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Management of adrenal masses in patients with Beckwith–Wiedemann syndrome

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Abstract

Beckwith–Wiedemann syndrome (BWS) is a genetic overgrowth and cancer predisposition syndrome, associated with both benign and malignant adrenal findings. Literature review and an institutional case series elucidate the wide spectrum of adrenal findings in BWS patients. The altered expression of the 11p15 region is likely related to adrenal gland hyperplasia and growth dysregulation. Given the absence of guidelines for managing adrenal findings in BWS, we propose a systematic approach to adrenal findings in BWS patients, to allow for maximum detection of potentially malignant pathology without posing additional risk to patients.

KEYWORDS

11p overgrowth, adrenal cytomegaly, adrenal mass, Beckwith–Wiedemann syndrome, cancer predisposition, isolated hemihypertrophy, tumor screening

1 | INTRODUCTION

Beckwith–Wiedemann syndrome (BWS, OMIM #130650) is a genetic overgrowth and cancer predisposition syndrome characterized by hemihypertrophy, macroglossia, macrosomia, organomegaly, hyperinsulinism, omphalocele/umbilical hernia, and distinct facial features.[1] Patients with BWS are also at risk for embyronal tumors such as Wilms tumor, hepatoblastoma, and neuroblastoma in the first 8 years of life.[1–5] BWS is caused by genetic or epigenetic changes on chromosome 11p15, with either specific gene mutations or changes in DNA methylation in imprinting centers, known as imprinting center 1, H19/IGF2:IG-DMR (IC1), and imprinting center 2, KCNQ1OT1:TSS-DMR 2 (IC2), leading to a dysregulation in genes affecting growth.[1] BWS is more generally classified as the 11p overgrowth spectrum, which includes the spectrum of patients from classic BWS to those with isolated hemihypertrophy (IHH).[6,7] For the purposes of these recommendations, we will henceforward refer only to BWS, but would recommend these screening guidelines for any patient within the 11p overgrowth spectrum, including BWS and IHH.

The overall risk of intra-abdominal tumor development in BWS is somewhere between 5 and 10%.[2–5] Patients with BWS are screened with serial abdominal ultrasounds to evaluate for Wilms tumor and neuroblastoma, and alpha-fetoprotein (AFP) measurements to evaluate for hepatoblastoma, allowing early detection and management of these high-risk malignancies. Adrenocortical carcinoma is the next most common tumor type reported; additionally, other malignant and nonmalignant adrenal masses are reported.[4] Given this frequency, a consistent approach for evaluating adrenal masses in BWS is warranted.

Recommendations for following an incidentally noted adrenal mass have been developed for otherwise normal patients,[8] but there are no

Abbreviations: ACTH, adrenocorticotropic hormone; AFP, alpha-fetoprotein; BWS, Beckwith–Wiedemann syndrome; CDKN1C, cyclin-dependent kinase inhibitor 1C; COG, Children's Oncology Group; DHEAS, dehydroepiandrosterone sulfate; IC1, imprinting center 1; IC2, imprinting center 2; IGF2, insulin-like growth factor 2; LOH, loss of heterozygosity; IHH, isolated hemihypertrophy; MIBG, meta-iodobenzylguanidine; pUPD11, paternal uniparental disomy 11

recommendations for adrenal evaluation in patients with BWS. These patients have an increased risk of malignancy, and this must be considered and weighed against the risk of further diagnostic evaluation with biopsy or resection. The objective of this study is to review the adrenal findings in a large number of BWS patients evaluated at a BWS referral center, propose a potential underlying mechanism for the higher incidence of adrenal findings, and delineate steps for the evaluation of an adrenal mass detected during surveillance screening.

2 | METHODS

We conducted a literature review most recently updated in September 2016 via PubMed and the Cochrane Library for case reports and series involving patients with BWS and adrenal findings. These were compiled and analyzed for inclusion based on their relevance to the subject matter included in this review.

Our institutional database of patients with BWS (Children's Hospital of Philadelphia, IRB #13-010658) was reviewed for patients with adrenal findings. Evaluation and clinical decisions for these patients were made in accordance with currently available literature regarding adrenal mass management in pediatric patients. Age subdivision and size classification were based on the Children's Oncology Group (COG) guidelines for the management of infants with adrenal masses concerning for neuroblastoma.[9] Additionally, a comprehensive literature review was conducted to review both any available guidelines for management of incidentally noted adrenal masses in adults, as well as prior studies of expectant management of infantile neuroblastoma detected by mass screening in Japan.[8,10] Guidelines were established using this available literature and institutional experience with BWS.

3 | RESULTS

Literature review reveals a significant variation in the type of adrenal mass detected in BWS (Table 1).[11–36] We subcategorized these masses into the three most commonly reported adrenal findings: adrenal hyperplasia and cysts, adrenal adenoma, and neuroendocrine tumors; we also report other masses and tumors such as adrenal calcification and adrenal carcinoma. As previously noted, the risk of tumor development in BWS is highest in the first 8 years of life, and the majority of adrenal masses are also uncovered within this time frame. Although a genetic subtype of BWS was not available for all patients included in our literature review, the majority had hemihypertrophy, and those patients without clear hemihypertrophy had other clear indicators of BWS (Table 1). The majority were uncovered on screening ultrasound, often in the perinatal period. In each case, the follow-up was dependent upon institutional standards or best practice. However, no clear criteria for evaluation and follow-up of adrenal masses in these patients have been proposed.

The case series from our institution given in Supplementary Table S1 included nine patients with genetically confirmed BWS and an adrenal mass. Each adrenal mass in our series was picked up on imaging. Mass type varied and included four patients with adrenal hemorrhage (one bilateral), two patients with an adrenal adenoma, one patient with neuroblastoma, one patient with bilateral pheochromocytoma, and one patient with adrenal hyperplasia. Follow-up was based on the algorithm to be presented in the following section.

4 | DISCUSSION

The literature review and our institutional findings demonstrate significant diversity in adrenal findings in BWS patients. As these patients are predisposed to multiple cancer types, including adrenocortical carcinoma, it is important to appropriately screen and treat these patients when masses are uncovered on routine screening. In the following sections, we propose a system for evaluation of patients with BWS and adrenal findings based on the increased risk of malignancy in these patients.

4.1 | Underlying physiology of adrenal findings in BWS

There are several genetic changes that lead to the BWS phenotypic spectrum, most important of which are upregulation of insulin-like growth factor 2 (*IGF2)* and downregulation of *H19* and cyclin-dependent kinase inhibitor 1C (*CDKN1C)*; all three genes are major growth regulators in early development. IC1 gain of methylation on the maternal chromosome leads to increased expression of *IGF2* and decreased expression of *H19*; alternately, IC2 loss of methylation leads to a decrease in *CDKN1C* expression.[1,37] Both changes occur in paternal uniparental disomy (pUPD11).[1,37] Hereditary causes of BWS are responsible for 10–15% of cases, most commonly involving mutations in *CDKN1C* and less frequently involving one or both of the 11p15 imprinting centers, leading to aberrant 11p15 methylation.[38] These alterations in expression of *IGF2* and *CDKN1C* can lead to deviations in fetal adrenal development.

Development of the fetal adrenal gland is a complex and highly regulated process, and *IGF2* is a major modulator in fetal adrenal growth and steroidogenesis.[39,40] In two large sequencing projects evaluating pediatric patients with adrenocortical tumors, *IGF2* was overexpressed (with 11p loss of heterozygosity) in the majority of tumors.[41,42] *IGF2* overexpression promotes adrenocortical carcinoma, but its expression alone is not sufficient for adrenal carcinogenesis.[43] Thus, an increase in *IGF2* expression seen in BWS could similarly affect fetal adrenal development.

Alterations in CDKN1C expression have also been tied to changes in adrenal growth and development. In a *Cdkn1c* knockdown mouse model, adrenal cell hyperplasia was noted, most notably in the adrenal cortex.[44] Alternatively, patients with gain of function *CDKN1C* mutations are phenotypically growth restricted, and in particular have adrenal hypoplasia.[38]

Therefore, *IGF2* overexpression and *CDKN1C* downregulation in patients with BWS is a plausible explanation for adrenal cortex hypertrophy, as well as predisposition to adrenocortical malignancy. In our case series, epigenetic changes leading to dysregulated *IGF2* expres-

TABLE 1 Adrenal masses in BWS, literature review

					Other BWS findings				
Category	Adrenal finding	Sex	Age at diagnosis	Presentation	Hemihypertrophy	Macroglossia	Hypoglycemia/ hyperinsulinism	Umbilical hernia/ omphalocele	Reference
Cysts	Adrenal cysts (bilateral, hemorrhagic)	Male	Prenatal	Prenatal ultrasound	X				11
	Adrenal cysts (bilateral)	Male	23 days	Screening ultrasound	X	X	X		12
	Adrenal cyst	Male	Birth	Screening ultrasound		X		X	13
	Adrenal cysts (bilateral)	Male	Birth	Palpable masses at birth	X	X	X		14
	Adrenal pseudocysts	Male	2 days	Palpable masses at birth	X	X			15
	Adrenal cyst (hemorrhagic)	Male	Prenatal	Prenatal ultrasound	X	X		X	16
	Adrenal cyst (hemorrhagic)	Male	Prenatal	Prenatal ultrasound	X		X		16
	Adrenal cyst	Female	Birth	Palpable mass at birth	X	X	X		16
	Adrenal cyst (hemorrhagic)	Male	Birth	Palpable mass at birth	X		X		16
	Adrenal cyst (hemorrhagic)	Male	Birth	Palpable mass at birth	X				16
	Adrenal cyst (hemorrhagic)	Unknown	Prenatal	Prenatal ultrasound	X				16
	Adrenal cyst	Male	Prenatal	Prenatal ultrasound	X	X			17
	adrenal cyst (hemorrhagic)	Female	Birth	Screening ultrasound		X	X		18
	Adrenal cysts (bilateral)	Female	22 days	Palpable masses at birth	X	X	X	X	19
	Adrenal cysts (bilateral)	Female	Prenatal	Prenatal ultrasound	X	X	X	X	20
Adenoma	Adrenal adenoma (virilizing)	Female	15 years	Virilization	X	X	X	X	18
	Adrenal adenoma	Female	6 months	Screening ultrasound	X	X			21
	Adrenal adenoma (bilateral, virilizing)	Female	16 months; 4 years	Virilization		X			22
	Adrenal adenoma (virilizing)	Female	17 months	Increased cortisol production	X	X		X	23
	Adrenal adenoma (bilateral, virilizing)	Female	6 years; 13 years	Virilization		X		X	24
	Adrenal adenoma	Male	5 months	Increased cortisol production	X	X		X	25

(continues)

TABLE 1 *(Continued)*

Category	Adrenal finding	Sex	Age at diagnosis	Presentation	Other BWS findings				Reference
					Hemihypertrophy	Macroglossia	Hypoglycemia/ hyperinsulinism	Umbilical hernia/ omphalocele	
	Adrenal adenoma	Male	8 months	Screening ultrasound	X	X	X		16
Neuro-endocrine tumor	Neuroblastoma	Male	2 days	Prenatal ultrasound	X	X	X		26
	Pheochromocytoma	Female	8 years	Screening ultrasound		X	X		20
	Pheochromocytoma (bilateral)	Male	6 years	Screening ultrasound	X		X	X	27
	Neuroblastoma	Female	6 months	Screening ultrasound	X	X			21
	Pheochromocytoma	Female	4 years; 12 years	Headache, hypertension	X	X			28
	Pheochromocytoma (bilateral)	Female	20 years	Hypertension, malaise	X		X	X	29
Adrenal hyperplasia	Adrenocortical hyperplasia	Female	Birth	Cushing/virilization	X				30
	Adrenocortical hyperplasia	Female	Prenatal	Cushing/virilization	X		X		30
	Adrenal cytomegaly	Male	Birth	Subclinical Cushing	X				30
	Adrenal cytomegaly	Female	Postmortem	AVM leading to heart failure	X				31
Other	Hemangioendothelioma	Female	7 months; 18 months	Screening computed tomography abdomen	X				32
	Ovarian thecal metaplasia	Female	17 years	Screening ultrasound	X				33
	Adrenal hemorrhage (bilateral)	Male	Prenatal	Screening ultrasound	X	X			34
	Adrenal carcinoma	Female	4 years; 12 years	Cushing/virilization	X				35
	Adrenal calcifications	Female	7 years	Incidental finding	X	X		X	36
	Adrenal calcifications	Female	4 years	Incidental finding	X	X		X	36

sion was present in 78% (7/9) of the patients with adrenal findings, and the other two patients had IC2 loss of methylation and decreased *CDKN1C* expression (Supplementary Table S1). Based on previous research showing that these aberrations lead to abnormal fetal adrenal development and potentially predispose to malignancy, this is a plausible explanation for the increased frequency of adrenal findings in BWS. The patients in our institutional case series had a spectrum of adrenal change, from adrenal hemorrhage or adrenal cytomegaly to malignant tumors such as neuroblastoma. Further investigation is necessary for a better understanding of the genetic mechanism leading to adrenal masses in BWS.

Recent studies of patients with BWS have shown that the epigenotype influences the phenotypic risk of cancer; yet to date, no molecular subgroup is predictive of risk of adrenocortical tumors.[3,7,45] It is possible that with further understanding of mechanism, patients at higher risk of adrenal masses may be identified based on their epigenotype. In the absence of an epigenetic stratification, we propose a method to identify and evaluate patients with BWS at higher risk of adrenal malignancy.

4.2 | Clinical evaluation of adrenal masses in BWS

As shown in a review of available literature and in our own institutional case series, adrenal findings are common in BWS patients and require further evaluation given the increased adrenal tumor risk in these patients, as compared with patients without BWS. Our recommended general approach to adrenal findings discovered on routine surveillance screening in patients with BWS is shown in Figure 1. Our goal is to risk stratify patients based on age and clinical features to prevent adverse outcomes without leading to unnecessary imaging or invasive procedures in these patients.

We first evaluate patients for the presence of high-risk features, as defined below, and the nature of the mass (cystic vs. solid). In the case of a solid mass without high-risk features, we then stratify patients based on age, as detailed below. Our recommendations are based on the currently available literature for adrenal masses in patients less than 6 months old, as they are less likely to have a malignant mass and/or a mass requiring further intervention as compared with those patients 6 months or older.[10,46–49] Of note, we would not include patients with clear and isolated adrenal hemorrhage (without cystic component or mass) in this treatment schema or ongoing surveillance, as adrenal hemorrhage is present the general population at a similar rate and does not imply any inherent risk of malignancy.[50]

4.2.1 | High-risk features

Regardless of age, patients should be evaluated for the presence of high-risk features, which include signs or symptoms of underlying metastatic disease and signs of adrenocortical hormone production. These features are considered high risk because they require a more systemic evaluation and imply that the mass is inherently not benign. Patients should be regularly evaluated via examination and careful history to uncover any underlying symptoms of systemic or metastatic disease. Patients should also be evaluated for any signs of excess adrenocortical hormone, resulting in virilization and hypertension. If these symptoms occur, patients should have further evaluation including full body imaging and adrenocortical hormone levels: random cortisol level, adrenocorticotropic hormone (ACTH), 17(OH) progesterone, dehydroepiandrosterone sulfate (DHEAS), androstenodione, and testosterone. If an adrenocortical tumor is suspected, it should be fully resected; residual tumor in a patient with an adrenocortical tumor would lead to a worse overall outcome for that patient.

Increasing the size of an adrenal mass during the observation period should also raise concern, with the patient requiring closer follow-up evaluations and more regularly scheduled surveillance imaging. A 50% increase in size was established by COG in monitoring adrenal masses in patients less than 6 months of age, and has been effective in risk-stratifying patients with high-risk lesions in this population; 5 mm has been used in other observational studies.[9,48] If the size of the mass increases by 50% or more during the observation period (2 years after finding or until it is no longer present), the mass should undergo complete resection. If the mass increases by less than 50%, the patient should have imaging at 3–6-week intervals until the mass size stabilizes (or until the mass is resected).

4.2.2 | Cystic masses

For patients with cystic masses without high-risk features, regardless of age, observation alone with ultrasound imaging every 3 months is adequate, as the majority of these cysts represent an adrenal cyst or hemorrhage. For a mixed cystic/solid mass, we recommend evaluation based on patient age.

4.2.3 | Age

Adrenal masses in patients less than 6 months of age are less likely to be malignant or require surgical intervention.[46] Several studies have shown that systematic and close observation in these patients, with careful monitoring parameters, is a safe approach.[46,47] Observation of patients with adrenal masses less than 6 months of age has been shown prospectively by COG to capture all high-risk lesions with 100% survival, and this is now the standard of care.[9] We have adopted the COG proposed criteria for expectant observation in adrenal masses less than 6 months, with some modifications given the increased risk of tumor in patients with BWS.[4] The majority of these masses are a localized neuroblastoma with favorable outcome, and the remainder are more likely to be benign.[46] This critical approach allows sparing of surgery in these patients, as surgery poses a higher risk to these patients than localized neuroblastoma.[9]

4.2.4 | Less than 6 months

Based on the COG criteria, in a patient less than 6 months of age with an adrenal mass, observation alone is acceptable if the mass meets certain criteria[46,47]: for a small, solid adrenal mass (≤16 ml volume/3.1 cm diameter) or mixed solid and cystic adrenal mass less than or equal to 65 ml (if >25% cystic), a first step evaluation includes urine catecholamine metabolites, whole body imaging, and a radiolabeled metaiodobenzylguanidine (MIBG) scan to evaluate for neuroblastoma and potential metastasis. In patients less than 6 months of age, ultrasound can adequately distinguish a cystic adrenal lesion, and thus magnetic

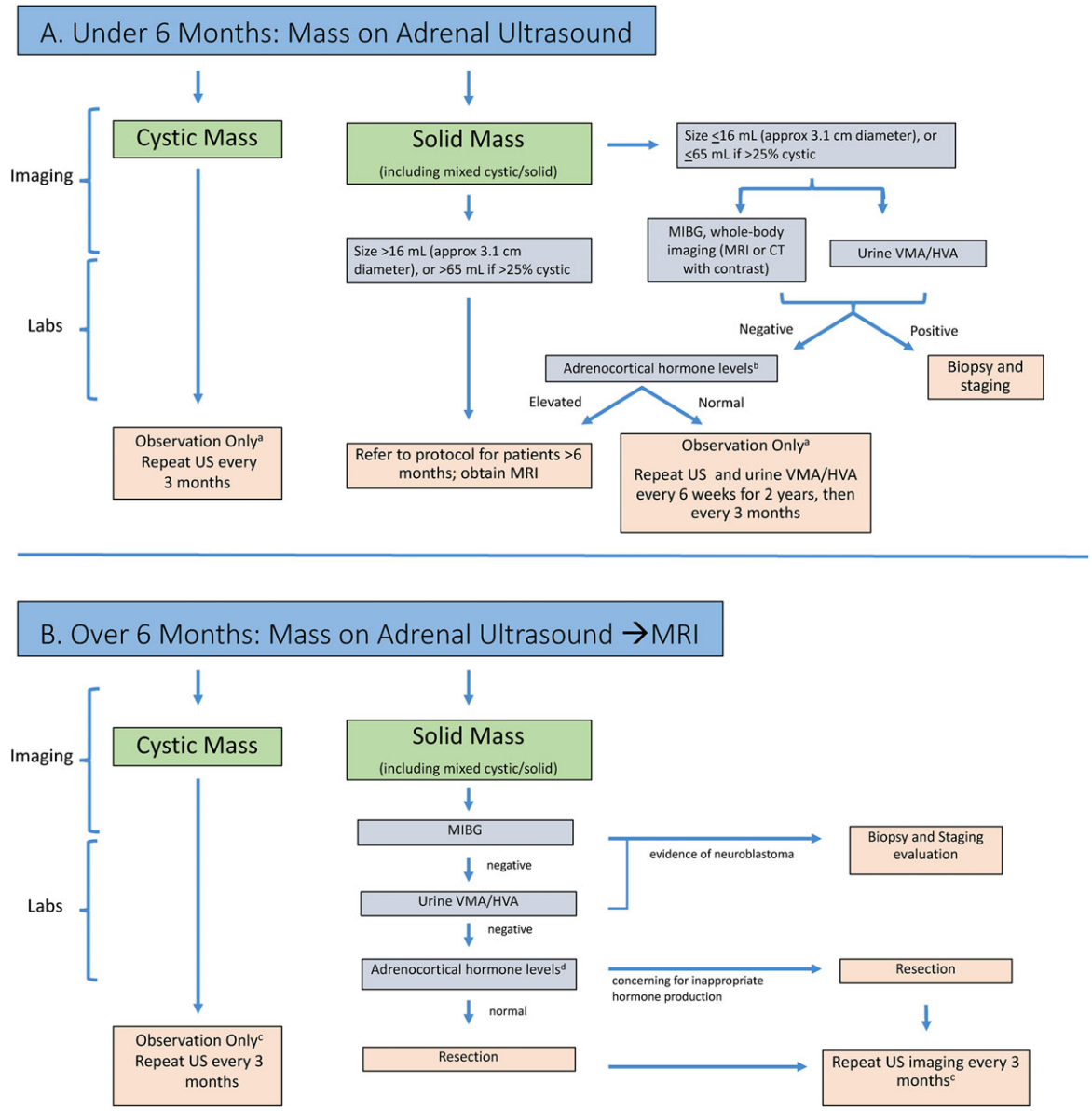

FIGURE 1 Adrenal masses in BWS. (A) Patients under 6 months; (a) concerning features requiring further evaluation during period of observation include increase in size of mass (if ≥50% should undergo resection, if <50% should have imaging at 3-week intervals until mass no longer growing or resected), increase in urine VMA/HVA (increase ≥50% above previous value, assuming values above normal range), virilization, or any clinical concern for metastatic disease; (b) concern for metastatic disease without MIBG avidity or elevation in urine catecholamines, should first check adrenocortical hormone levels: random cortisol, ACTH, 17(OH) progesterone, DHES, testosterone, and androstenodione. (B) Patients 6 months or older; (c) assuming no concerning clinical features, including features of adrenal hormone production (hypertension, hirsutism, virilization) or symptoms of systemic or metastatic disease; (d) cortisol, ACTH, 17(OH) progesterone, DHES, testosterone, and androstenodione

resonance imaging/computed tomography is not warranted.[51] If there is evidence of neuroblastoma via either imaging or laboratory studies, the mass should be biopsied and staged.

In a patient with BWS with normal urine catecholamine metabolites and an adrenal mass that lacks MIBG avidity, an adrenocortical tumor should be considered. Although we recommend physical examination for all patients to evaluate for elevated adrenocortical hormones, clinical signs may not be present in all patients. For this reason, we recommend that patients with a small solid/cystic mass should have adrenocortical hormone levels (random cortisol, ACTH, 17(OH) progesterone, DHEAS, androstenodione, and testosterone) checked. A tumor suspected to be an adrenocortical carcinoma should be fully resected without biopsy. Abnormal adrenocortical hormone levels, should they be present, will provide a biomarker after surgical resection. Additionally, for patients with abnormal laboratories, involvement of endocrinology may be warranted for their pre- and postoperative management.

If the proposed imaging and laboratory studies are reassuring, these patients can be followed with an ultrasound evaluation every 6 weeks for up to 2 years after the initial mass is seen, then transitioned to every 3 months until 8 years of age. The end of surveillance can also be modified if a patient has high-risk features, or a tumor that is at high

risk of late recurrence, such as pheochromocytoma. For patients with high-risk features as previously defined, or patients with a mass that is larger than the size cutoff (16 ml or 3.1 cm diameter, or 65 ml if >25% cystic), should be referred to the pathway for patients 6 months or older.

4.2.5 | At and over 6 months

In patients 6 months of age or older, solid adrenal masses are more likely to be malignant, and thus these patients require a more thorough evaluation. Additionally, in the case of a BWS patient with an adrenal mass, the increased risk of adrenocortical carcinoma should be considered; the risk of adrenocortical tumor is higher in these patients than in the general population of patients with an adrenal mass, and a biopsy of an adrenocortical carcinoma without proper preparation will increase risk to the patient.

In any patient with BWS with an adrenal mass, either solid or mixed solid/cystic, the first step should be further imaging evaluation with a magnetic resonance imaging to better delineate the mass and to prepare for a possible surgical approach. After initial imaging, additional evaluation for a neuroblastoma including an MIBG and urine catecholamine metabolites are recommended. If these assessments are consistent with diagnosis of neuroblastoma, biopsy and staging can be completed. If MIBG and urine catecholamine metabolites are negative, an adrenocortical hormone panel including random cortisol, ACTH, 17(OH) progesterone, DHEAS, androstenodione, and testosterone should be sent. This will help in planning a full surgical resection should the mass be considered high risk for adrenocortical carcinoma. Regardless of adrenal cortical hormone panel results, the patient should undergo complete resection of mass and further staging workup, as adrenocortical tumor or other malignancy remains on the differential, and it is not possible to delineate risk further without pathology.

5 | CONCLUSIONS

Adrenal masses are more frequent in patients with BWS than in the general population. Based on our institutional experience with this patient population, we propose an evaluation pathway for these patients in addition to BWS protocols. The proposed evaluation pathway balances the risks of unnecessary testing and procedures, while still ensuring that high-risk adrenal masses are diagnosed and treated appropriately. Additionally, these guidelines more broadly outline the available recommendations for evaluating adrenal masses in the pediatric patient; while they account for the increased risk of adrenal malignancy in the BWS population, a similar schema could be considered for any child with an adrenal mass.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

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