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Association between Rubenstein-Taybi Syndrome and hyperinsulinaemic hypoglycaemia

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BACKGROUND

- Rubenstein-Taybi Syndrome (RSTS) is a rare multiple congenital anomaly syndrome
- Prevalence - 1:100,000 - 1:125,000
- Classically characterized by:
  - postnatal growth deficiency, microcephaly, learning difficulties, broad thumbs and halluces, facial dysmorphisms (highly arched eyebrows, long eyelashes, downslanting palpebral fissures, prominent beaked nose and characteristic grimacing or abnormal smile) and increased risk of tumour formation
- 50-60% of cases are caused by mutations in the CREBBP (CREB-binding protein; CBP) gene and 10% by mutations in the paralogous gene, EP300 (CREB-binding protein; p300)
- CBP/p300 are multi-functional transcriptional co-activators, participating in a broad spectrum of intracellular processes
- An expanding phenotype for RSTS is being recognised and hyperinsulinaemic hypoglycaemia (HH) has been identified as a novel association (3 cases reported in the literature so far)

OBJECTIVE

To report two new cases of Rubenstein-Taybi Syndrome associated with hyperinsulinaemic hypoglycaemia

	Case 1	Case 2
Gestation and birth weight	38 weeks, BW = 2.6Kg	38 weeks
Sex	Female	Male
Dysmorphic features	Mild non-specific dysmorphic features	Coarse facies typical of RSTS, broad and angulated thumbs, broad halluces
Other clinical features	Bilateral choanal atresiae, GORD, unsafe swallow, silent aspirations, developmental delay	Bilateral undescended testes, GORD, unsafe swallow, mild laryngomalacia, left cataract
Age at diagnosis of Rubenstein-Taybi Syndrome	2.38 years	Suspected in 1st few days of life
Genetics	Truncating mutation in the EP300 gene following genetic testing as part of the Deciphering Developmental Disorders (DDD) study. Negative for mutations in known in genes causing congenital HH	Heterozygous frameshift mutation c.1044delT in CREBBP gene
Age at diagnosis of hyperinsulinaemic hypoglycaemia	1.54 years	Day 24 (glucose requirement 12mg/m2/min) Diagnosed with post-prandial HH at 0.16 years.
Results of hypoglycaemia screen / diagnostic fast	Detectable insulin at the time of fasting hypoglycaemia	Hypo screen (day 24): Glucose 1.6mmol/l, Insulin 26pmol/l, C-peptide 612pmol/l, urine no ketones, normal lactate and ammonia. Hypo screen (0.16 years): Glucose 2.5mmol/l, Insulin 11.3pmol/l post-feed. No hypo during 6 hour fast. OGTT: Glucose 2.5mmol/l, insulin 6.2pmol/l 3 hours post-glucose load. Protein load test normal.
Other investigations	Diffuse uptake of 18F-DOPA on PET/CT scan	MRI brain showed white matter changes and delayed myelination
HH medications	Started treatment with diazoxide at 1.54 years. Unresponsive to diazoxide, octreotride and nifedipine. Good response to Sirolimus (2mg/m2/day)	Started on diazoxide (5mg/kg/day) at day 38. Stopped for 14 days due to fluid retention and then restarted and finally stopped at 0.77 years. Response could not be completely assessed due to lack of parental compliance. Unresponsive to Nifedipine.
Other medications / surgery	Gastrostomy insertion at age 1.54 years	Nissen's fundoplication and gastrostomy at 0.77 years. Started on acarbose with feeds at 4.38 years
Feeding regime at discharge	Bolus feeds during day and continuous feeds at night	Continuous feeds
Feeding regime at last clinic visit	3 pureed meals and snacks at 3.98 years	Normal feeding at 6.51 years

CONCLUSIONS

- ✓ A number of conditions involving histone modification such as RSTS and Kabuki syndrome are associated with HH
- ✓ The mechanism of HH associated with these disorders requires further investigation
- ✓ Additional cases are needed to confirm the association between RSTS and HH, particularly in EP300 mutations which have a wider phenotypic spectrum

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