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Brief Clinical Report

Chest Wall Hamartoma With Wiedemann-Beckwith Syndrome: Clinical Report and Brief Review of Chromosome 11p15.5-Related Tumors

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A girl born with a left chest wall hamartoma, macroglossia, nevus flammeus of the middle forehead, and a small umbilical hernia developed left lower extremity hemihypertrophy by 1 year of age and is assumed to have Wiedemann-Beckwith syndrome. Hamartoma of the bladder and a cardiac fibrous hamartoma have been reported previously in association with Wiedemann-Beckwith syndrome. Infantile hamartomas are exceedingly rare and add to the spectrum of tumor formation in the syndrome.

KEY WORDS: Wiedemann-Beckwith syndrome; hemihypertrophy; chest wall hamartoma

INTRODUCTION

Wiedemann-Beckwith syndrome (WBS) is an overgrowth disorder associated with macrosomia, macroglossia, omphalocele, ear creases, and hemihypertrophy. Cancer occurs in 4% to 7.5% of children with WBS within the first 7 years of life, and most tumors are intraabdominal [Sotelo-Avila et al., 1980; Wiedemann, 1983; DeBaun and Tucker, 1998]. The average annual incidence of cancer in the first 4 years of life is 0.027 cancer per person year. Limb asymmetry is associated with an increased relative risk (RR) of cancer (RR 4.6, 95% CI: 1.5–14.2) [DeBaun and Tucker, 1998]. Serial abdominal ultrasound scans have been recommended every 3 months up to 4 years of age, and every 6 months up to age 7 years to screen for malignancies [Wiedemann, 1983; see also Shah, 1983; Andrews and Amparo, 1993]. After age 7 years, the risk of tumor is reduced [DeBaun and Tucker, 1998]. Most tumors associated with Wiedemann-Beckwith syndrome are intraabdominal and are typically Wilms tumor, adrenal cortical carcinoma, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma [Sotelo-Avila et al., 1980; Wiedemann, 1983; DeBaun and Tucker, 1998]. Benign neoplasms reported in WBS include adenoma, hamartoma, myxoma, ganglioneuroma, fibroadenoma, and carcinoid tumor [Sotelo-Avila et al., 1980]. We report a case of a female with a left chest wall hamartoma, and WBS.

Hamartomas of the chest wall in infancy have been reported in only approximately 50 cases and have not been associated previously with congenital anomalies [Dounies et al., 1994; Troum et al., 1996]. Only one case of malignant transformation has been observed. A pulmonary hamartoma has been associated with the development of pulmonary adenocarcinoma in an otherwise normal 11-year-old boy [Kojima et al., 1993]. En bloc resection of chest wall hamartomas appears to be curative. Postoperative scoliosis is reported in 24% of patients with chest wall hamartoma [Dounies et al., 1994]. Only eight cases of bladder hamartoma have been reported [Brancatelli et al., 1999], one of which was in an infant with WBS [Williams et al., 1990]. A cardiac hamartoma occurred in a 2-year-old with WBS [Reddy et al., 1972]. Also interesting is a report of multiple lung hamartomas in a 15-year-old girl with a history of Wilms tumor 7 years earlier but without a diagnosis of WBS [Lindner and Willnow, 1987]. Hamartomas of the subcapsular renal cortex are a common finding in patients with Wilms tumor [Bove and McAdams, 1976]. Because of the extreme rarity of these hamartomas, careful examination for other features of WBS is recommended.

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CLINICAL REPORT

An African-American girl was born to an 18-year-old G_2P_{1001} mother at 38 weeks' estimated gestation. Her mother had a history of anemia, sickle cell trait, and no prenatal care. Birth weight was 2,990 g (50th centile), length was 48 cm (50th centile), and occipital-frontal circumference (OFC) was 35 cm (75th–90th centile). A left chest wall deformity and mass was noted at birth. Chest radiography and computed tomography showed a large rounded mass situated posteriorly in the left part of the chest with involvement of several ribs (Fig. 1).

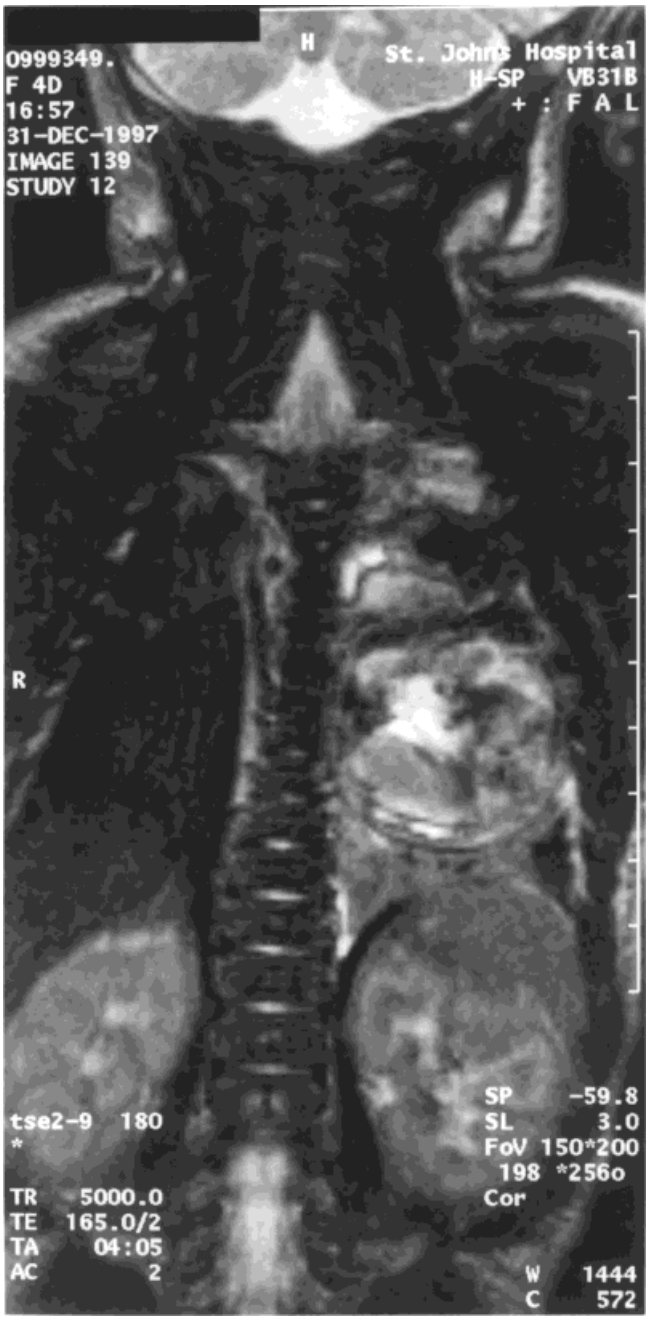

Fig. 1. Abdominal computed tomography scan showing left chest wall hamartoma in infant who later demonstrated left hemihypertrophy.

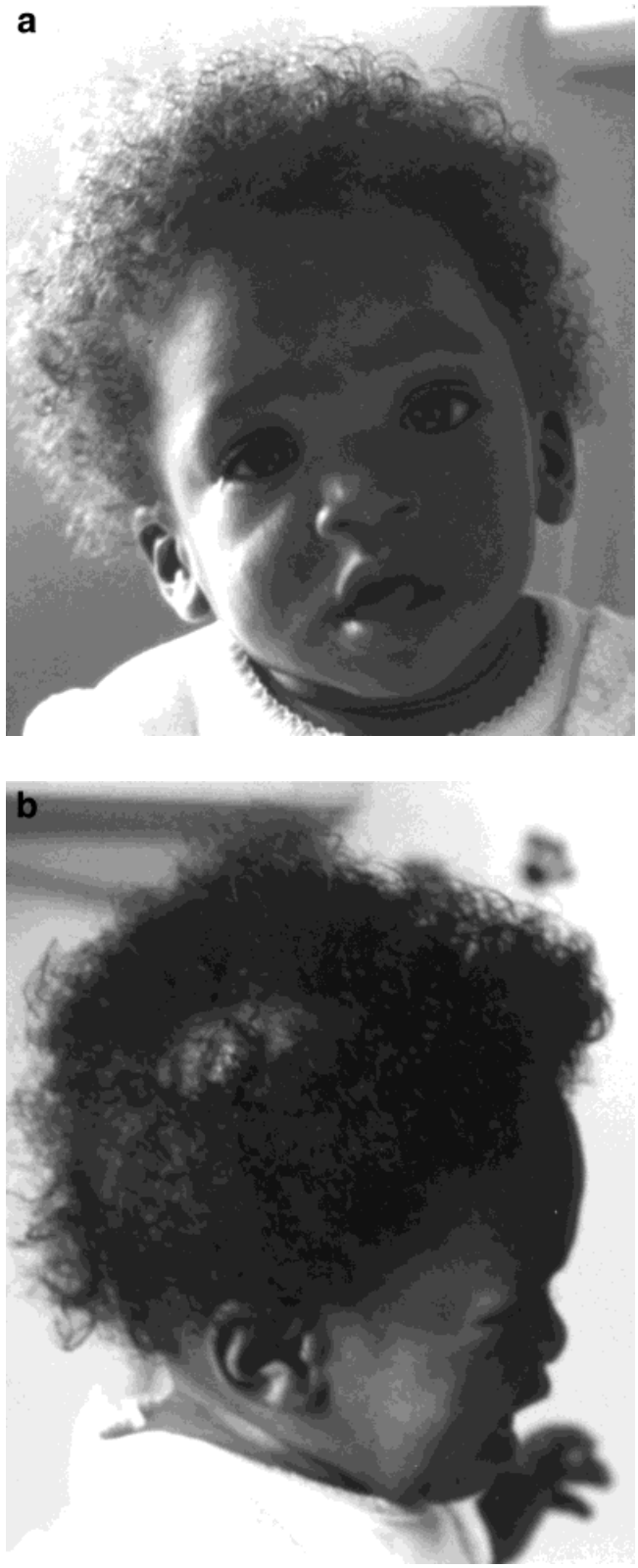

Fig. 2. Patient with Wiedemann-Beckwith syndrome and left chest wall hamartoma at age 1 year. Note nevus flammeus, macroglossia with open mouth, and small umbilical hernia in frontal view (**a**); indentation of the ear lobe in lateral view (**b**).

TABLE I. Selected Imprinted Genes Associated With (Wiedemann-Beckwith Syndrome) and/or Tumorigenesis on Chromosome 11p15.5

Gene	Proposed function	Comments	Parental expression
IGF1	Embryonic growth	Somatic overgrowth by *IGF2* overexpression [Morison et al., 1996; Sun et al., 1997]	Paternal allele [DeCharia et al., 1991]
H19	Embryonic growth suppression		Maternal allele [Bartolomei et al., 1991]
$P57^{KIP2}$	G(1) Cyclin-kinase inhibitor related to p21CIPI/WAFI (a potential mediator of p53 tumor suppression)	11p15.5 [Hoovers et al., 1995]. Mutations in 2/9 cases of WBS in Hatada et al., 1996b. Mice lacking $p57^{KIP2}$ had altered cell proliferation and some WBS phenotypic features [Zhang et al., 1997]	Maternal allele [Matsuoka et al., 1996]
TSSC3	Apoptosis	15 kb from nonimprinted *hNAP2* gene [Lee and Feinberg, 1998]	Maternal allele [Lee and Feinberg, 1998]

Also noted at birth were macroglossia, nevus flammeus of the middle forehead, and a small umbilical hernia. Serum glucose was monitored closely during the first 36 hr and ranged from 59 to 63 mg/dl without specific treatment. Kidneys were normal in size and appearance and no abdominal mass was found on ultrasound on day 1. An echocardiogram on day 2 revealed no abnormalities. High-resolution karyotype of the patient's lymphocytes and tumor were both 46,XX. WBS was suspected, but the patient did not fulfill the criteria for diagnosis. On day 11, the mass was removed en bloc with the affected ribs two through five of the posterior left hemithorax. Histological analysis demonstrated a cartilaginous vascular hamartoma with aneurysmal bone cyst formation.

The patient was reevaluated at 6 months at her mother's request for leg length asymmetry. The left leg was longer by 1.25 cm (8.5%) and the left midthigh diameter was 0.7 cm greater (4.2%). On examination, her weight was 5.3 kg (25th–50th centile), length was 63.5 cm (25th–50th centile), and OFC was 43 cm (25th–50th centile). There were horizontal ear creases on the back of the pinnae, but they were atypical for WBS. She had persistent macroglossia. There was a prominent nevus flammeus of the midforehead and occiput (Fig. 2). There was no clinical evidence of

TABLE II. Tumorigenesis With Formation Related to the 11p15 Locus*

Tumor	Gene(s) in population with link to WBS	RR in WBS and comments
Hepatoblastoma	Loss of imprinting of H19 expression [Rainier et al., 1995]. Normally, both parental *IGF2* alleles are expressed postnatally in liver. In hepatocellular carcinoma only paternal *IGF2* allele is expressed [Takeda et al., 1996]	RR 2280 less than age 4 years; 928–1165 at 95% CI [DeBaun et al., 1998]. 10% and 6%, of WBS tumors reported by Sotelo-Avila et al. [1980] and Wiedemann [1983], respectively
Wilms	Biallelic *IGF2* expression with down-regulation of *H19* [Ogawa et al., 1993]. Loss of $p57^{KIP2}$ maternal allele expression [Hatada et al., 1996a]	RR 816 less than age 4 years; 359–1156 at 95% CI [DeBaun et al., 1998]. Sotelo-Avila et al. [1980] 32%; Wiedemann [1983], 44% of WBS tumors
Neuroblastoma	Loss of *H19* and *IGF2* Imprinting not observed [Wada et al., 1995]	RR 197 less than age 4 years; 22–711 at 95% CI [DeBaun et al., 1998]
Adrenocortical	11p15 loss of maternal allele or paternal allele duplication occurs in 93% of malignant and 9% of benign tumors with a suggested role in late tumorigenesis [Gicquel et al., 1997]	22% and 15% of WBS tumors reported by Sotelo-Avila et al. [1980] and Wiedemann [1983], respectively (12 cases)
Rhabdomyosarcoma (embryonal or alveolar histology)	LOH with overexpression of *IGF2* allele and suppression of *H19* allele [Zhan et al., 1994; Casola et al., 1997]. Point mutation rhabdomyosarcoma cell line *TE125-T BWR1A* gene [Schwienbacher et al., 1998]	3% and 0% of WBS tumors reported by Sotelo-Avila et al. [1980] and Wiedemann [1983], respectively (1 case)
Sporadic breast cancers	LOH at 11p15.5: 19% [Gudmundsson et al., 1995]; 35% with effects late in disease progression [Winqvist et al., 1995]. Biallelic expression of *IGF2* [Wu et al., 1997]. Insertion leading to stop codon seen in *BWR1A* gene in breast cancer cell line *BT549* [Schwienbacher et al., 1998]	Benign breast fibroadenoma reported by Sotelo-Avila et al. [1980]
Lung cancers	LOH—11p15 Ha-ras locus in 27% of non-small cell patients [Chan et al., 1996]. Loss of maternal $p57^{KIP2}$ allele in 37% of patients with 11p15 deletions [Kondo et al., 1996]	
Stomach adenocarcinoma	LOH—11p15.5 in 62% of patients [Baffa et al., 1996]	
Malignant gliomas	LOH at 11p15.5 in 31% of patients [Sonoda et al., 1995]	Brainstem glioblastoma [Sotelo-Avila et al., 1980]; two "intracranial malignomas" [Wiedemann, 1983] (5% tumors)
Prostatic cancers	LOH at 11p15.5 in 25% of patients [Dahiya et al., 1997]	
Chronic myeloid leukemia	Hypermethylation of calcitonin gene on 11p15 coincided with a *p53* gene mutation [Mills et al., 1996]	

*RR, relative risk; CI, confidence interval; LOH, loss of heterozygosity; WBS; Wiedemann-Beckwith syndrome.

cardiomegaly. The liver and spleen were palpable 2.5 cm below the right and left lower sternal border, respectively. A reducible 3-mm umbilical hernia was present. The upper part of her body appeared symmetric. Considering the presence of two major features (macroglossia and umbilical hernia), three minor features (hemihypertrophy, nevus flammeus, and ear creases), and chest wall hamartoma, she was thought to fulfill criteria for WBS [Elliott and Maher, 1994]. At 12 months of age, her left leg length was 40.5 cm and her right leg measured 38.5 cm. At age 18 months, her right kidney was 5.3 cm (5–10%) and the left kidney was 6.3 cm (30%). Her mother did not have features of WBS, and her father was not available for examination.

DISCUSSION

WBS is a heterogeneous overgrowth disorder. Approximately 85% of WBS cases appear to be sporadic and 15% are familial [Elliott and Maher, 1994; Li et al., 1997]. In both types, differential expression of the two parental alleles occurs in a chromosomal region known to contain a cluster of imprinted embryonal growth factors. Linkage studies in familial WBS have identified linkage with chromosome 11p15.5 [Koufos et al., 1989; Ping et al., 1989]. It has been hypothesized previously that local paracrine growth factor abnormalities may explain hamartoses and other features of WBS [Kousseff, 1990]. An imbalance of (paternal) growth-promoter activity over (maternal) growth-suppresser activity is further suspected to cause the features of WBS and the susceptibility to tumor formation. Four of the 11p15.5 gene products are reviewed in Table I. A detailed review of the molecular genetics of WBS can be found in Li et al. [1997].

The clear association of WBS and a wide variety of tumors, such as the chest wall hamartoma in this report, demonstrates the significance of the 11p15.5 locus. The specific events leading to this chest wall hamartoma formation are unknown, but reports of tumor formation related to the 11p15.5 locus are numerous (Table II).

The finding of a chest wall hamartoma in a patient with WBS emphasizes the variety of tumors possibly influenced by a cluster of imprinted gene loci on chromosome 11p15.5. Although follow-up screening recommendations remain controversial, suspicion of many tumors, common and uncommon, should be high with the syndrome. We suggest that WBS be considered in infants with chest wall hamartomas.

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