ISOLATED AND CONGENITAL ACTH DEFICIENCY - REPORT OF TWO CASES

DR GRACELIN – MD Postgraduate

DR J DHIVYALAKSHMI – Consultant Pediatric Endocrinologist

DR BINU NINAN – HOD, Dept of Neonatology, SRMC & RI

INTRODUCTION

- HYPOCORTISOLISM can be
  - Primary – Adrenal Disorders
  - Secondary – Pituitary causes

- Isolated/Congenital ACTH deficiency - Rare & Fatal
  - Not associated with lack of Aldosterone
  - Diverse clinical presentation

- If unrecognised leads to a fatal course due to hypocortisolism

- We present Two cases of ACTH deficiency with diverse presentation.

Case 1

45 days old male child

- Concern:
  - Fever x 1 day
  - Seizures GTCS one episode lasting for 5 minutes
- HOPI:
  - FTNVD, Birth Wt: 2.84 kg, Cried immediately after birth (OUTBORN)
  - Received vaccination – DTwP+Hib+Hep B – morning
  - Same day – 8 hours later – Fever with GTCS
  - No h/o feeding difficulties, Respiratory distress, loose stools, vomiting, lethargy, no S/S dehydration, hypovolemic shock, salt wasting

Case 1

- Past history:
  - D3 of life – hypoglycemic seizures
  - CBG – **30 mg/dl**, S. calcium – 9 mg/ dl,
  - Critical samples – **S. Cortisol – 2 µg/dl,** S. Insulin – 1. 4 µIU/ml, Urine – ketones – negative.
- Family history:
  - 2nd baby born to 3rd degree consanguinous marriage
  - Elder brother - healthy
  - No family history of seizures
- Developmental milestones – social smile (+)
- **On examination:**
  - Child was in post ictal state
  - Wt: 3.5 kg length: 53 cm HC: 38 cm
  - Vitals – stable
  - No neurocutaneous markers
  - AF – At level, no bulging
  - SMR: Prepubertal

Case 1

- CBG : **20mg/dl**
- Critical samples sent, glucose bolus given
- 3 hours – hypoglycemia – 20 mg/dl, glucose infusion started.
- Hypoglycemic spells recurred whenever the glucose infusion was stopped
- Critical samples
  - Na: 128 mmol/L K+:6.0 mmol/L
  - Serum Cortisol: **<0.2 ug/dl,** S. Insulin – 1.2 µIU/ml
  - Urine Ketone – Negative
  - Reducing Substance – Negative
- Hydrocortisone started. 17 OHP and S.Cortisol sent.
- Glucose infusion was stopped.
- Sepsis work up – negative
- TFT – Normal

Case 1

- Other investigations:

- 17 –OHP - 0.8 ng/ml
- S. Cortisol - **< 0.27 µg/dl**
- S.Testosterone - 148 ng/dl
- DHEAS - 1.96 µg/dl

- Since there was no hyperpigmentation – D/S as suspected ACTH deficiency
- Upon follow up – planned to do ACTH stimulation test after stopping hydrocortisone for 24 hours.

At 6 months of age – After stopping hydrocortisone for 24 hours (Under supervision)

- **ACTH STIMULATION TEST**

Serum	0 min	30 min	60 min
ACTH	**18pg/ml**		
CORTISOL	**< 0.2**	**0.27**	**0.49 µg/dl**
17 OH P	2	1.65	2.13 ng/ml
SODIUM	130 mmol/L		
POTASSIUM	5.0 mmol/L		
CHLORIDE	101 mmol/L		
BICARB	25 mmol/L		

- MRI Brain & Pituitary - normal
- Final Diagnosis – Isolated & Congenital ACTH deficiency

Case 2

Two day old term SGA boy child

Concern:

Referral given for bilateral undescended testis

1 episode of asymptomatic hypoglycemia

BIRTH HISTORY

- FTLSCS
- IVF Pregnancy
- Mother's age: 31
- Birth Weight: 1.66 kg
- Cried immediately after birth (INBORN)
- No maternal history of Still birth, abortion

Case 2

O/E

- Length: 50 cm
- Weight 1.66kg
- HC: 35 cm
- Vitals stable
- No neurocutaneous markers
- AF @ level, No bulging
- No dysmorphism
- Bilateral testis not palpable
- SPL: 3 cm
- Scrotal folds: undeveloped
- External masculization score: 9
- Investigated for 46XYDSD

Case 2 - Workup

- FSH : 4.8 mIU/ml
- LH : 38.62 mIU/ml
- Serum Cortisol: 1 µg/dl
- Testosterone: 144 ng/dl
- DHT : 178 pg/ml
- TFT : WNL
- 17OHP: 2.37 nmol/L
- Karyotyping: 46XY
- USG: testis visualised in inguinal canal

ACTH STIMULATION TEST

Serum	0 min	30 min	60 min
ACTH	**24.5 pg/ml**		
CORTISOL	**4.48**	10.17	10.74 µg/dl
17 OH P	11.02	11.04	11.00 ng/ml

- MRI Brain & Pituitary – normal
- Serum electrolytes-Na-135,K-5.5,cl-101,bicar-17
- Final Diagnosis – Isolated & Congenital ACTH deficiency

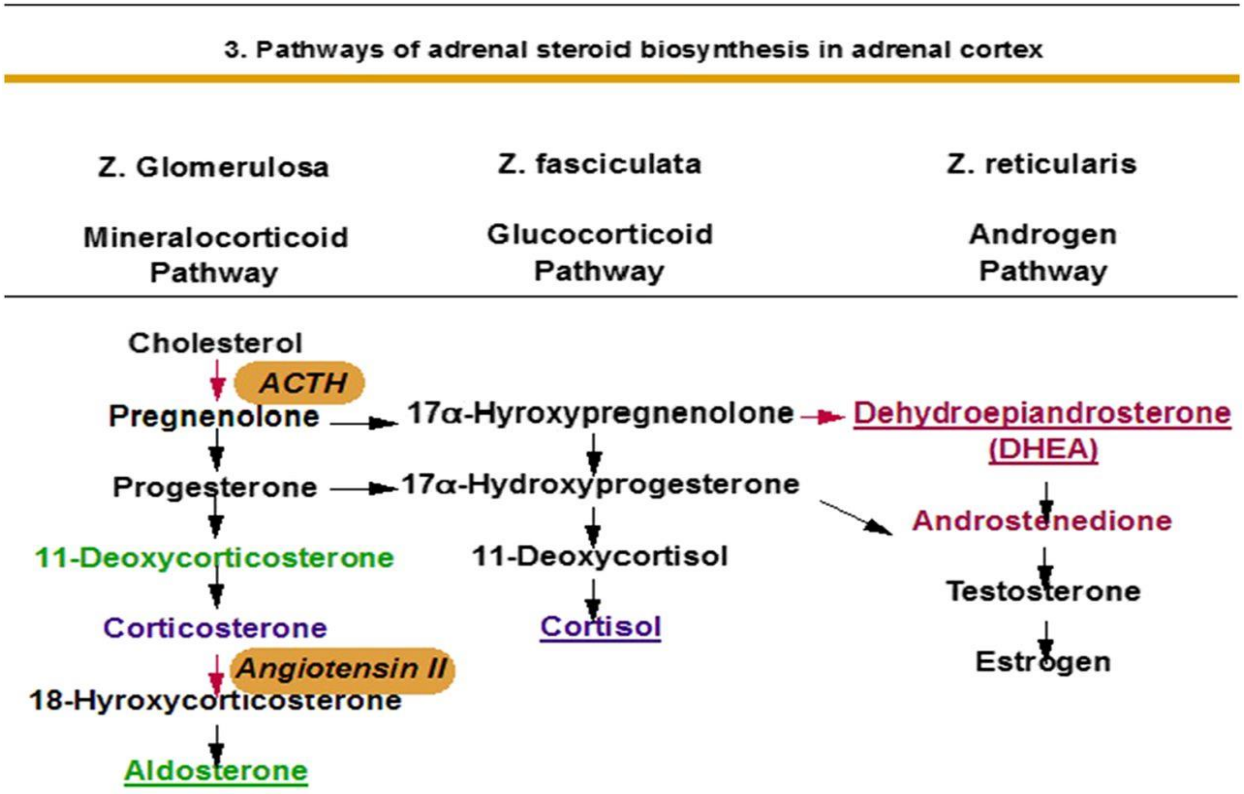
- No rise in S.cortisol & 17 hydroxyprogesterone following ACTH stimulation test
- Poorly developed adrenal - Congenital ACTH deficiency.
- started on hydrocortisone (6-8 mg/m^2/day).
- underwent diagnostic laproscopy with orchidopexy for B/L undescended testis.

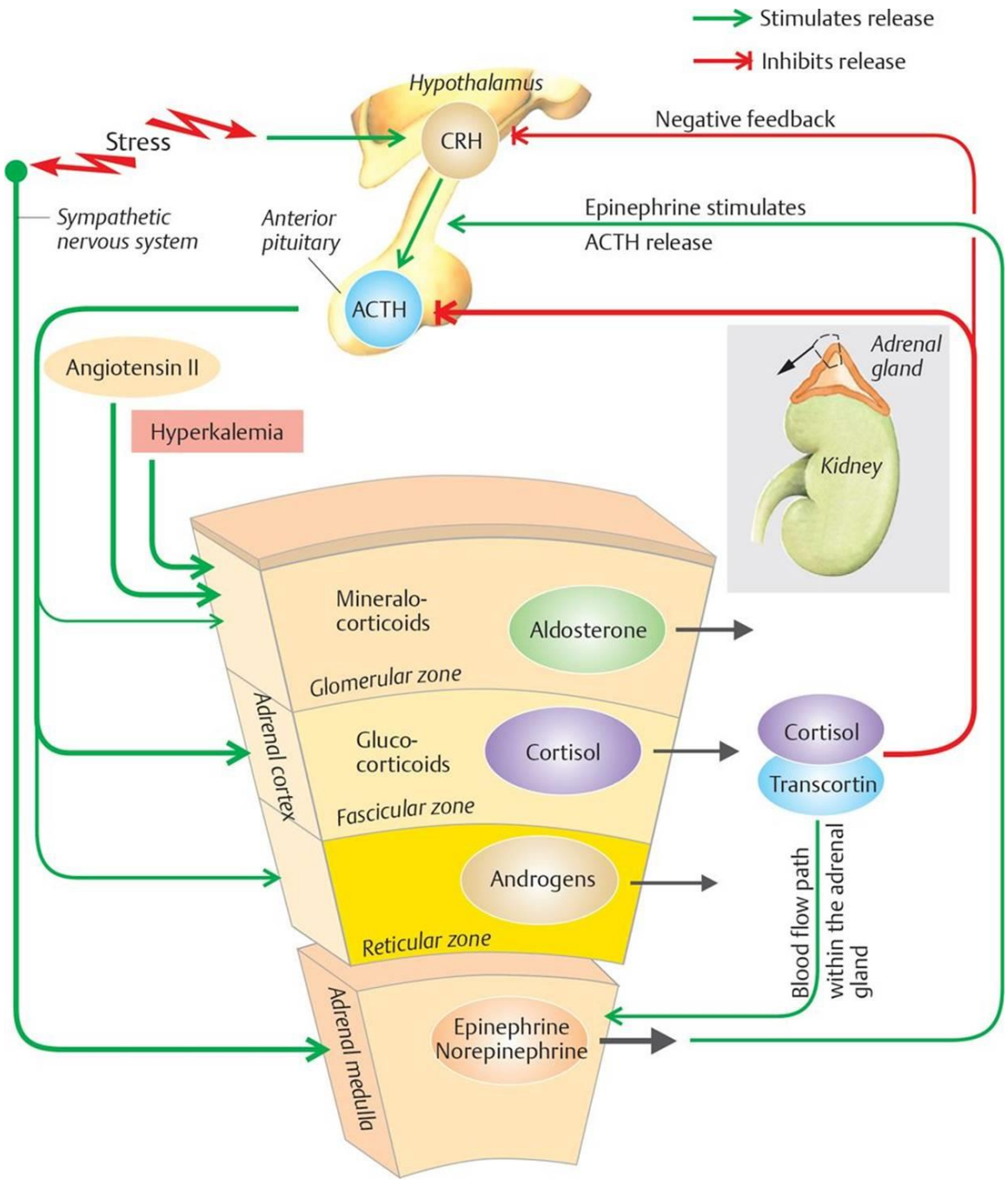
FOLLOW UP

	CASE 1	CASE 2
AGE	3 years	2 1/2 years
HEIGHT	90	85
WEIGHT	13.5	15
MEDICATIONS	HYDROCORTISONE	HYDROCORTISONE
	ACTH stimulation test done after stopping hydrocortisone- S.cortisol still low	Plan to do ACTH stimulation test at follow up
	Thriving well	Thriving well

DISCUSSION

PHYSIOLOGY OF ADRENAL HORMONE SYNTHESIS




Stimulates release
Inhibits release
Hypothalamus
CRH
Stress
Negative feedback
Sympathetic nervous system
Anterior pituitary
Epinephrine stimulates ACTH release
ACTH
Angiotensin II
Hyperkalemia
Adrenal gland
Kidney
Mineralo-corticoids
Aldosterone
Glomerular zone
Adrenal cortex
Gluco-corticoids
Cortisol
Fascicular zone
Androgens
Reticular zone
Cortisol
Transcortin
Blood flow path within the adrenal gland
Adrenal medulla
Epinephrine
Norepinephrine

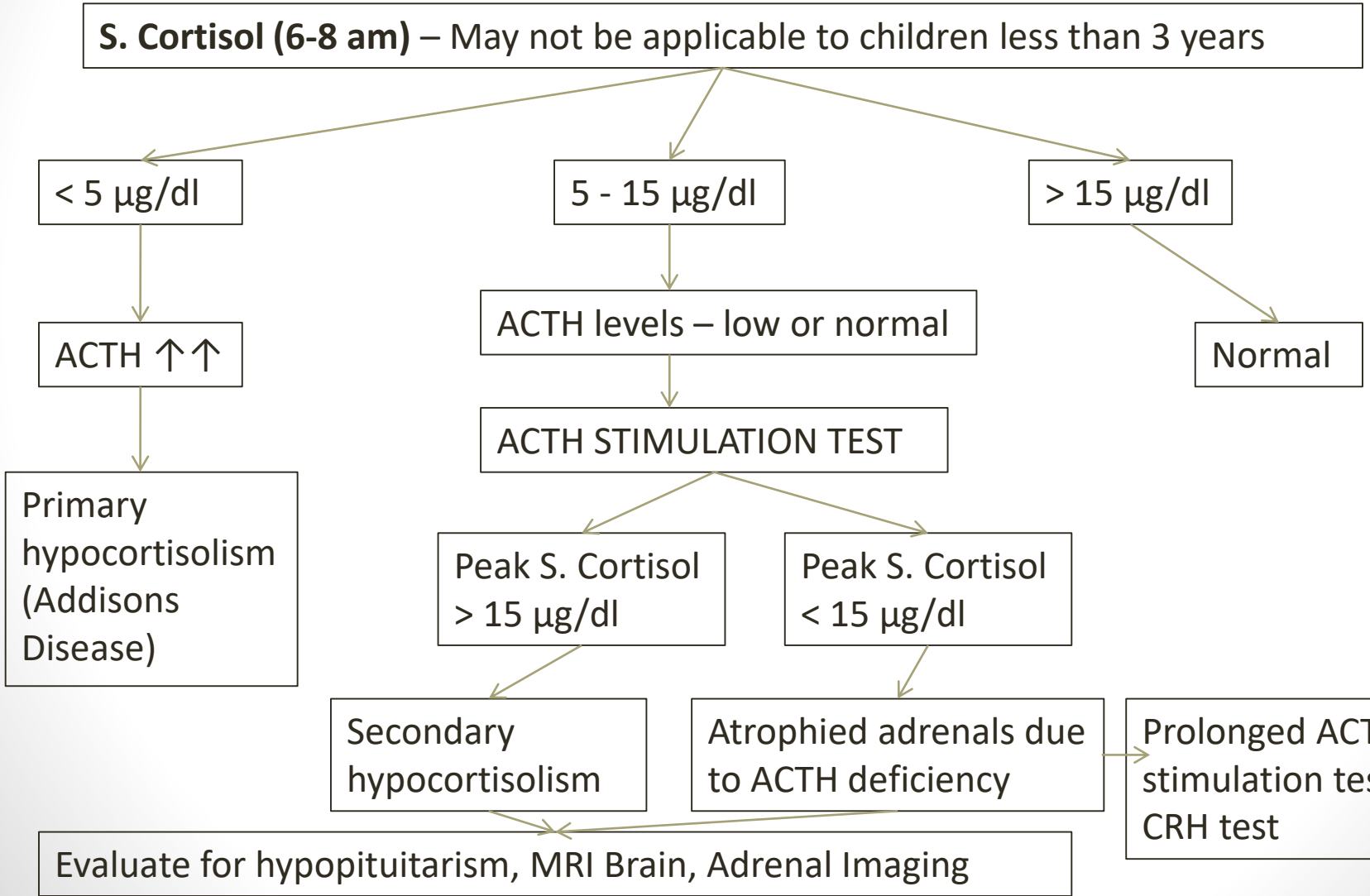
DISCUSSION

SECONDARY CAUSES OF HYPOCORTISOLISM

- Long-term glucocorticoid therapy
- Craniopharyngioma
- Germinoma
- Pituitary Surgery or Radiation
- Traumatic Brain injury – abrupt onset
- Septo optic Dysplasia
- Prader Willi Syndrome
- ISOLATED ACTH Deficiency- Rare
- Transient ACTH deficiency

	PRIMARY	SECONDARY- ACTH DEF
HYPERPIGMENTATION	PRESENT	ABSENT
ACTH LEVELS	HIGH	LOW
CORTISOL	REDUCED	REDUCED
ALDOSTERONE	DECREASED	NORMAL to DECREASED
TREATMENT	HYDROCORTISONE (10-12mg/m2/day) FLUDROCORTISONE	HYDROCORTISONE (6-8mg/m2/day)
STRESS STEROID PROTOCOL	FOLLOWED	FOLLOWED

Approach to Hypocortisolism in Children



STRESS STEROID PROTOCOL

- child -unwell –not tolerating oral hydrocortisone
- IM injection of Hydrocortisone (stat followed by 6-8 hrly)
  - 0 to 1 yr-25mgs
  - 1 to 5 yrs- 50mgs
  - 5 yrs-100mgs
- Once able to take orally - Double or triple oral hydrocortisone for next 24 to 48 hrs
- Shift to usual dose of hydrocortisone

FEW CASE REPORTS

- **Mahdi alsaleem et al. Neonatal isolated ACTH deficiency : a potentially life threatening but treatable cause of neonatal cholestasis**
  - **BMJ case reports 2016;doi:10.1136/bcr-2016-215032**
- Term baby boy at D11 of life.
- Presented with poor feeding, apnoea lasting for 20 sec, Icterus.
- On evaluation, CBG-19mg/dl given glucose bolus, critical sample cortisol-<0.2µg/dl , ACTH-low ,S.cortisol no rise, sepsis work up-negative, MRI brain-Normal
- Started with Hydrocortisone , child is thriving well

- **Michael Y Torchinsky et al. Severe hypoglycemia due to Isolated ACTH deficiency in Children;**
  - **International journal of paediatrics,vol,2011,Article ID 784867**
- 7 year old girl with seizures
- CBG-21mg/dl ,S.cortisol-0µg/dl ,Serum electrolytes-N,
- ACTH stimulation test-ACTH <5pg/ml,cortisol-0µg/dl,
- MRI brain-Normal.
- started with hydrocortisone, child thriving well.

KEY MESSAGE

- **Isolated /congenital ACTH deficiency is a rare disorder.**
- **High suspicion is needed for any child presenting with hypocortisolism without hyperpigmentation.**
- **Key to diagnosis - ACTH levels.**
- **Dosage is different for primary and secondary hypocortisolism.**
- **Long term follow up is necessary.**
- **Stress steroid protocol should be followed.**

- THANK YOU