Diagnostic criteria and tumor screening for individuals with isolated hemihyperplasia

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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 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 HEMIHYPERPLASIA

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 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.

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

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productive technology is a risk factor for IH because of 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 reproduction for these molecular defects may actually have UPD. The authors noted that of the two UPD patients with tumors, two were conceived by assisted reproductive technologies, raising the question of whether assisted reproduction is a risk factor for IH because of UPD and associated high tumor risk.

Niemitz et al., 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 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 reproduction is a risk factor for IH because of UPD and associated 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 in both 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 high levels of AFP at birth which fall rapidly to the normal adult level by 10 –12 months of age, the test is not helpful.

Findings, some of which have led to invasive surgeries, have been reported. 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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