



Surveillance Imaging for Inherited Cancer in Pediatric Patients

- Pediatric patients with congenital diseases, including tuberous sclerosis complex (TSC), von Hippel-Lindau (VHL) disease, and Beckwith-Wiedemann syndrome (BWS), are at risk for developing renal, hepatic, and nervous system tumors
- Targeted imaging surveillance is often necessary to detect developing cancers in the early stages to maximize treatment benefits and survival
- Ultrasound and MR are the primary imaging modalities used for surveillance
- Pediatric patients often require sedation or general anesthesia when undergoing MR examinations

Several rare congenital conditions including tuberous sclerosis complex (TSC), Beckwith-Wiedemann syndrome (BWS), and von Hippel-Lindau (VHL) disease, increase the risk of developing cancer or life-threatening tumors. Periodic imaging of patients with these conditions is recommended (Table 1) to aid in the detection of tumors that are relatively common and more easily managed if detected early, in order to decrease morbidity and mortality. MR and ultrasound are the preferred imaging modalities for tumor surveillance in pediatric patients due to the lack of ionizing radiation. Although MR has superior soft tissue contrast, these prolonged examinations in a closed bore MR may be difficult for young children to tolerate without sedation. Ultrasound can typically be performed very quickly in children without sedation, however the tissue contrast and resolution are much less compared to MR.

Tuberous Sclerosis Complex (TSC)

TSC is a rare autosomal dominant disease that occurs in about one in 6,000 newborns. Tuberous lesions and subependymal nodules are found in the brain of 90% of patients with TSC. Subependymal giant cell astrocytomas (SEGAs), which can cause hydrocephalus (Figure 1), develop in 6-14% of patients with TSC and are more likely to occur in children than adults. Although not malignant, these tumors can become locally invasive. Therefore, if detected early, they can be completely removed before symptoms develop, preventing tumor recurrence.

By age 10 years, almost 75% of TSC patients develop angiomyolipomas (Figure 2A). They are more prevalent in patients with *TSC2* (vs. *TSC1*) gene mutations. Although these tumors are benign and most are asymptomatic, large angiomyolipomas are often highly vascular and can bleed, causing life-threatening

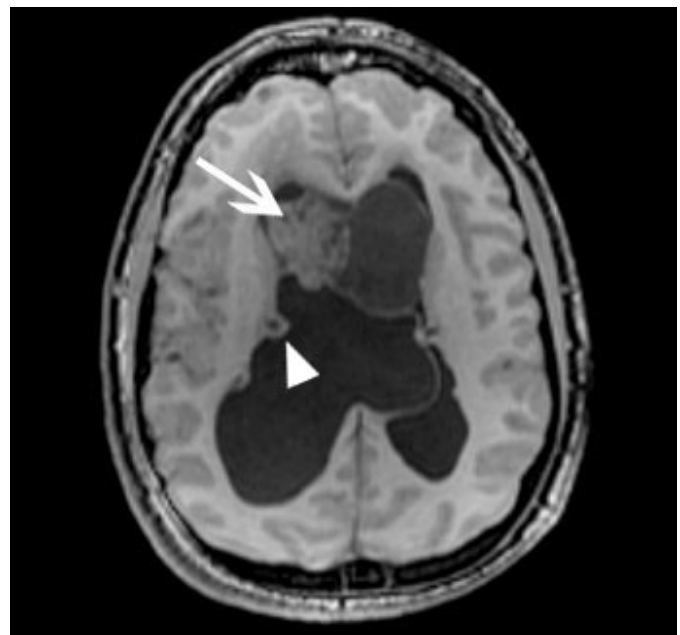


Figure 1. T1-weighted Brain MRI demonstrates multiple subependymal nodules as well as a subependymal giant cell astrocytoma (arrow) at the right foramen of Monro causing hydrocephalus.

hemorrhage. A small percentage of TSC patients develop renal cell carcinoma (RCC) (Figure 2B), the incidence of which is probably higher than the general population. The mean age of developing RCC is about 30 years but there are sporadic reports of cases in infants and children. At around puberty, a baseline chest CT examination is recommended because of the later risk of developing lymphangioleiomyomatosis (LAM), a less common but potentially devastating pulmonary manifestation of TSC.

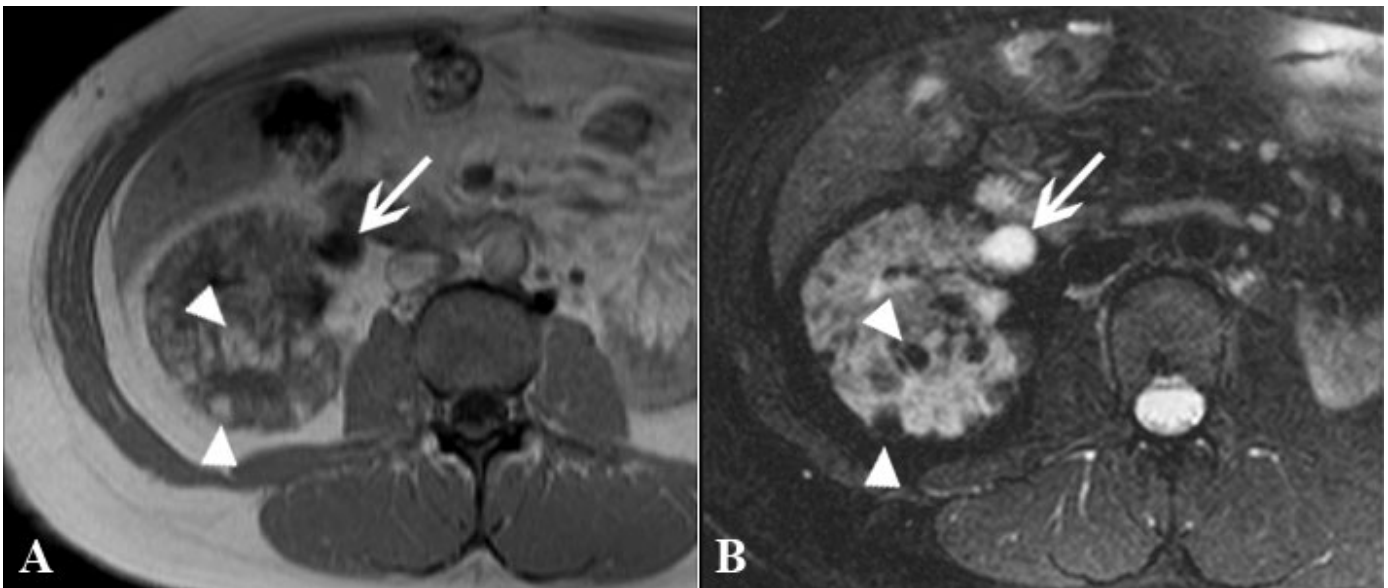


Figure 2. T1 (A) and T2 fat-suppressed (B) images of the kidneys in a TSC patient demonstrating an exophytic renal cyst (arrow) as well as multiple angiomyolipomata (arrowheads)

Table 1. Imaging Surveillance for Disease Associated with Congenital Disease

Congenital Disorder	Disease	Modality	Interval	Age range
Tuberous sclerosis complex	Angiomyolipoma	Abdominal MRI or Abdominal Ultrasound	Annual	From diagnosis until age 19
	Renal cell carcinoma		1-3 years	20 years onward
	Subependymal giant cell astrocytoma	Brain MRI	Annual	From diagnosis until 20 years
	Lymphangiomyomatosis	Chest CT	Baseline	Around puberty (14-17 years)
Von Hippel-Lindau disease	Renal cell carcinoma and pancreatic neuroendocrine tumors	Abdominal MRI or Abdominal Ultrasound	Annual	11-19 years
			Abdominal MRI	Annual
	Hemangioblastoma	Brain and spinal MRI	2 year	11 - puberty
Annual			After puberty	
Beckwith-Wiedemann syndrome	Wilms tumor	Abdominal Ultrasound	3 month	From birth to 8 years
	Hepatoblastoma	Abdominal Ultrasound	3 month	From birth to 4 years

Brain and abdominal MR imaging surveillance is recommended for children, starting at the time of diagnosis and continuing annually to detect and monitor subependymal nodules, SEGAs, angiomyolipomas, and RCC. MR is more sensitive than ultrasound for detecting and diagnosing renal tumors. Angiomyolipomas that grow ≥ 4 cm may be treated with embolization to minimize the risk of tumor hemorrhage.

Subependymal nodules and SEGAs have a similar appearance on MR imaging. Lesions that grow or are larger than 10 mm are suspected to be SEGAs. Suspected SEGAs should be monitored by MR annually to assess growth and determine whether they threaten to cause the development of hydrocephalus.

Von Hippel-Lindau (VHL) Disease

VHL disease is another autosomal dominant disease that occurs in about one in 40,000 births. Specific germ line mutations categorize patients into VHL Type I and

Type II. VHL is associated with the development of a variety of benign and malignant tumors. The morbidity and mortality of the disease have been significantly reduced by close surveillance protocols, monitoring tumor growth rates, and organ sparing interventions in the case of tumor development.

Hemangioblastomas (including hemangioblastomas of the retina) can develop anywhere in the central nervous system (Figure 3), first appearing at around 10 years and ultimately developing in 44-72% of VHL patients. These lesions, along with renal cell carcinomas, are primarily responsible for the morbidity and mortality of the disease.

VHL patients are also at risk for developing multiple, bilateral renal cell carcinomas during early adulthood. Other tumors include pancreatic simple cysts, papillary cystadenomas, and neuroendocrine tumors of the pancreas. Type II but not Type I VHL patients are at risk for development of pheochromocytoma. Other VHL

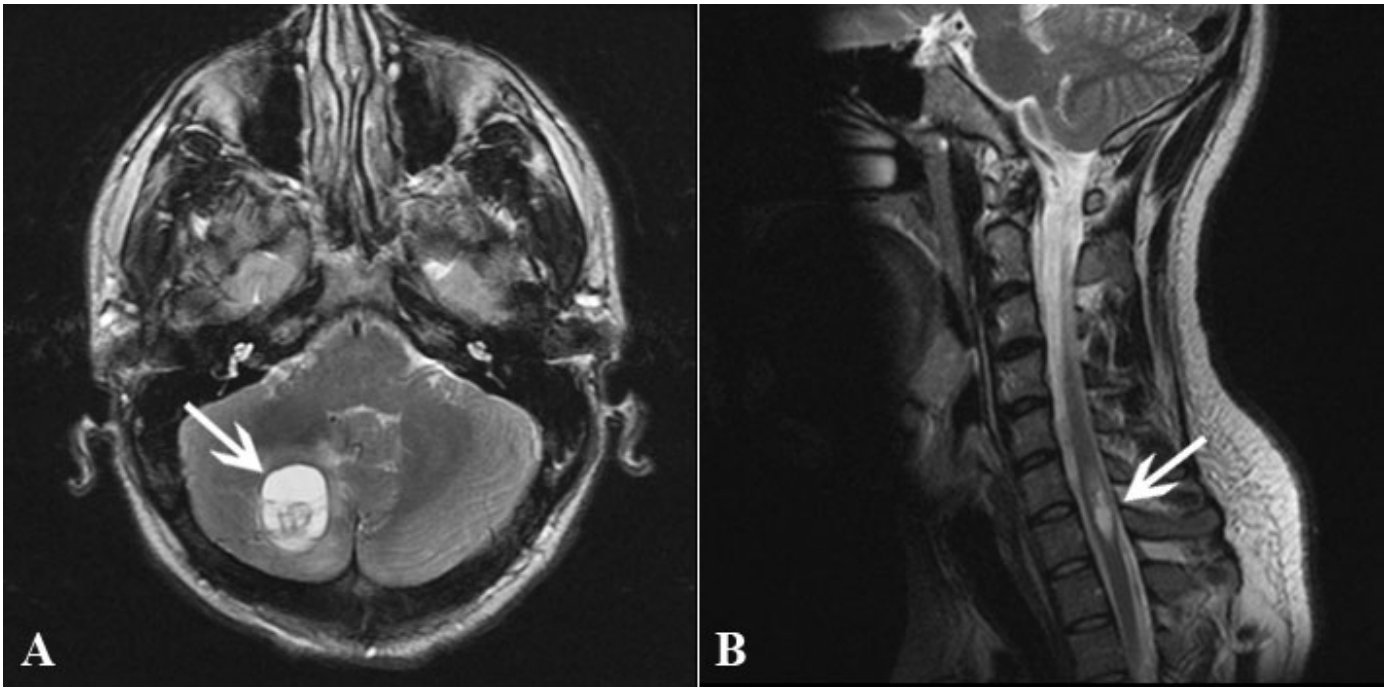


Figure 3. MR surveillance in a patient with VHL disease shows hemangioblastomas (arrows) in **(A)** Brain and **(B)** Spine.

associated lesions include endolymphatic sac tumors of the middle ear and papillary cystadenomas of the adnexal area or epididymis.

Annual brain and spinal MR imaging is recommended to detect hemangioblastomas and to monitor their progression, starting at age 10 years. Multiple hemangioblastomas often develop and their growth is variable, affecting the timing of surgery or radiation treatment. Retinal lesions may occur in childhood and early retinal examination shortly after birth is recommended.

Annual abdominal MR imaging is recommended starting at age 18 years to detect RCC and complex renal cysts, which can regress over time or develop to become RCCs. Tumors are usually monitored if they are <3 cm maximal diameter. RCCs approaching 3 cm are treated with nephron sparing surgery or thermal ablation ([Radiology Rounds, August 2008](#)). Patients at risk for pheochromocytoma should also undergo yearly surveillance by measuring plasma catecholamines, starting at childhood.

In addition, yearly MR examinations of the pancreas are warranted to survey for development of pancreatic neuroendocrine tumors. Pancreatic neuroendocrine tumors approaching 2 cm should be referred for resection.

Beckwith-Wiedemann Syndrome (BWS)

BWS is another rare congenital disorder that is usually recognized at birth. The risk of neoplasia in BWS is greatest in the first decade of life, with an estimated risk of about 9%. Wilms tumor (Figure 4A) accounts for 43% of the neoplasias and 99% of these develop before age 10 years. Because the cure rate for Wilms

tumor is high, surveillance is unlikely to affect mortality but is likely to reduce treatment-related morbidity. The growth rate of Wilms tumor is rapid, with a doubling rate of 11-40 days. Ultrasound is recommended for surveillance, at 3-4 month intervals until age 8 years.

Hepatoblastoma (Figure 4B) accounts for 20% of the neoplasias in patients with BWS and nearly always develops before the age of 4 years. Early tumor detection improves survival rates. If hepatoblastoma is diagnosed at stage I, event-free survival at 5 years is 91%, compared to 64% and 25% if diagnosed at stages III and IV, respectively. Ultrasound surveillance is recommended for hepatoblastomas, as well as laboratory tests for serum alpha-fetoprotein to detect rising levels of this marker.

Patient Preparation

Anesthesia is generally necessary for MR examinations of pediatric patients under the age of 5 years. Some children between 5 and 15 years of age may require conscious sedation for MR. Therefore, infants should not have any formula 6 hours prior or breast milk 4 hours prior to the examination. Children up to age 15 should not have food or milk. Both children and infants may receive clear liquids up to 2 hours prior to the exam. There are no food restrictions prior to ultrasound, which can be performed on awake children of any age.

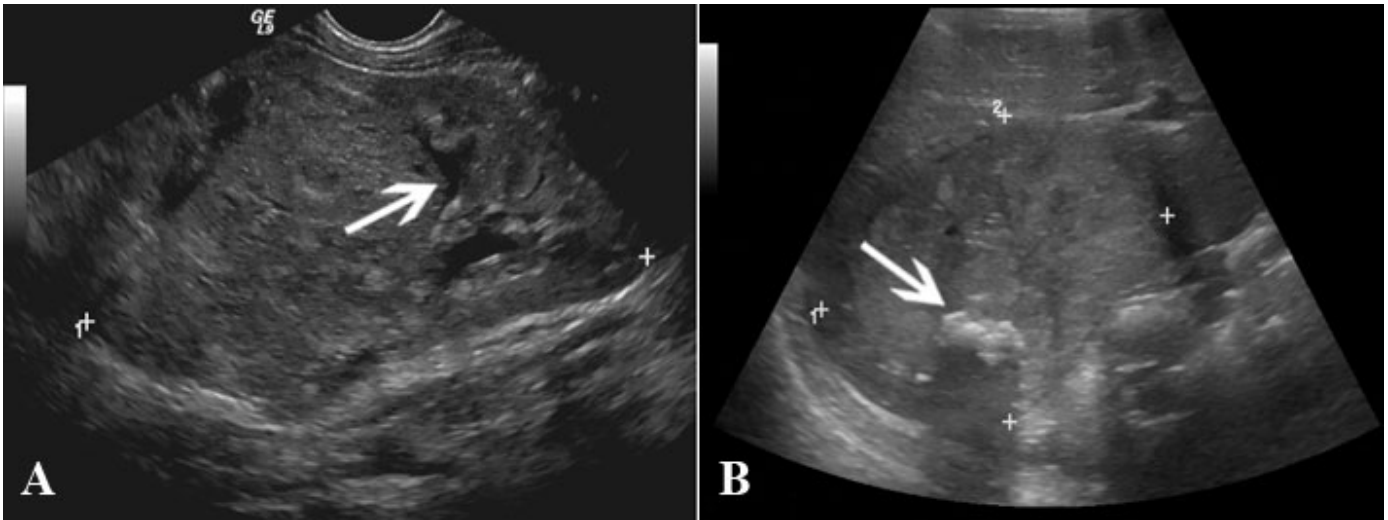


Figure 4. Ultrasound surveillance in BWS. **(A)** Typical appearance of Wilms tumor as intrarenal mass with "claw sign" (arrow) formed by interface with normal renal parenchyma. **(B)** Typical appearance of hepatoblastoma as intrahepatic mass with dense calcifications.

Further Information

For further questions on surveillance imaging for pediatric cancers, please contact [Michael S. Gee, M.D., Ph.D.](#), Pediatric Radiology, (617-724-4207).

Recommendations for VHL genetic screening and guidelines for surveillance of VHL patients can be found in the web page of the [MGH VHL/Familial Renal Cell Carcinoma Clinic](#). More information about TSC can be found at <http://www2.massgeneral.org/livingwithtsc/>.

We would like to thank Michael S. Gee, M.D., Ph.D., Elahna Paul, M.D., Ph.D., Pediatric Nephrology, Elizabeth Anne Thiele, M.D., Ph.D., MGH Tuberous Sclerosis Complex Comprehensive clinic, and Othon Iliopoulos, M.D., MGH Cancer Center, for their advice and assistance in preparation of this article.

References

- Baskin, HJ, Jr. (2008) *The pathogenesis and imaging of the tuberous sclerosis complex*. *Pediatr Radiol* **38**: 936-52
- Goh, S, Butler, W and Thiele, EA. (2004) *Subependymal giant cell tumors in tuberous sclerosis complex*. *Neurology* **63**: 1457-61
- Leung, RS, Biswas, SV, Duncan, M and Rankin, S. (2008) *Imaging features of von Hippel-Lindau disease*. *Radiographics* **28**: 65-79; quiz 323
- Roach, ES, DiMario, FJ, Kandt, RS and Northrup, H. (1999) *Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation*. *National Tuberous Sclerosis Association*. *J Child Neurol* **14**: 401-7
- Tan, TY and Amor, DJ. (2006) *Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice*. *J Paediatr Child Health* **42**: 486-90
- Winterkorn, EB, Daouk, GH, Anupindi, S and Thiele, EA. (2006) *Tuberous sclerosis complex and renal angiomyolipoma: case report and review of the literature*. *Pediatr Nephrol* **21**: 1189-93

Scheduling

MR and ultrasound examinations can be ordered through ROE (<http://mghroe/>) or by telephone **617-724-XRAY (9729)** for all locations. When general anesthesia is required, the MR imaging examinations are performed on Ellison 2 on the main campus. Ultrasound examinations and MR examinations without general anesthesia are performed on the main campus and at Mass General West Imaging, Waltham. Patient information on [preparation for sedation and anesthesia](#) of pediatric patients and [discharge information](#) for pediatric patients who have received sedation is available on the Department of Radiology website.

©2009 MGH Department of Radiology

Janet Cochrane Miller, D. Phil., Author
Raul N. Uppot, M.D., Editor