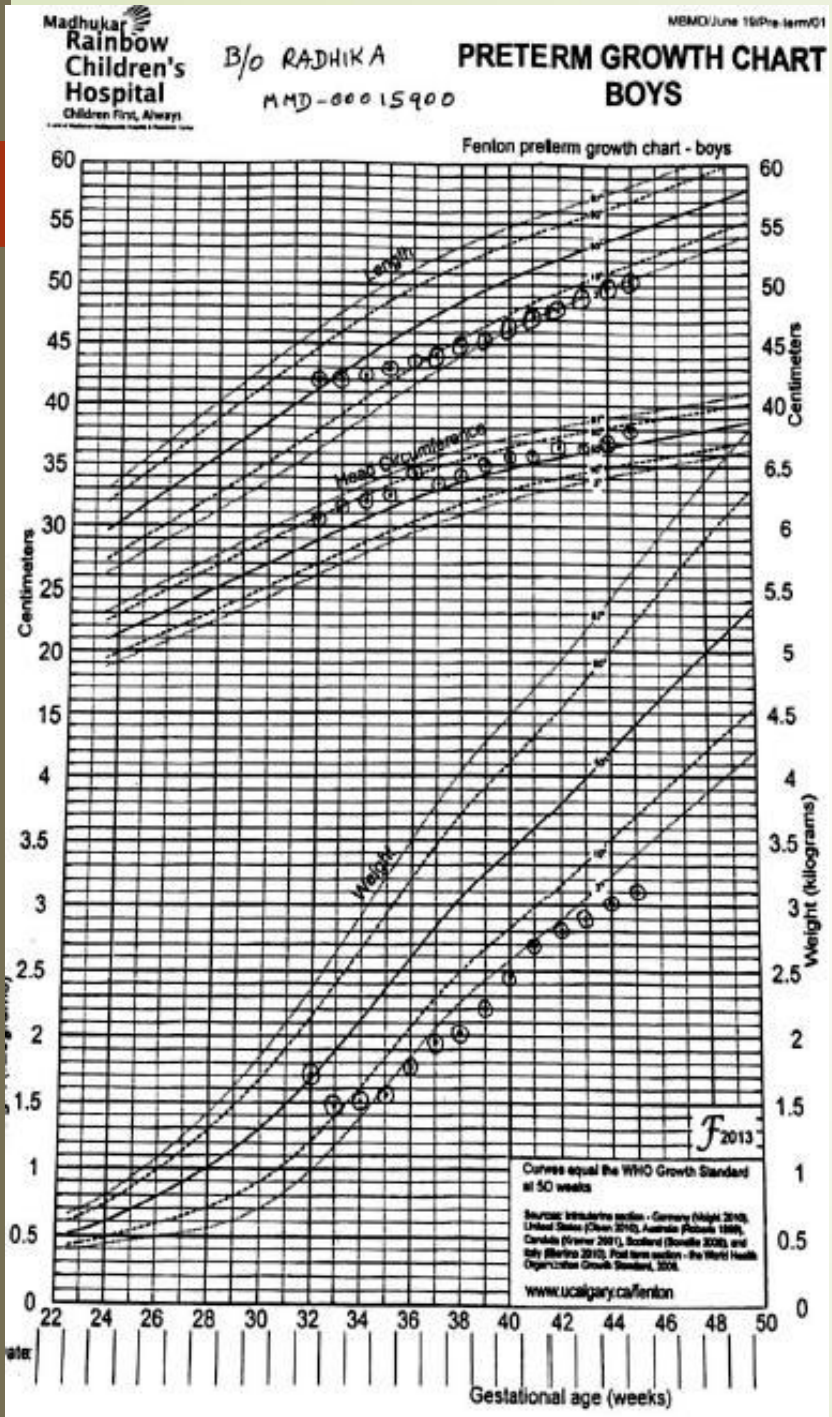
- Omaya reservoir was placed on 88th day of life
- Baby was discharged from hospital on D95 of life
- *Diagnosis – Type 1 Bartter syndrome with candida ventriculitis with hydrocephalus*
- Regularly followed up
- VP shunt done at age of 6.5 months of life

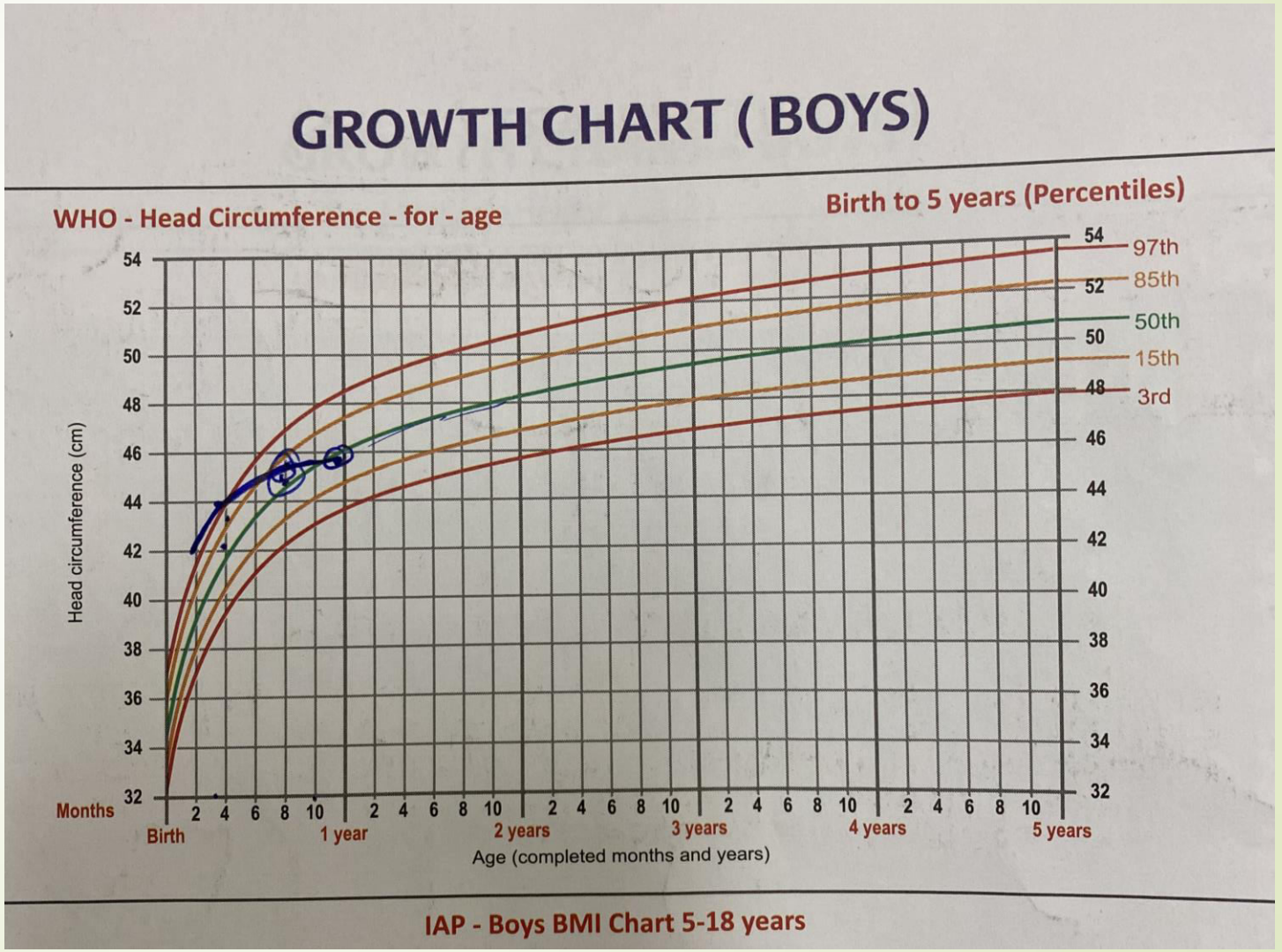
Current Status

- 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





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..

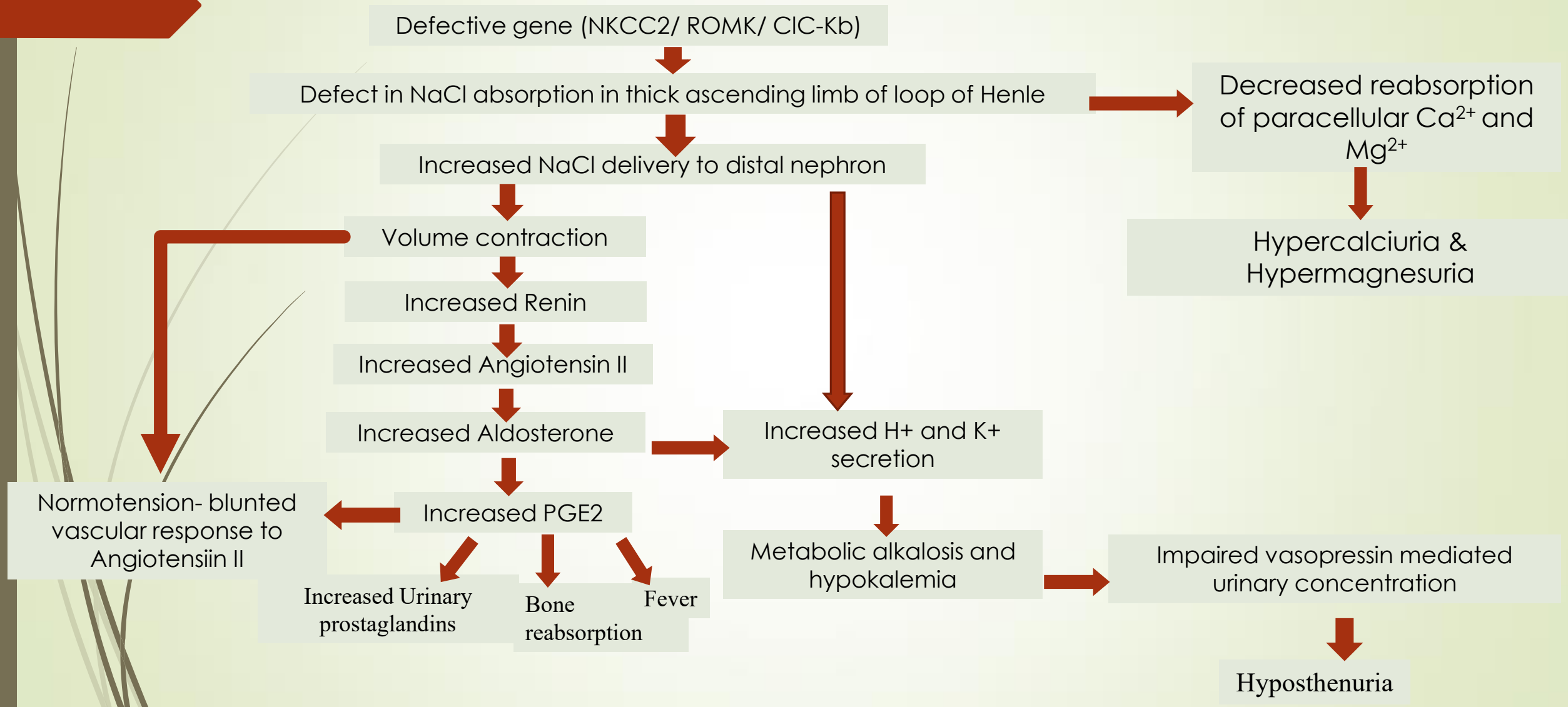
- fetal polyuria
- early onset maternal polyhydramnios
- intrauterine growth restriction
- Preterm birth
- postnatal polyuria
- episodes of dehydration
- recurrent vomiting
- failure to thrive

- Types I, II, and III have severe antenatal symptoms
  - Usually delivered prematurely
  - Poor post natal weight gain and failure to thrive
- IV is a mild salt losing nephropathy with mild antenatal symptoms

Bartter's Syndrome continued..

Type	Subtype	Gene affected	Ion channel affected	Site of Renal Tubule	Pharmacological
I	Antenatal	SLC12A1/15q 21.1	Na-K-2Cl cotransporter	Thick Ascending limb (TAL)	Pure Furosemide type
II	Antenatal	KCNJ1/11q24	Kir1.1 potassium channel	Thick Ascending limb	Thiazide type
III	Classic	CLCNKB/1p36	ClC-Kb chloride channel	Distal convoluted tubule (DCT)	Thiazide type
IV	Bartter Syndrome with Sensorineural Deafness	BSND/1p31 or CLCNKACLC NKB/1p36	Barttin, ClC-Ka and ClC-Kb chloride channels	Both TAL and DCT	Thiazide-Furosemide type

Barter's Syndrome pathophysiology..



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

Hydrocephalous

- 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

Literature Review

- 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

Simopoulos AP (1979) Growth characteristics in patients with Bartter's syndrome. Nephron 23(2–3):130–135

Literature Review

- 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 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

2) Kim J, Jung Y. Increased aquoporin-1 and Na-K-2Cl cotransporter 1 expression in choroid plexus leads to blood cerebrospinal fluid barrier disruption and necrosis of hippocampal CA1 cells in acute rat models of hyponatremia. J. Neurosci. Res. 2012; 90: 1437–44

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