Challenging management of Costello syndrome with severe Congenital Hyperinsulinaemic Hypoglycaemia

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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 hyoglycaemia in some cases. It has also been documented in association with Hyperinsulinaemic Hypoglycaemia (HI), being usually mild and medically-responsive. The exact mechanism that links Costello syndrome and HI is still unknown.

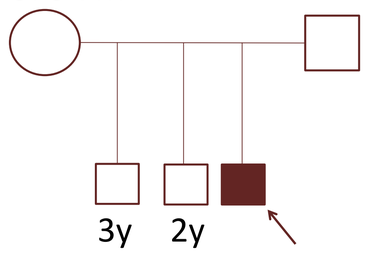
OBJECTIVE

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 0.4th centile, macroglossia, low set ears, deep palmar and plantar creases, wide spaced nipples , soft systolic murmur upper left sternal edge, and abdominal distension (normal genitalia).

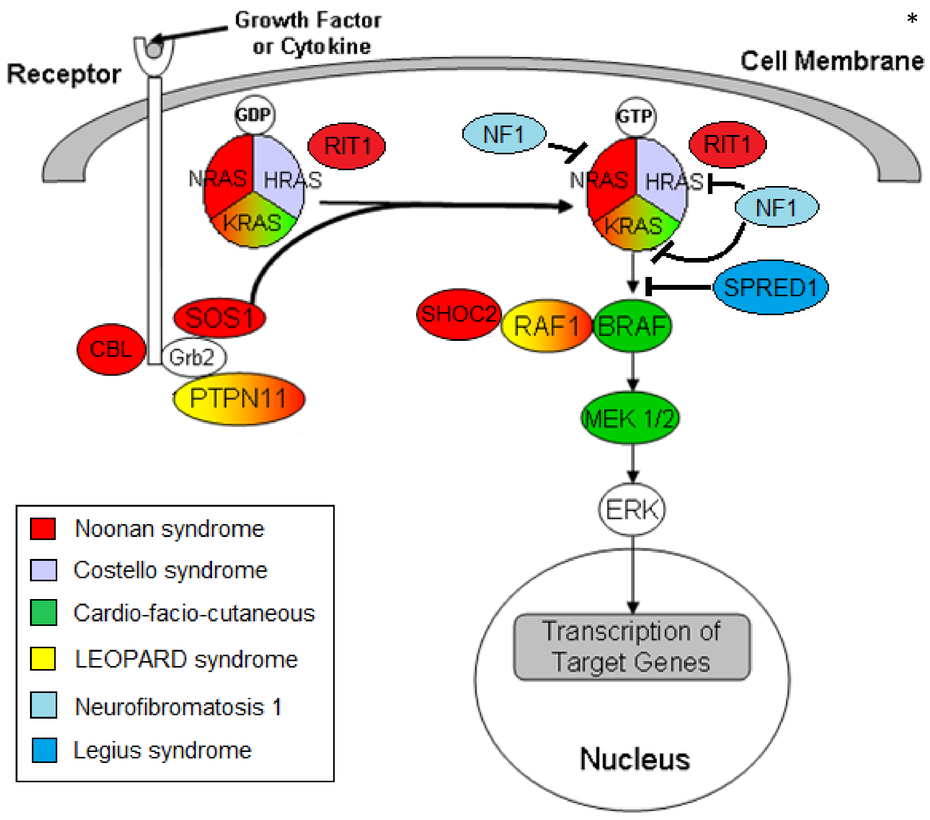


*Image from: http://personalizedmedicine.partners.org/laboratory-for-molecular-medicine/tests/rasopathies-noonan/expanded-rasopathy-panel.aspx

INVESTIGATIONS

Initial hyposcreen

	RESULTS
BG (mmol/l)	2.9
Lab glucose (mmol/l)	**2.4**
Cortisol (nmol/l)	122
Insulin (mU/L)	**2.2**
C- peptide	**134**
GH (ug/l)	5.3
IGF-1 (ng/ml) [55-327]	**<25**
IGFBP-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**
Acylcarnitine	Normal
PAA	Normal
Glucagon 4pmol/l (<50) ACTH 20.2ng/l	

Initial blood glucose profile (on 24h Neocate continuous feeds)

Time	0800	0900	1000	1100	1200	1500	1600	1700	1800	1900	2000	2100	2200	2300	2400	0100	0200	0300	0400	0500	0600	0700	0800
BG Mmol/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	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 (nmol/l)	134	588

MRI brain: Normal pituitary gland

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

TIME (min)	GH (ug/l)	CORTISOL (nmol/l)	LAB GLUCOSE (mmol/l)
-30	**7.3**	97	4.6
0	3.6	210	4.0
+30	1.9	-	-
+60	1.6	-	3.6
+90	2.8	-	**2.8**
+120	2.7	225	3.3
+150	2.4	177	3.4
+180	1.5	174	4.2

Genetics: Negative for BWS, *PTPN11, ABCC8, KCNJ11, HNF4A* genes.
De novo mutation in *HRAS* (c.466T>C), 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)

⇩

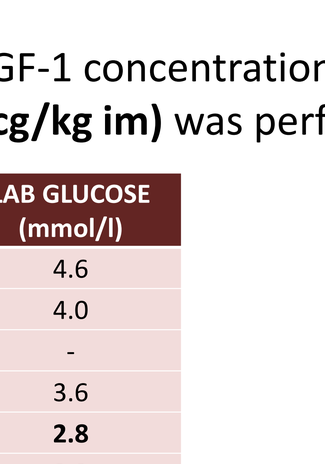
Hypoglycaemia persisted → octreotide injections + continuous enteral feeds

⇩

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**



Haematoxylin and Eosin staining.
x10
x40

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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