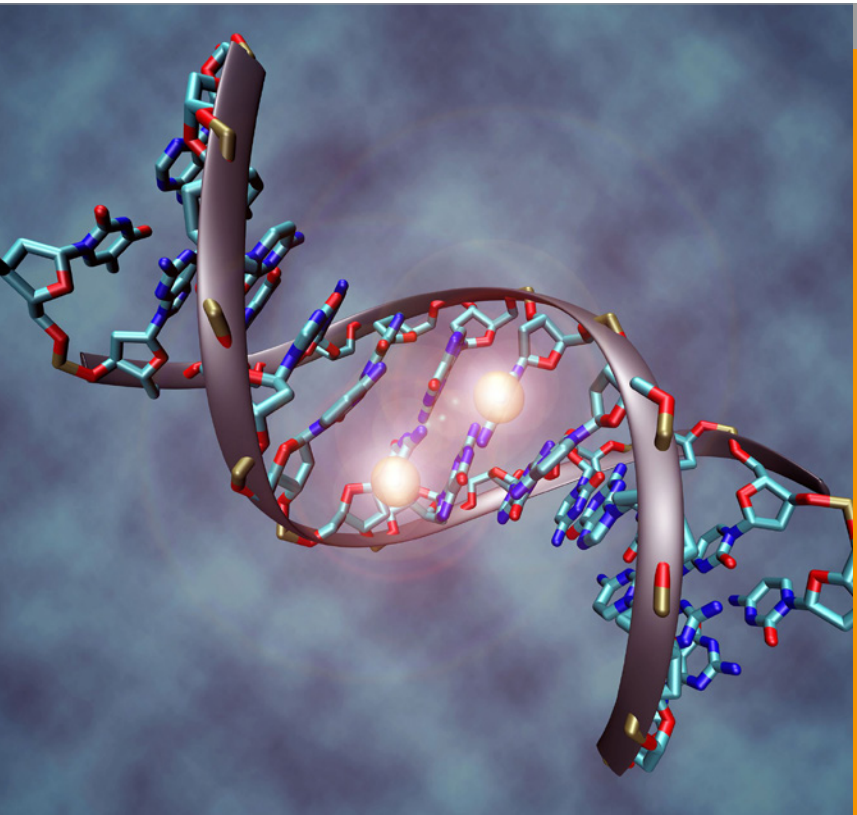
SWISS SOCIETY OF NEONATOLOGY

Hemihypertrophy of one leg and congenital retroperitoneal tumor: Beckwith-Wiedemann syndrome



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Title figure:
Representation of a DNA molecule that is methylated:
the two white spheres represent methyl groups
(source: www.wikipedia.org).

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) belongs to the so-called imprinting disorders and has an incidence of 1:15'000 – 26'000 (1). It is characterized as an overgrowth syndrome with variable expression of symptoms such as exomphalos, macroglossia, neonatal hypoglycemia, earlobe creases, hemihypertrophy, perinatal overgrowth and an increased risk of embryonic tumors (2).

Genomic imprinting leads to an altered expression of gene parts dependent on parental heredity due to DNA-methylation. The affected (imprinted) regions in BWS are typically located on chromosome 11p15.5. The respective genes have regulatory function for cellular growth with the epigenetic changes leading to either decreased inhibition or increased expression of growth promoting genes (3).

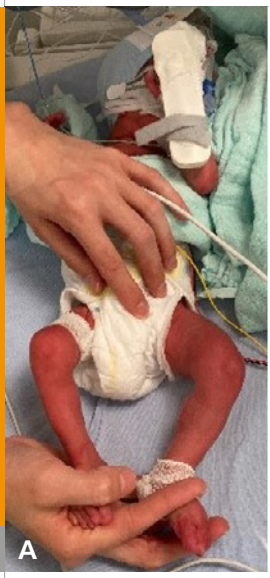
In BWS, about 50 % of the infants show a loss of methylation in the Imprinting Control Region (ICR)-2, normally expressed by the maternal chromosome only, leading to a reduced expression of a growth inhibitor gene (CDKN1C) [4]. In 5 – 10 % of BWS, gain of methylation in the telomeric ICR-1 results in an increased expression of the insulin-growth-factor-2 gene (usually only expressed by the paternal allele) and a reduced expression of the oncosuppressor gene H19 which is usually expressed by the maternal allele (4). 20 – 25 % of patients with BWS show paternal uniparental disomy (UPD) of chromosome 11 (patUPD11) resulting in an

altered methylation at both regions ICR-1 and ICR-2 with only paternal alleles (4). In 10 % of all BWS cases, the reason remains unclear with unknown molecular defects.

At 29 0/7 weeks of gestation, fetal ultrasound examination in a healthy 35-year-old G1/P1 revealed isolated polyhydramnios. Based on a pathological oral glucose tolerance test, gestational diabetes was diagnosed. Preterm premature rupture of membranes occurred at 31 1/7 weeks of gestation prompting the referral to the perinatal center at the University Hospital of Zurich. At this time, fetal sonography additionally showed hypertrophic cardiomegaly. Amniocentesis was performed with normal results in the karyogram.

Due to progressive maternal tachydyspnea and non-reassuring CTG, Cesarean Section was performed after a complete course of antenatal corticosteroids at 31 4/7 weeks of gestation. The boy adapted well with Apgar scores were 8, 8 and 9 at 1, 5 and 10 minutes, respectively, and an umbilical arterial cord pH of 7.27. Birth weight was 1600 g (P25–50), body length 42 cm (P25–50)25th and head circumference 30.5 cm (P50–75).

Continuous positive airway pressure (CPAP) was applied due to persisting respiratory distress. The newborn was transferred to the neonatal intensive care unit. Physical examination on admission showed asymmetric growth of the legs with a length difference of about 1 cm and a circumferential difference of about 2.5 cm in favor of the left side (Fig. 1). No other signs of (hemi-)hypertrophy or visceromegaly could be found. Minor stigmata were a simian crease on both sides and a wide nose.



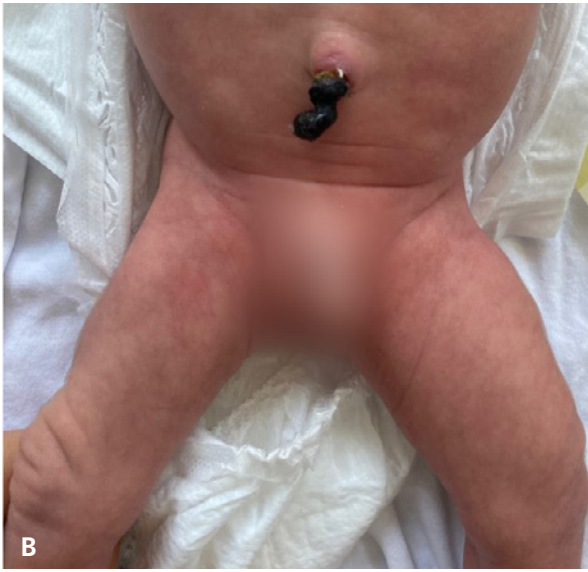


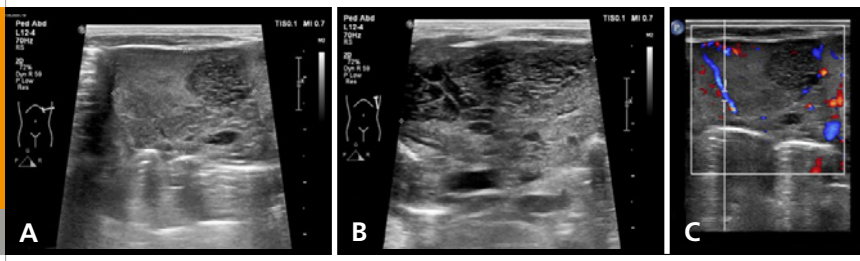
Fig. 1 A B

Asymmetric growth of legs favoring the left side with a length difference about 1 cm (A) and circumferential difference about 2.5 cm (B).

Because a cardiac abnormality had been suspected prenatally an echocardiography was performed on day of life 1 (DOL 1), showing muscular hypertrophy of the left ventricle without any further abnormalities.

To exclude lymphatic or venous stasis as explanation for hemihypertrophy of the leg, abdominal sonography was also performed on DOL 1. A complex, inhomogeneous, partly solid, partly multi-cystic tumor measuring 2.8 × 2.0 × 4.0 cm was seen above the left kidney in the retroperitoneum. There were no signs of calcifications or infiltrations of other organs (Fig. 2).

Fig. 2



Abdominal ultrasound (DOL 1): inhomogeneous, partly multicystic, partly solid mass above the left kidney (A, B); on Duplex sonography, perfusion of the mass could be demonstrated (C).

Several follow-up ultrasound examinations showed steady dimensions of the tumor and no signs of calcification; the small to medium-sized multi-cystic parts developed into a more solid structure. Considering the tumor's appearance and location, the differential diagnoses included neuroblastoma, nephroblastoma, extrathoracic pulmonary sequestration or adrenal hemorrhage. The stable size and intact perfusion of the tissue over time excluded adrenal hemorrhage (Fig. 3). Due to the non-infiltrating growth pattern and lack of parenchymal communication with the kidney, a nephroblastoma was unlikely. Neuroblastoma was suspected, but laboratory investigations showed normal values of homovanillic acid, vanilla mandelic acid, uric acid, and lactate dehydrogenase.

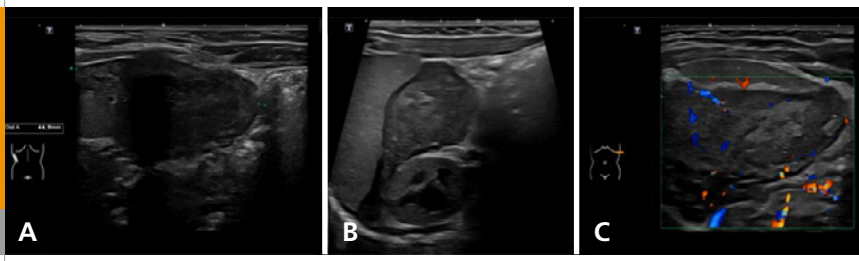


Fig. 3

Abdominal ultrasound at 10 weeks of life: the mass has become more solid with fewer multicystic areas (A, B); Duplex sonography continued to demonstrate perfusion of the mass (C).

Because of hemihypertrophy of the leg and myocardial hypertrophy BWS was supsected. Extended paternal uniparental disomy in chromosomes 6q24.4, 7p12.2, 7q32.2, 11p15.5 and 14q32.2 by (epi-)genetic examination confirmed BWS. Although there was no mosaic detectable in the boy's blood cells, mosaicism with normal biparental alleles in other body cells is likely, because such extended patUPD most likely would result in a non-viable infant.

On DOL 26, at a postmenstrual age of 35 0/7 weeks, the boy was transferred to the Children's Hospital in Zurich for further diagnostic work-up. MRI scan showed a complex T2-weighted heterogenous tumor with cystic parts and diffusion-restricted, contrast-enhancing solid parts in the left adrenal space and anterior pararenal space. Additionally, two small liver lesions with typical features of a hemangioma were detected (Fig. 4). No arterial feeding vessel could be found, and an extrathoracic pulmonary sequestration could be excluded. An MIBG positron emission tomography (PET) scan at the age of 14 months was normal (Fig. 5). Furthermore, at the age of 16 months, the tumor was no longer detectable by ultrasound.

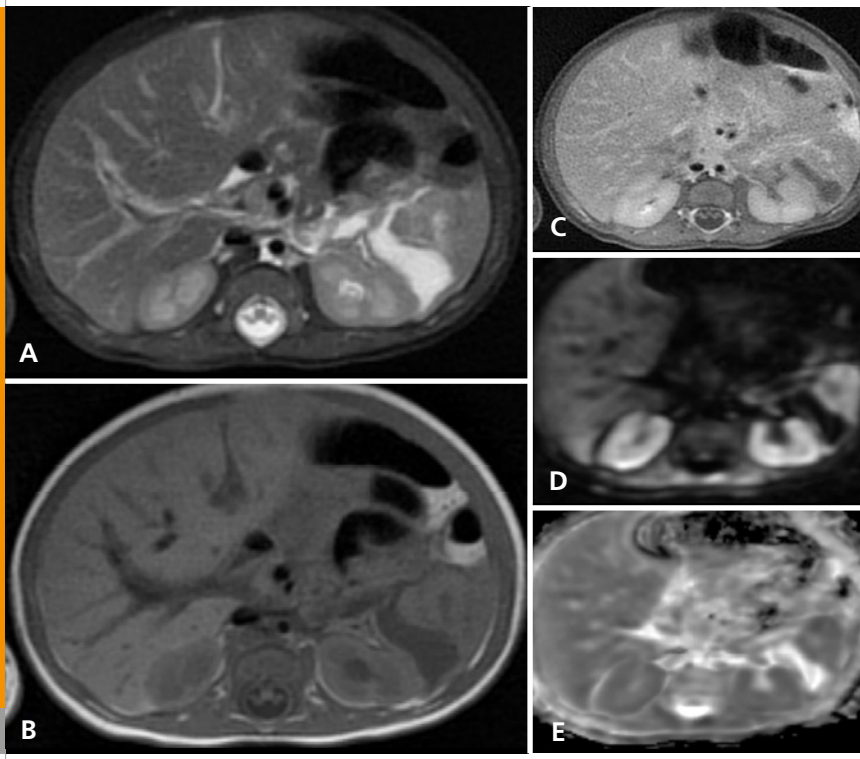


Fig. 4

MR Imaging (1.5 T) at age of 2 months: axial T2-weighted fat-saturated spin echo sequence and T1-weighted fat-saturated spin echo sequence reveals an inhomogeneous, partially-cystic, partially-solid mass in the anterior pararenal space on the left (A, B); axial contrast-enhanced T1-weighted sequence: enhancement of the anterior, solid parts of the mass (C); restricted diffusion of the solid parts can be shown in axial diffusion-weighted imaging (D, E).

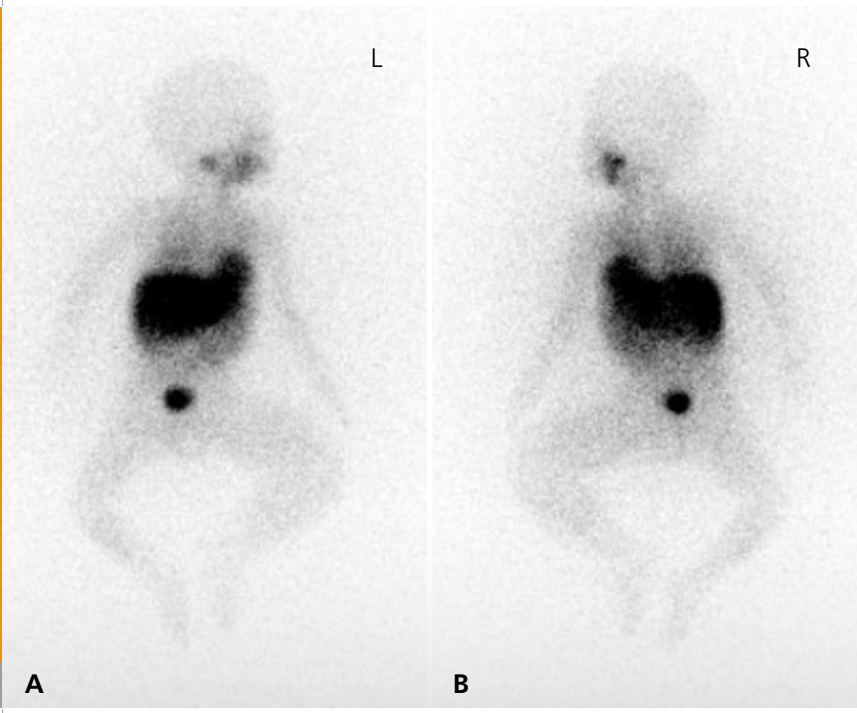


Fig. 5

Whole-body scintigraphy with 53 MBq I-123 MIBG at the age of 14 months: no evidence of a MIBG-storing tumor in anterior (A) and posterior (B) image captures.

On follow-up examinations, the hemihypertrophy of the left leg became even more pronounced (Fig. 6), and ecocardiography show persistent hypertrophy of the left ventricular myocardium. Isolated elevation of alpha-fetoprotein (AFP, maximum 705 µg/l) normalized spontaneously; its clinical significance remained unclear.

Our patient takes part in a BWS surveillance and interdisciplinary follow-up program with examinations every three months until the age of 7 years; up to the date of publication there were no signs of additional embryogenic tumors.

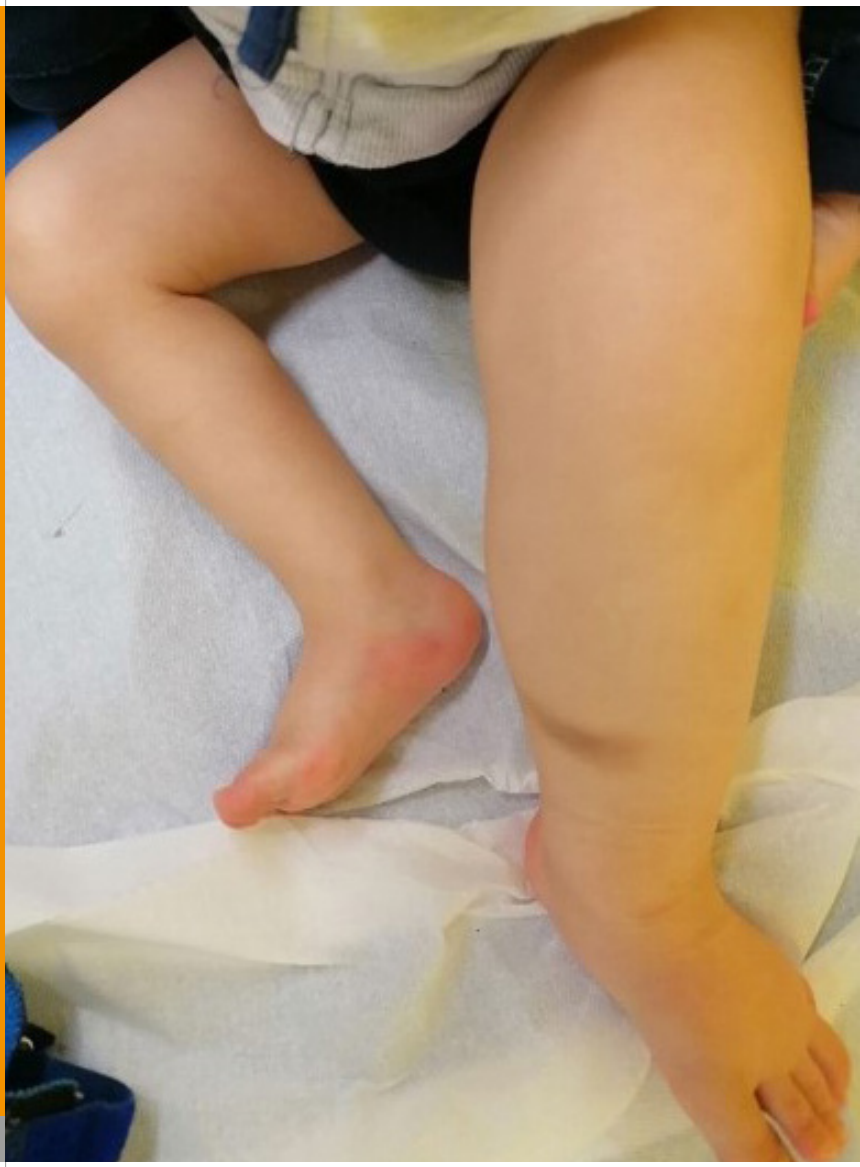


Fig. 6

At the age of 18 months, hemihypertrophy of the left leg is even more pronounced.

DISCUSSION

This case report of a moderately preterm infant illustrates the clinical course of BWS presenting with hemihypertrophy of the leg and an intraabdominal tumor. Previous studies have shown that patients with BWS can show different phenotypes depending on their genomic imprinting pattern.

A variety of imprinting disorders with UPD of a single allele, for example Silver-Russel syndrome or Angelman syndrome, are well known. However, genome-wide UPD is not viable, but mosaicism of genome-wide UPD can be, as shown in a few case reports on mosaic genome-wide paternal UPD, resembling BWS (5).

Generally, infants with BWS are at higher risk for developing embryonic tumors especially during the first 4 years of life. These include nephroblastoma (Wilms tumor), hepatoblastoma, neuroblastoma, adrenal carcinoma and rhabdomyosarcoma with a prevalence ranging from 4 – 21 % (2). Patients with patUPD11 have a five- to seven-fold increased risk of hepatoblastoma and adrenal carcinoma, as well as a thirteen-fold increased risk for Wilms tumors compared to BWS patients with ICR-2 defects (4). Regular tumor screening with abdominal ultrasound every 3 – 4 months is recommended for at least 5 years (6); at our center, follow-up examinations are performed up to the age of 7 years. Determination of AFP concentrations should be done out up to the age of 4 years.

In our case, the entity of the tumor mass remains speculative. However, with complete involution within the first year of life, and despite normal results of specific laboratory parameters (HMA, HMVA, LDH) and a negative MIBG PET scan, the (retrospective) diagnosis of a congenital neuroblastoma is very likely.

CONCLUSION

In newborn infants, hemihypertrophy with or without visceromegaly are suspicious for BWS and should lead to molecular (epi-)genetic diagnostic evaluation and sonographic screening for embryonic tumors. If BWS is confirmed, tumor screening with very strict and frequent follow-up examinations should be initiated.

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