

# Diagnostic criteria and tumor screening for individuals with isolated hemihyperplasia

Carol L. Clericuzio, MD<sup>1</sup>, and Rick A. Martin, MD<sup>2</sup>

**Disclaimer:** This guideline is designed primarily as an educational resource for health care providers to help them provide quality medical genetic services. Adherence to this guideline does not necessarily assure a successful medical outcome. This guideline should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the geneticist should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from this guideline.

**Abstract:** Isolated hemihyperplasia, formerly termed isolated hemihypertrophy, is a congenital overgrowth disorder associated with an increased risk for embryonal tumors, mainly Wilms tumor and hepatoblastoma. This practice guideline will set forth the diagnostic criteria and tumor screening recommendations for children with isolated hemihyperplasia, based on the best information available. There is clinical overlap between isolated hemihyperplasia with Beckwith-Wiedemann syndrome. The majority of Beckwith-Wiedemann syndrome patients have a molecular abnormality involving the imprinted cluster of genes at 11p15.5. In contrast, the preponderance of isolated hemihyperplasia patients studied have no identified etiology. Tumors have developed in isolated hemihyperplasia patients with and without molecular abnormalities. For this reason, molecular diagnostics are not helpful in identifying the subset of isolated hemihyperplasia patients with tumor risk and all isolated hemihyperplasia patients should undergo tumor screening. *Genet Med* 2009;11(3):220–222.

**Key Words:** hemihypertrophy; hemihyperplasia; hepatoblastoma Wilms tumor overgrowth

## DIAGNOSTIC CRITERIA FOR ISOLATED HEMIHYPERTROPHY

Isolated hemihyperplasia (IH, OMIM 23500) is most succinctly defined as asymmetric regional body overgrowth because of an underlying abnormality of cell proliferation in individuals without any other underlying diagnosis. There are no widely accepted criteria for defining IH as distinct from normal growth variation in children, and therefore the pragmatic

From the <sup>1</sup>Department of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque, New Mexico; and <sup>2</sup>Department of Pediatrics, St. Louis University, St. Louis, Missouri.

Carol Clericuzio, MD, University of New Mexico Health Sciences Center, MSC10 5590; 1 University of New Mexico, Albuquerque, NM 87131-0001. E-mail: cleri@salud.unm.edu.

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case definition is that IH should be apparent “from the end of the bed.” The asymmetry can be due to differences in the growth of bone, soft tissue, or both.

The diagnosis of IH should be made by a clinical geneticist experienced in the differentiation of IH from other causes of body asymmetry, including regional body undergrowth, seen for example with mild fibular hemimelia and hemiatrophy. Known overgrowth syndromes, including Beckwith-Wiedemann syndrome (BWS), proteus syndrome, neurofibromatosis Type 1, mosaic trisomy 8, and disorders associated with vascular malformations including Klippel-Trenaunay syndrome and megalencephaly-cutis marmorata telangiectatica congenital, must be ruled out.

## TUMOR OCCURRENCE IN INDIVIDUALS WITH IH

The increased risk of embryonal tumors in individuals with IH is well documented in case reports and clearly substantiated by the only prospective study, which was reported by Hoyme et al.<sup>1</sup> in 1998. They followed 168 children with IH for 10 years and reported 10 tumors in 9 individuals. There were six Wilms tumors (WTs), one hepatoblastoma (HBL), two adrenal cell carcinomas, and one small bowel leiomyosarcoma, giving a tumor incidence of 5.9%. In a review of 134 tumors in IH patients, Lapunzina<sup>2</sup> noted that the types of tumors in IH patients are similar but not identical to those seen in BWS. As in BWS, the IH tumors were mostly embryonal, 94% occurred in the abdomen, and usually diagnosed before 10 years of age. The six extraabdominal tumors involved the brain, testes, lung, uterine cavity, and bone marrow.

## ASSOCIATION BETWEEN OCCURRENCE AND TYPES OF TUMORS WITH EPIGENETIC CAUSES OF IH

Recognition that IH and BWS have clinical overlap and similar tumor associations has led to the search for the same constitutional epigenotypes involving the gene cluster at 11p15.5 in IH patients, that are known to underlie BWS. As of early 2008, a minority of IH patients have indeed been found to have one of the three most common epigenotypes found in

BWS, namely uniparental paternal disomy of 11p15 (UPD), loss of maternal methylation of *KCNQ1OT1*, and hypermethylation of maternal *H19*.<sup>3–8</sup>

Shuman et al.<sup>8</sup>, in 2006, reported the largest single cohort of IH patients (51) studied for these molecular defects. They found that 40 (78%) had no identified abnormality but had six tumors, i.e., a tumor incidence of 15%. Eight (16%) patients had UPD of whom four developed tumors for a tumor incidence of 50%. Three (6%) had loss of maternal methylation of *KCNQ1OT1* and none had tumors. No patients had hypermethylation of maternal *H19* alone. The authors point out that because UPD is always mosaic, it can be missed and therefore it is likely that a subset of patients without identified molecular defects may actually have UPD. The authors also noted that of the four UPD patients with tumors, two were conceived by assisted reproductive technologies, raising the question of whether assisted reproductive technology is a risk factor for IH because of UPD and associated high tumor risk.

Niemitz et al.<sup>9</sup>, in 2005, reported the results of similar molecular studies on 15 IH children with WT, and noted that 12/15 (80%) had no identified abnormality, and all three of those with abnormalities had hypermethylation of maternal *H19*, two because of UPD and one an isolated methylation defect only. These authors suggested that the methylation defect of *H19* per se, with or without UPD, confers a high tumor risk.

Overall, the preponderance of IH patients with or without tumors who have undergone epigenetic studies have no identified etiology. This is in contrast to BWS, 70% of whom have an identified epigenetic or genetic etiology. Tumors have developed in IH patients with and without molecular abnormalities. Therefore, current molecular techniques are not helpful in identifying the subset of IH patients with tumor risk and so all IH patients should be screened for tumors. Similarly, data on tumor risk for specific molecular defects is too limited to be clinically useful at this time, although the studies noted above have reported high tumor risk with methylation of *H19* with or without UPD.

## EVIDENCE FOR EFFECTIVENESS OF EXISTING TUMOR SURVEILLANCE PROTOCOLS

The purpose of tumor surveillance in high-risk individuals is to facilitate identification of tumors at an early stage when treatment is most effective and least invasive. The most frequent tumors in children with IH are WT and HBL, but other tumors including neuroblastoma, adrenocortical tumors, and sarcomas occur. The vast majority of tumors occur in the abdomen and, given the ready availability and noninvasiveness of diagnostic ultrasound, abdominal ultrasound is the screening modality of choice for most tumors.

Beckwith in 1998 recommended abdominal ultrasound every 3 months until age 7 or 8 years for children with BWS. These are the ages that 90% and 93%, respectively, of WT are diagnosed.<sup>10</sup> He based his recommendation on the epidemiology and biology of WT (including rapid WT growth), benefits, risks, and cost of monitoring for WT in BWS patients. Data on the effectiveness of this protocol are somewhat limited for IH, as studies have been retrospective and most studied patients have had BWS. One such study is that by Choyke et al.<sup>11</sup>, who looked at whether screened patients with BWS or IH who developed WT had less late-stage disease than those not screened. Their results suggested strongly that ultrasound screening at intervals of 4 months or less reduced the proportion of late-stage WT. Beckwith's original protocol has also been recommended by

Tan et al.<sup>12</sup>, in 2006, after a comprehensive review of the literature. All of the above authors have recognized the potential adverse effects of ultrasound screening, primarily false positive findings, some of which have led to invasive surgeries.<sup>11</sup>

Tan et al. have also recommended that serum alpha-fetoprotein (AFP) be measured every 3 months until age 4, by which time 90% of HBL will have developed. They cite a case report with this recommendation by Clericuzio et al.<sup>13</sup>, of five children (three with BWS and two with IH) with normal hepatic ultrasounds for whom rising serial AFP measurements prompted additional imaging and ultimate diagnosis of early stage HBL. Caution in interpretation of infant AFP levels is necessary, given the high levels of AFP at birth which fall rapidly to the normal adult level by 10–12 months of age.<sup>14,15</sup>

Lastly, one of the authors (C.L.C.) is an advocate of teaching parents the “daily caretaker abdominal examination” for young children with IH.<sup>16</sup> On the basis of this author's personal experience, most parents are eager to take an active role in their child's care. Those that are too anxious to do the exam are fully supported in not doing so. The benefits of this practice are anecdotal: one parent found a WT half-way through the 3 month screening interval (personal observation). As there is no evidence of an adverse effect of teaching parents the abdominal examination, it seems reasonable to offer this education as an option.

## Recommendations

1. Any child with suspected IH should be referred to a clinical geneticist for evaluation.
2. Abdominal ultrasound every 3 months until 7 years.
3. Serum alpha-fetoprotein measurement every 3 months until 4 years.
4. Daily caretaker abdominal examination at the discretion of the provider/parent.

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