BACKGROUND
Costello syndrome is a disorder of the Ras/MAPK pathway characterised by mental retardation, coarse facies, loose skin, cardiovascular abnormalities, skeletal abnormalities and predisposition to neoplasias. Endocrine deficiencies have been reported, including GH and cortisol, leading to hypoglycaemia in some cases. It has also been documented in association with Hyperinsulinemic Hypoglycaemia (HI), being usually mild and medically-responsive. The exact mechanism that links Costello syndrome and HI is still unknown.

OBJECTIVE
To describe the clinical characteristics, biochemical findings and challenging management of a case of Costello syndrome with severe HI.

METHODS
Review of the patient’s medical records.

CASE
Pregnancy: polyhydramnios.
Birth: 40+5 weeks, NVD, BW 3.5kg (-0.45 SDS), good Apgar scores.

Problems: hypoglycaemia, feeding intolerance and tracheomalacia since day 1 of life. Subsequently found to have failure to thrive, biventricular hypertrophy with pulmonary stenosis and gastroesophageal reflux disease with possible abnormal gastric emptying, requiring gastrostomy feeds.

Phenotype: Weight and height 0.4 SDS),  good Apgar scores.

INITIATIVES

- Initial hypoglycemia
  - BG (mmol/l) 2.9
  - Lab glucose (mmol/l) 2.4
  - Cortisol (mmol/l) 122
  - insulin (mU/l) 2.2
  - C-peptide 134
  - GH (ug/l) 5.3
  - IGF-1 (ng/ml) [55-327] <25
  - IFRP-3 (mg/l) [0.7-3.6] 0.91
  - Lactate (mmol/l) 0.7-2.1 0.7
  - Ammonia (umol/l) (≥40) 23
  - NEFA (mmol/l) 0.42
  - BHOB (mmol/l) 0.13
  - Acyclovirine Normal
  - PAA Normal
  - Glucagon 4pmol/l (<50)
  - ACTH 20.2ng/l

- Initial blood glucose profile (on 24h Neonate continuous feeds)
  - BG Mmoll/l 3.2 3.7 3.7 3.3 3.4 4.3 3.2 5.7 2.7 5.2 5.7 5.7 5.4 5.2 4.7 5.0 4.8 4.8 5.3 5.4 4.8 4.4 5.2 4.1

Glucagon for HI diagnosis (1mg im):
BM 2.5mmol/l → 4.6mmol/l

OGTT and Protein load:
Did not trigger hypoglycaemia

Standard synacthen test
- Time 0h00m 0h30m
- Cortisol Normal 134 588

MRI brain:
Normal pituitary gland

Given poor growth and undetectable IGF-1 concentrations, a Glucagon test for GH secretion (100mcg/kg) was performed

- TIME (min) 0 -30 0 +30 +60 +90 +120 +150 +180
- GH (ug/l) 7.3 3.6 3.6 1.9 1.6 2.8 2.7 2.4 1.5
- CORTISOL (mmol/l) 97 210 - 3.6 - 225 177 - 174
- LAB GLUCOSE (mmol/l) 4.6 4.0 - 3.6 - 3.3 - 3.4 -

GENETICS:
Negative for BWS, PTPN11, ABCCB, KCNJ11, HNF4A genes.
De novo mutation in HRAS (c.466>T>G), not previously described.

MANAGEMENT
Diazoxide (10mg/kg/day) ± octreotide (38mcg/kg/day) ± sirolimus (1.6mg/m2/day)
+ 24h continuous Neocate LCP 16% feeds → NO glycaemic control

- 95% laparoscopic pancreatectomy (Histology: No abnormal pancreatic tissue)

- Hypoglycaemia persisted → octreotide injections + continuous enteral feeds
- Tachyphylaxis to increased doses of octreotide. Ongoing hypoglycaemia

To avoid further surgery and potentially increased insulin sensitivity → Prednisolone (= 4mg/m2/day hydrocortisone) + continuous feeds Neocate 16% (116ml/kg/day) + Vitajoule 10% (8.2mg/kg/min of glucose) → satisfactory glycaemic control

CONCLUSIONS
Costello can present with severe medically and surgically unresponsive HI. In view of potentially increased insulin sensitivity in some of these patients the use of steroids might help avoid further surgery.


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DOI: 10.3252/pso.eu.55ESPE.2016

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