Severe hypothyroidism developing in an infant with hepatoblastoma and Beckwith Wiedemann syndrome – could there be a link?

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Introduction

Hypothyroidism in an extremely unwell infant with hepatoblastoma presented a diagnostic challenge and indicates a possible link between severe hypothyroidism and Beckwith Wiedemann syndrome (BWS).

- Incidence of congenital hypothyroidism 1:3000
- Incidence of BWS 1:12000 to 1:13700 of live births [2]

Clinical Details

- Antenatal polyhydramnios and foetal abdominal mass.
- Male infant by normal vaginal delivery at 38+4 weeks, weight 4007g.
- Small nose, low set ears and inverted V-shaped mouth.
- Transient hypoglycaemia day 1
- Pretext IV hepatoblastoma (all lobes) diagnosed causing abdominal expansion, IVC compression and artificial ventilation requirement.

Progress

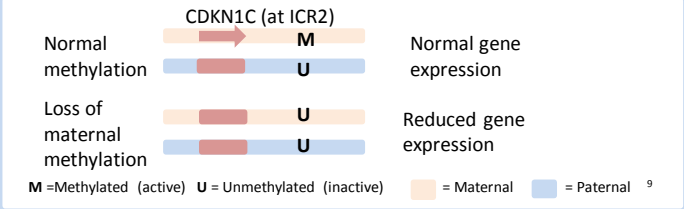
- 2 weeks: commenced Cisplatin / Doxorubicin
- Liver transplant discussed for curative treatment.
- Array CGH: 16p11.2 microduplication
  - maternally inherited not clinically significant.
- Neurologically: paucity of limb movements, abnormal tone, not fix and follow. Developed seizures. EEG: right sided abnormalities.
  - MRI: oedema and bilaterally small hippocampi.
- Hypoalbuminaemia and possible hepatorenal syndrome
- 3 months: Emergence of Severe Hypothyroidism
- 4 months: Died from sepsis, increased ventilation and worsening neurology

Age	TSH mU/L	Free T4 pmol/L	
	Normal		Newborn screening
3 months	> 100	< 2.6	
3 ½ months	74	11.9	After thyroxine started
4 months			Died

Hypothyroidism: Aetiologies considered in this infant	Factors against / comments
Congenital Hypothyroidism	Normal Guthrie, normal ultrasound
Autoimmune	Too young
Chemotherapy	None of the agents implicated
Significance of small hippocampi?	Association not causative?
Hepatoblastoma	Not reported
Hypoalbuminaemia and renal leak	Renal protein loss leads to loss of Thyroxine Binding Globulin and reduced Total T4 but normal Free T4 and hence normal TSH [3, 4]
Iodine exposure eg long-line	Some reports, but contentious [8]

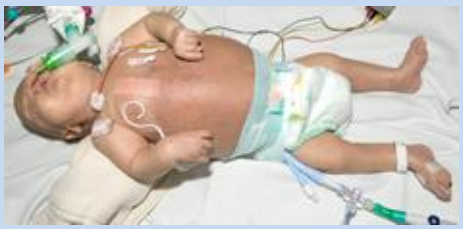
Post mortem genetic results

- Loss of methylation at 11p15.5 on the maternal chromosome at Imprinting Centre 2 (ICR2 /KvDMR1) is consistent with BWS (commonest mechanism, causative in 50% of cases)
- Leads to reduced expression of CDKN1C (growth / tumour suppressor gene) at ICR2



Features explained by BWS

- Hepatoblastoma and hypoglycaemia
- Yet phenotype severe, worse than expected in BWS
- Considered that there may be an additional genetic mechanism



Does the BWS explain the hypothyroidism?

Reported association in the literature, but all different

Cases	Thyroid problem
n = 2	Thyroxine binding globulin deficiency but no hypothyroidism [3,4]
n = 3	Congenital hypothyroidism: might reflect normal incidence of congenital hypothyroidism rather than causality [1,5,6]
n = 1	Latent hypothyroidism: Mild goitre but normal TFTs at 5 years. Increased goitre at 11 years and TSH rise 4.6 to 34.3 mU/L after 200 ug TRH IV [7]
n = 1	Same genetic mutation as in our case but with central hypothyroidism (TSH deficiency) due to hypopituitarism [2]

Conclusion

BWS and hypothyroidism coexist in small number of reports. This case is the first with onset in infancy. Also severity of phenotype atypical for BWS leaving possibility there could be an additional genetic mechanism.

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