First Report of Congenital Adrenal Cysts and Pheochromocytoma in a Patient with Mosaic Genome-wide Paternal Uniparental Disomy

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TO THE EDITOR,

Mosaicism for genome-wide paternal uniparental disomy (MGWpatUPD), also known as biparental/androgenetic mosaicism, is thought to be the result of complex early embryonic events following a normal conception. The resulting phenotype may be complex and highly variable. Descriptions of the 10 individuals with MGWpatUPD reported in the literature to date have all included features consistent with Beckwith-Wiedemann syndrome (BWS) or its associated Wilms tumor as the presenting clinical diagnoses [Bertoin et al., 2015; Gogiel et al., 2013]. Individuals may demonstrate features consistent additional imprinting disorders [Darcy et al., 2015; Gogiel et al., 2013; Inbar-Feigenberg et al., 2013; Yamazawa et al., 2011] and the increased risk of malignant tumors of embryonic origins seen in BWS is also characteristic of the MGWpatUPD phenotype [Bertoin et al., 2015; Gogiel et al., 2013].

MGWpatUPD is known to underlie placental mesenchymal dysplasia (PMD), previously felt to be a distinct and rare condition. PMD is characterized by cystic placental histology, intrauterine growth

retardation and high rates of fetal demise in which BWS features were noted in up to one third of individuals [Jauniaux et al., 1997; Paradinas et al., 2001; Pham et al., 2006]. Wilson et al described 2 females diagnosed with PMD on the basis of cystic placental histology, and BWS-type phenotypes in whom confirmatory genetic analyses demonstrated MGWpatUPD [Wilson et al., 2008]. A clinical description of the first patient included typical BWS-like features and multiple chronic medical issues. Her course was further complicated at 8 years of age by the discovery of an asymptomatic unilateral cystic adrenal mass which was identified on routine abdominal ultrasound screening and confirmed histologically as a pheochromocytoma. Contralateral adrenalectomy was subsequently required for a second pheochromocytoma, rendering her steroid dependent. Both procedures were complicated by cerebrovascular events and severe hypertensive encephalopathy in the post-operative period. At the time, this was the first published description of pheochromocytoma in the MGWpatUPD setting, with only two previous reports of pheochromocytoma in the setting of BWS.

To further add to the literature base in MGWpatUPD, we hereby provide a clinical update on the second of the two females who presented with a unilateral pheochromocytoma subsequent to publication of the initial article [Wilson et al., 2008]. The clinical course of this girl (Patient 2 in the original description), now aged 14 years, is summarized below.

As the only child, naturally conceived, of non-consanguineous parents, preterm rupture of membranes preceded delivery at 29+6 weeks gestation. The infant had a small umbilical hernia and hepatomegaly but no other phenotypic features of BWS at birth. Severe hyperinsulinism within hours of delivery ultimately necessitated a subtotal pancreatectomy which was performed at age 6 weeks. Hemihyperplasia with limb length discrepancy developed by 10 months of age.

Hepatoblastoma at age 18 months required partial hepatectomy.

Antenatal sonography at 18, 22, and 28 weeks gestation had documented bilateral cystic adrenomegaly which 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. Over 12 months of surveillance the lesion increased in size to a dimension of 3.7 x3.1 x3.6cm in association with progressive elevations in noradrenaline and dopamine secretion on serial urinary and serum catecholamine analyses. Pheochromocytoma was confirmed after an uneventful adrenalectomy. Regular surveillance for recurrence or development of a second contralateral lesion is ongoing. No evidence of pheochromocytoma was demonstrated following targeted radiological investigations following the recent detection of mild elevations in plasma and urinary normetanephrine.

Pheochromocytomas in the pediatric population are most commonly identified within high risk genetic conditions such as von Hippel Lindau syndrome, multiple endocrine neoplasia syndrome type 2, neurofibromatosis type 1 and germline mutations of the succinate dehydrogenase subunits [Neumann et al., 2002]. Adrenal anomalies and adrenomegaly are inherent to the BWS phenotype [Beckwith J.B. 1969; Wiedemann 1964] and pheochromocytomas, while infrequent, are reported to comprise a very small percentage of tumors in this condition [Lapunzina 2005]. Radiological screening guidelines mainly focus on early identification of the most common tumors, hepatoblastoma and Wilms tumors. It is generally accepted that radiological screening is not typically warranted beyond the first decade of life in BWS [Teplick et al., 2011].

In addition to MGWpatUPD, one further condition, namely isolated hemihyperplasia (IH), has features overlapping with BWS and also carries this increased risk of malignancy. IH is a congenital growth disorder where the majority of affected individuals have no identified genetic etiology or underlying methylation defects at 11p15 [Clericuzio and Martin 2009]. However a higher tumor risk is seen in a minority of individuals who do demonstrate abnormalities in this region [Hoyme et al., 1998; Shuman et al., 2006]. A review of the available literature identified only 7 previous case reports of pheochromocytoma occurring up to the age of 20 years in any of BWS (n= 2, both

bilateral) [Baldisserotto et al., 2005; Bemurat et al., 2002], IH (n= 4) [Kalish et al., 2013; Pikilidou et al., 2014; Schnakenburg et al., 1976; van den Akker et al., 2002] and MGWpatUPD (n= 1, bilateral) [Wilson et al., 2008] which are summarized in Table I. The relative risk of pheochromocytoma in MGWpatUPD versus isolated 11p15 patUPD syndromes is not clear from the knowledge base to date. However there is the suggestion that the former may be associated with a particularly high predisposition, possibly due to imprinting defects at multiple loci [Bertoin et al., 2015; Gogiel et al., 2013]. In addition, it is conceivable that the phenotypes of some individuals with atypical features of 11p15 patUPD may in fact be attributable to MGWpatUPD which is more readily detected with contemporary genome-wide techniques. MGWpatUPD may still be underdiagnosed if analysis is restricted to the 11p15 region [Inbar-Feigenberg et al., 2013; Yamazawa et al., 2011]. Therefore it may be prudent to include whole genome analyses as standard in individuals with atypical BWS or IH phenotypes with confirmed 11p15 patUPD. This is the first report of pheochromocytoma in an individual who was noted to have had congenital adrenal cysts in one of these entities. Outcomes in 17 individuals with clinical diagnoses of BWS or IH have previously been described, in whom adrenal cysts were surgically removed in the neonatal period for 11 cases [Akata et al., 1997; McCauley et al., 1991; Merrot et al., 2004; Taide et al., 2010; Walton et al., 1991], with conservative management of the remaining 6 individuals [Anoop and Anjay 2004; Ciftci et al., 1997; Gocmen et al., 2005; Rahmah et al., 2004; Teh and Ong 2007; Zenker et al., 1999], Table IS. A contralateral adrenal adenoma developed at 8 months of age in one individual [McCauley et al., 1991] but no other adrenal pathology was reported at follow up. Non-adrenal sequelae (hepatoblastoma and Wilms tumor) were subsequently noted in two individuals [McCauley et al., 1991; Teh and Ong 2007]. On the basis of these reports it is not unreasonable to generally consider these congenital adrenal cysts to be benign lesions. However, given the fact that the natural history of the majority of reported lesions was attenuated by surgical removal in the neonatal period, this may not be a correct assumption. We may speculate them to be precursors of future adrenal pathologies, warranting long term surveillance beyond the time of apparent resolution . An increased awareness of the clinical

course of individuals with MGWpatUPD may have implications for counselling and clinical surveillance, particularly if antecedent adrenal cystic lesions have been identified. Conservative management of these lesions in infancy may be considered after exclusion of neuroblastoma. However careful and continued radiological screening is necessary, and may be appropriate beyond the standard recommended BWS-type screening protocols in conditions with MGWpatUPD and loss of maternal methylation in the 11p15 region. Given that pheochromocytomas in both of these populations have now been reported to occur up until the third decade of life[Bemurat et al., 2002], long term follow up into adulthood is warranted. Ongoing surveillance should, at a minimum, encompass regular blood pressure measurement and periodic ultrasonography, with targeted investigations if an adrenal lesion is detected.

This updated review of the reported cases of congenital adrenal cysts and pheochromocytoma in MGWpatUPD serves to raise awareness among clinicians and geneticists alike to facilitate appropriate follow up strategies for individuals with this uncommon condition.

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Table I. Reports of pheochromocytoma 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	Mosaic genome-wide patUPD	Mosaic genome-wide patUPD following an initial finding of 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 11p.15; 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 pheochromocytoma tissue demonstrated mosaic deletions of 8p12pter, 21q21.1qter, 22q11.23qter; commonly seen in pheochromocytomas. In addition, mosaic 11p15.3pter homozygosity was noted	Yes	18 months	Not reported

Pikilidou et al., 2014	1	Isolated hemihypertrophy	No epigenetic alterations in 11p15.5, which included investigation for hypomethylation at KCNQ1OT1 and hypermethylation at ICR1. No 11p15.5 uniparental disomy (UPD) was found	Yes	6 years	Not reported
Current case	1	Mosaic genome-wide patUPD	Mosaic genome-wide patUPD; partial loss of maternal methylation at 11p15.3	No	11 years	Yes

Table IS 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,	Yes	Surgical removal; benign hemorrhagic macrocysts and	None reported

		macroglossia, umbilical hernia, hepatomegaly		adrenocortical cytomegaly	
		2) BWS,: hemihypertrophy, hemi-macroglossia, hypoglycemia, hepatomegaly	Yes	Surgical removal; adrenocortical cytomegaly, macrocystic changes and acute hemorrhage, microcystic changes in definitive cortex	Contralateral adrenal adenoma removed at 8 months of age
		3) BWS: hemi- macroglossia, hypoglycemia, hepatomegaly	Yes	Surgical removal; epithelium lined cystic spaces, macrocysts containing blood and adrenal cytomegaly	None reported
		4) BWS: hypoglycemia, supraventricular tachycardia, hemihypertrophy from 2 months of age	Yes	Surgical removal; multiple cysts, interstitial hemorrhage and adrenomegaly	Wilms tumor at 29 months of age with associated mortality
		5) Isolated hemihypertrophy	Yes	Surgical removal; multiple hemorrhagic cysts and adrenomegaly	None reported
		6) Isolated hemihypertrophy	Yes	Surgical removal; multilocular hemorrhagic cysts	None reported
Akata et al., 1997	1	BWS: somatic hypertrophy,	Yes	Surgical removal of bilateral hemorrhagic macrocysts and	None reported

		hypertrophy, macroglossia		hemorrhagic macrocysts and cortical cytomegaly	
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; hemorrhagic 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 MRI 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	PMD: umbilical hernia, hypoglycemia, hemihypertrophy from 10 months	No	Resolved by 5 months of age	Hepatoblastoma at 18 months of age, unilateral pheochromocytoma at age 11

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