A novel mutation causing Pseudohypoaldosteronsim

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Introduction

- We present a case of a neonate with a rare cause of life threatening hyperkalaemia, hyponatraemia and metabolic acidosis.
- We discuss the important investigations and differential diagnoses in an infant with these electrolyte abnormalities.
- A novel mutation in SCNN1A was found, this is the first case in Northern Ireland

Case History

8 day old girl presented to Emergency dept with 12 hour history of poor feeding and vomiting

Past medical history:

- Term, NVD, birth weight 3.5kg
- First born child, parents consanguineous
- Breastfed, previously well

Examination

- Mottled, cool peripheries, drowsy & floppy
- HR 66, RR 30, SpO_2 88% r/a, CRT 4 seconds, Temp 34.9^{0}C, 5% dehydrated
- HS: 1 & 11 & ^{0}, Femorals not palpable
- RS: good AE R=L
- Abdomen: soft, non tender, no organomegaly or masses, normal female genitalia

Initial management

- O_2, bag & mask ventilation → HR>100
- 3 x 10mls/kg Saline boluses
- Cardiac monitoring – periods of VT
- IV Cefotaxime & Amoxicillin
- IV Hydrocortisone given empirically
- Venous gas: Ph 7.16, CO_2 8.6, O_2 3.6, HCO_3 23.1, BE - 5.5,
- **Na 121 mmol/L, K 10.5 mmol/L**
- Blood sugar 3.8mmol/L
- Urgent echo, renal US: normal

Management of hyperkalaemia

- Nebulised Salbutamol continuously
- Cardiac monitoring in PICU
- IV Calcium gluconate 10% 0.2mls/kg
- Insulin infusion 0.05 units/kg/hr
- IV fluids 10% dextrose with NaCl @ 2/3 maintenance
- Sodium bicarbonate IVI 1mmol/kg/hr
- Calcium resonium 1.5g NG stat

Differential Diagnosis

- Congenital adrenal hyperplasia (21 OH deficiency, 3β HSD deficiency)
- Aldosterone synthase deficiency
- Adrenal hypoplasia congenita
- Antenatal Bartter's syndrome (loss ROMK)
- Pseudohypoaldosteronism Type 1 (Renal or Multiple Target Organ Disease)
- Secondary pseudohypoaldosteronism (UTI, urinary obstruction)

Investigations	Results
U&E, CRP	Na 116, K >10, Ur 13, Cr 53, CRP 5
FBC	Hb 20.7 WBC 15.3 Plt 369
Cortisol	793nmol/L
Insulin	16.7mU/L
ACTH	10ng/L
17 OHP	4.7nmol/L
Urine electrolytes	Na 165, K 8
Trans-tubular K gradient	0.6 ↓↓↓
Fractional excretion Na	3.9%↑
Urine steroid profile	Not CAH, aldosterone synthase def
Aldosterone	45, 200 pmol/L ↑↑↑
Renin	>34 ng/ml/h ↑

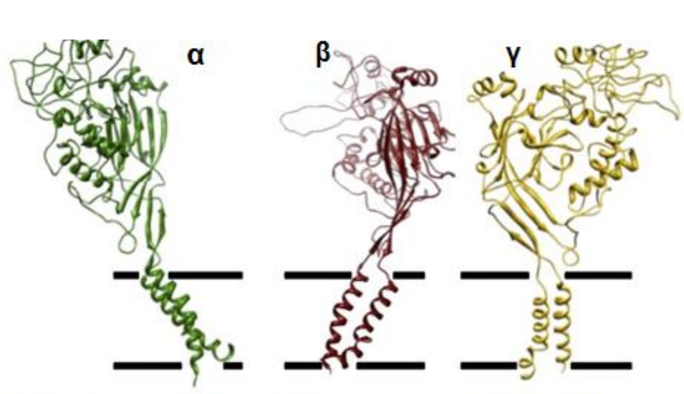
Pseudohypoaldosteronism

- Rare syndrome of resistance to Aldosterone
- 2 clinically distinct forms
- **Systemic form:** mutation ENaC, a highly Na selective channel, expressed in the distal nephron, colon, lung and exocrine glands
- **Renal form:** mutation mineralocorticoid receptor, mild salt losing, improves by early childhood[3]
- Sweat test useful to differentiate 2 forms

	Generalised PHA 1	Renal PHA 1
Genes	SCNN1A, SCNN1B, SCNN1G	NR3CG
Encoding	ENaC (kidney, respiratory tract, colon, salivary glands, sweat ducts)	Mineralocorticoid receptor
Inheritance	AR, sporadic	AD, sporadic
Clinical characteristics	Severe hyponatraemia & hyperkalaemia Risk of shock, cardiac dysrhythmias, collapse and cardiac arrest Recurrent cough/wheeze Seborrhea like skin rashes (lips/nose) Cholelithiasis	Mild renal salt wasting Vomiting Dehydration Failure to thrive
Investigations	↓ Na, ↑ K, metabolic acidosis ↑↑ Aldosterone, Renin	↓ Na, ↑ K, metabolic acidosis ↑↑ Aldosterone, Renin
Treatment	Na up to 50mmols/kg/day Low K diet +/- ion exchange resins	Na 3-20 mmols/kg/day Usually stop tx by 18-24 months
Prognosis	Life long, may improve with age Recurrent life threatening episodes of salt loss Growth/puberty delay if non complaint	Improves with age – up regulation of MC axis – high Aldosterone levels persist

Genetic Results

- Sequencing of the SCNN1A gene revealed a homozygous mutation c.1291T>G
- This results in the replacement of a cysteine residue with a glycine at position 413 of the amino acid chain.
- This cysteine is highly evolutionarily conserved, and the mutation is predicted to disrupt the structure of the extracellular domain of the protein, abrogating its function.
- Expected recurrence risk 25%



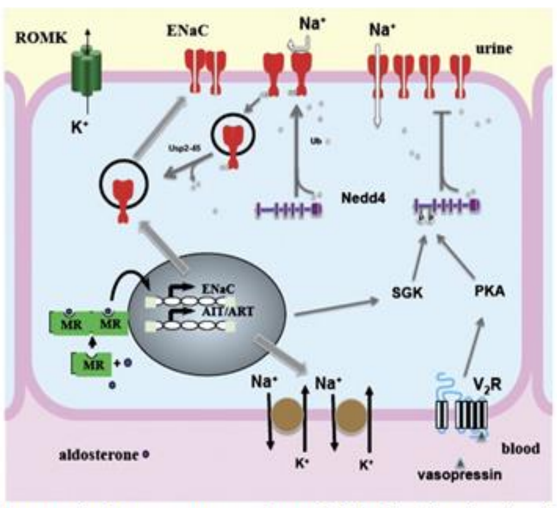
Model of ENaC subunits: α subunit is encoded by SCNN1A, required for channel activity; large extracellular loop, ENaC is a constitutively open channel –rate limiting step in Na reabsorption[1]

Epithelial sodium channel, ENaC

- Constitutively open channel
- Number of active channels at the apical cell surface of distal nephron have a profound affect on Na absorption, amount Na excreted in urine

Also expressed in

- Lung: maintains composition of air-surface liquid
- Exocrine glands: sets ionic composition of sweat
- Colon: mediates Na absorption from intestine



Aldosterone induces expression of ENaC at luminal cell surface in distal tubule, allowing Na to be actively exchanged with K[1]

Clinical progress

Our case is now 17 months old and well, with no further acute episodes of salt wasting to date.

Na, K normal on medication:

- Sodium Chloride 12.3 mmols/kg/day
- Sodium bicarbonate 3.3 mmols/kg/day
- Low K diet: 0.6mmols/kg/day

Growth: weight 91st % height 25th %

- 2 LRTIs, 1 hospital admission
- Café au lait macules
- Aldosterone 18,000pmol/L, Renin 148.5pg/ml

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