Phaeochromocytoma in placental mesenchymal dysplasia: who should we screen and for how long?

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Background: Beckwith Wiedemann syndrome (BWS) features have been noted in 25-30% of infants with placental mesenchymal dysplasia (PMD)[1,2,3], a distinct and rare condition characterized by cystic placental histology, mosaicism for genome-wide paternal uniparental disomy (patUPD) and a high incidence of fetal demise and intrauterine growth retardation[3]. The development of malignant tumors which are mainly of embryonic origins is well recognized in BWS and screening guidelines mainly focus on the early identification of the most common hepatoblastoma and Wilm's tumours. It is generally accepted that screening is not typically warranted beyond the first decade of life[4].

Case Report: As the only child, naturally conceived, of nonconsanguineous parents preterm rupture of membranes preceded delivery of this female infant at 29+6 weeks gestation at which time placental histology was suggestive of PMD. The infant had a small umbilical hernia and hepatomegaly but no other signs of BWS at birth; hemihyperplasia with limb length discrepancy developed by 10 months of age. Severe hyperinsulinism within hours of delivery ultimately necessitated a subtotal pancreatectomy which was performed at age 6 weeks and a partial hepatectomy was required for hepatoblastoma at aged 18 months. With specific regard to her adrenal glands, antenatal sonography at 18, 22, and 28 weeks gestation documented bilateral cystic adrenomegaly which had appeared to have regressed on postnatal imaging by 5 months of age. During subsequent screening which was prolonged beyond the standard timeframe at her parents' request, a unilateral asymptomatic right sided adrenal cystic lesion was noted at age 11 years which demonstrated no appreciable uptake on targeted MIBG imaging and no specific diagnostic features on serial MRI. It had increased in size over 12 months of surveillance to a dimension of 3.7 x3.1 x3.6cm with progressive noradrenaline and dopamine secretion identified on urinary and serum catecholamine analyses and was confirmed to be a phaeochromocytoma after an uneventful adrenalectomy following full alpha- and beta-blockade in the pre-operative period. Regular surveillance for recurrence or the development of a second contralateral lesion is ongoing using ultrasonography and catecholamine analysis, and she remains disease free at 18 months post resection.

Conclusion: The distinct entity of PMD is rare but an increased awareness of the clinical course of individuals with this condition may have implications for counselling and clinical surveillance, particularly if antecedent adrenal cystic lesions have been identified. Conservative management of these lesions may be considered after exclusion of neuroblastoma, as adrenalectomy will render the individual steroid dependent for life if bilateral cysts/masses are present. However careful and continued radiological screening is necessary, and may be appropriate beyond the standard recommended screening protocols in conditions with patUPD and loss of maternal methylation in the 11p15 region. Ongoing surveillance should at a minimum encompass regular blood pressure measurement and periodic ultrasonography, with targeted investigations if an adrenal lesion is detected.

Review of the literature: Adrenal anomalies and adrenomegaly are inherent to BWS[5] and phaeochromocytomas, while infrequent, are reported to comprise a small percentage of tumors in this condition. A review of the available literature identified only 8 previous case reports of phaeochromocytoma occurring up to the age of 20 years in BWS (n=2) ,the related isolated hemihypertriphy (IH) (n=3) and PMD (n=2), summarised in Table 1. It appears that this case is the first report of phaeochromocytoma in an individual who was noted to have had congenital adrenal cysts in one of these entities, although the natural history of the majority of such reported lesions may be attenuated by surgical removal in the neonatal period, Table 2. These cysts are generally considered to be benign lesions but may be the antecedents of future adrenal pathologies.

Table 1. Reports of phaeochromocytoma in BWS and related syndromes

Citation	n	Phenotype	Genotype	Bilateral	Age at onset	Congenital adrenal cysts
[Schnakenburg et al., 1976]	1	Isolated hemihypertrophy	Not known	No	12	Not reported
[van den Akker et al., 2002]	1	Isolated hemihypertrophy	Not known	Yes	19 years	Not reported
[Bemurat et al., 2002]	1	BWS	Not known	Yes	20	Not reported
[Baldisserotto et al., 2005]	1	BWS	Not known	Yes	8 years	Not reported
[Wilson et al., 2008]	1	PMD/BWS	Whole chromosome 11 patUPD; almost complete loss of maternal methylation at 11p15.5	Yes	8 years	None reported
[Kalish et al., 2013]	1	Isolated hemihypertrophy	Normal clinical methylation testing for 11p15; SNP array analysis of skin fibroblasts from the hyperplastic limb side demonstrated 5% mosaic paternal UPD for 11p15. Single-nucleotide polymorphism (SNP) array analysis of phaeochromocytoma tissue demonstrated mosaic deletions of 8p12pter, 21q21.1qter, 22q11.23qter; commonly seen in phaeochromocytomas. In addition, mosaic 11p15.3pter homozygosity was noted	Yes	18 months	Not reported
[Pikilidou et al., 2014]	1	Isolated hemihypertophy	No epigenetic alterations in 11p15.5, which included investigation for hypomethylation at KCNQ1OT1 and hypermethylation at ICR1, and also no 11p15.5 uniparental disomy (UPD) was found	Yes	6 years	Not reported
Current case	1	PMD/BWS	Whole genome patUPD; partial loss of maternal methylation at 11p15.3	No	11 years	Yes

Table 2. Reports of congenital adrenal cysts in BWS and related syndromes

Citation	n	Phenotype	Hemorrhagic component	Outcome	Associated tumors
[Walton et al., 1991]	2	Isolated hemihypertrophy	No	Surgical removal; unilateral benign adrenal cysts	None reported
[McCauley et al., 1991]	6	1) BWS: hemihypertrophy, macroglossia, umbilical hernia, hepatomegaly	Yes	Surgical removal; benign hemorrhagic macrocysts and adrenocortical cytomegaly	None reported
		2) BWS:, hemihypertrophy, hemi-macroglossia, hypoglycaemia, hepatomegaly	Yes	Surgical removal; adrenocortical cytomegaly, macrocystic changes and acute haemorrhage, microcystic changes in definitive cortex	Contralateral adrenal adenoma removed at 8 months of age
		3) BWS: hemi-macroglossia, hypoglycaemia, hepatomegaly	Yes	Surgical removal; epithelium lined cystic spaces, macrocysts containing blood and adrenal cytomegaly	None reported
		4) BWS: hypoglycaemia, supraventricular tachycardia, hemihypertrophy from 2 months of age	Yes	Surgical removal; multiple cysts, interstitial haemorrhage and adrenomegaly	Wilm's tumour at 29 months of age with associated mortality
		5) Isolated hemihypertrophy	Yes	Surgical removal; multiple haemorrhagic cysts and adrenomegaly	None reported
		6) Isolated hemihypertrophy	Yes	Surgical removal; multiocular hemorrhagic cysts	None reported
[Akata et al., 1997]	1	BWS: somatic hypertrophy, macroglossia	Yes	Surgical removal of bilateral haemorrhagic macrocysts and cortical cytomegaly	None reported
[Ciftci et al., 1997]	1	BWS	No	Exploratory laparotomy, adrenal pseudocysts	None reported
[Zenker et al., 1999]	1	BWS: Macrosomia, hemihypertrophy, hemi-macroglossia	No	Adrenal cysts	None reported
[Anoop and Anjay 2004]	1	BWS: macrosomia, macroglossia, hepatosplenomegaly, nephromegaly	Yes	Resolution of bilateral adrenal cysts on ultrasound, presumed to be hemorrhagic	None reported
[Rahmah et al., 2004]	1	BWS	No	Resolved within 24 months	Ectopic pancreatic tissue, surgically removed in neonatal period
[Merrot et al., 2004]	1	BWS: Macrosomia	No	Surgical removal; haemorrhagic macrocysts and adrenocortical cytomegaly	None reported
[Gocmen et al., 2005]	1	BWS: mild hemihypertrophy, hemimacroglossia	Yes	Decreased size on follow up imaging at 2 months of age	None reported
[Teh and Ong 2007]	1	BWS: macroglossia, hemihypertrophy, hepatosplenomegaly	No	Conservative follow up with US/CT and MR imaging	Hepatoblastoma at 11 weeks of age
[Taide et al., 2010]	1	Isolated hemihypertrophy	Yes	Surgical removal; benign cyst with adrenal rests suggestive of hemorrhagic cyst	None reported
Current case	1	BWS/PMD: umbilical hernia, hypoglycaemia, hemihypertrophy from 10 months	No	Resolved by 5 months of age; unilateral phaeochromocytoma developed at age 11	Hepatoblastoma

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Adrenal

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