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CASE REPORT

Acid Sphingomyelinase Deficiency in Beckwith – Wiedemann Syndrome

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We report the association of Beckwith-Wiedemann syndrome (BWS) and a residual acid sphingomyelinase (ASM) activity of about 35% in a 23 months old Hungarian boy. Besides the classical triad of exomphalos, macroglossia and gigantism some other BWS-related features: polyhydramnios (known from the praenatal history), hemihypertrophy, craniofacial dysmorphy, a mild mental retardation, bilaterally undescended testes, cardiac anomalies and a terminally developed, fatal embryonal rhabdomyosarcoma were present in the patient. The decreased activity of the ASM was measured in the patient's skin fibroblasts. This result, with hepatomegaly, mental retardation, feeding problems, a failure to thrive and muscle-hypotony, partially resembled the ASM-deficient forms of Niemann-Pick disease (NPD). Morphological analysis of the bone-marrow cells gave normal results. There was no chromosomal alteration found by conventional karyotyping of the patient's lymphocytes.BWS-associated genes as well as the human ASM gene (SMPD1) are all located at 11p15. DNA-studies by region specific markers as well as mutational analysis for the most common NPD-mutations are planned in the future. This is the first report on the simultaneous occurrence of BWS and ASM-deficiency. (Pathology Oncology Research Vol 6, No 4, 295–297, 2000)

Keywords: Beckwith-Wiedemann syndrome, acidic sphingomyelinase deficiency, embryonal rhabdomyosarcoma, simultaneous occurrence

Introduction

Beckwith-Wiedemann syndrome (BWS) is characterised by general overgrowth with a variable association of exomphalos, macroglossia and gigantism triad (EMG) in association with multiple abnormalities including hemihypertrophy, coarse facies, ear lobe creases and hypoglycaemia in the newborn infants.[1] The development of concomitant malignant tumors (Wilms tumor, hepatoblastoma, embryonal rhabdomyosarcoma etc.) is relatively frequent.[2,3]

BWS is a genetically heterogeneous disorder. Imprinted genes, located mainly at 11p15.5, like CDKN1C/p57KIP-2 and KvLQT1are supposed to be involved in the etiology of BWS and its concomitant malignancies.[4,5] Acid sphingomyelinase (ASM) catalyses the cleavage of sphingomyelin to phosphorylcholine and ceramide. A deficiency of sphingomyelinase have been demonstrated in the A- and B- forms of the Niemann-Pick group of lysosomal storage disorders (NPD). In the classical A form of the disease hepatosplenomegaly, severe neurological manifestations as well as mental and physical retardation are usually present. Group B patients remain free of neurologic disturbances despite massive visceral involvement.[6] The human ASM gene (SMPD1) has been located at 11p15.4.[7] In our case report we describe the concomitant occurrence of ASM-deficiency and BWS with a embryonal rhabdomyosarcoma developed terminally.

Case report

A 23 months old boy, with dysmorphic features and somatomental delay, was admitted to our department in order to establish a diagnosis. Similar symptoms had not occurred in his family before. The boy was born of Hungarian parents, from a second, polyhydramnionic pregnancy in the 36th. gestational week by Caesarean section,

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after a healthy daughter. His weight at birth was 5170 g. Up to 6 weeks of age he was treated in a neonatal intensive care unit with respiratory distress. He was fed through a gastrostomic tube because of early feeding problems. The specific deviations in his physical state: gargoyle-like features (coarse facies, low-set ears, ear lobe creases, wide-set, exophthalmic eyes, a high-arched palate and macroglossia) furthermore macrosomy, abdominal rectus diastasis, hemihypertrophy, systolic murmur above the heart and bilateral testis retention) were indicated by early examinations soon after birth. However, definitive diagnosis was not established that time.

By the time of his admission to our Department (*Figure 1*), physical examinations revealed a delay in weight and height gain; dry skin, a paste-like sensation of the subcutis by palpation, an open anterior fontanelle (as large as a finger-pad), a deformed chest, gracile extremities, hyperextensibility of all joints, hypotonic muscles and umbilical hernia, besides the above mentioned sympoms. When raised he was able to remain in sitting position. When put on his feet he was able to toddle with external help. He could observe his surroundings and he gurgled. He was able to understand simple requests and carry them out.

Clinical examination

Fasting blood glucose test, renal and liver function tests, abdominal ultrasound* and ophthalmological investigations (control of fundus and ocular pressure) all gave normal results. Cytogenetic analysis of the patient's lymphocytes revealed a normal karyotype. Brain ultrasound showed slightly widened ventricles and persisting cavum septum pellucidum. Brain CT and MRI showed cortical atrophy. Besides VEP-alterations, EEG and BAEP gave normal results. Echocardiography revealed small, AV type VSD, with slight mitral insufficiency. EMG raised the possibility of myopathy. Biopsy specimens taken from skin and muscle were evaluated by both light - and electron microscopic studies. EM revealed lipoid cells as well as acrofilamental aggregation in 30% of the muscle fibres. Wide-ranging metabolic investigations (including serum and urine metabolites as well as enzyme activities from skin fibroblast culture) gave normal results. The only exception was the activity of the acidic sphingomyelinase enzyme in skin fibroblasts. It was significantly below the lower edge of the accepted normal range (48 nmol/mg protein/hr vs. the normal range: 129–143 nmol/mg protein/hr).

A few weeks after his last discharge from the Department surgical intervention was necessary because of an acute ileus. A fist-sized abdominal tumor was removed. At that time hepatosplenomegaly was noted.

*Hepatomegaly was detected only later.

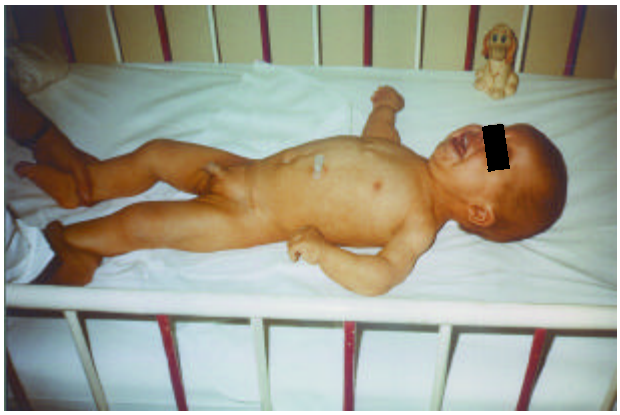

Figure 1.

Histologically the tumor was an embryonal rhabdomyosarcoma. There were no pathologic cells seen in the bone -marrow smears.

Clinically the tumor was rapidly growing (development within a month) with an unusual resistance to chemotherapy. Despite intensive cytostatic treatment (VP-16, Elobromol) the patient died a few months later.

Post mortem neurohistological investigations revealed the lack of neocortex layers V. and VI. Furthermore ectopic neuronal cells in the medullary substance, gracile pyramidal tract and a decreased number of the spinal motoneurons could be observed.

Discussion

BWS has no exactly described diagnostic criteria. The following guidelines can help in the establishment of the diagnosis: The presence of the three main features (pre- or postnatal overgrowth, macroglossia, closure abnormalities of the anterior abdominal wall) or the presence of two of the main features and three of the followings: ear lobe creases, facial naevus flammeus, hypoglycaemia, kidney enlargement, hemihypertrophy.[1]

The diagnosis of BWS syndrome in our case has been supported by the presence of all of the three main features, as well as by other characteristics like hemihypertrophy, craniofacial dysmorphy, a mild mental retardation , bilaterally undescended testes, cardiac anomalies, a embryonal rhabdomyosarcoma terminally developed as well as polyhydramnios known from the praenatal history. The symptoms of RDS after birth, well known from the patient's early medical reports, could have been mimicked by a neonatal hypoglycaemia, hidden at the background.

Basically, BWS syndrome has to be differentiated from Simpson-Golabi-Behmel syndrome (SGBS) and Perlman syndrome (PS).[1] In our case SGBS, which is inherited in an X-recessive mode, could be excluded by the lack of some characteristic features of this syndrome like normal

intelligence; bulldog-like face; supernumerary nipples; broad and short hands with polydactylia etc.[8]

PS is a rare disorder with an autosomal recessive inheritance. Although high neonatal mortality rate, hypoglycaemia, renal malformations and the development of Wilms tumor are symptomatic features, exomphalos and macroglossia are not characteristic of this syndrome.[9] With respect to further details as well as to other diseases characterised by overgrowth we refer to the scientific literature.[10,11]

The ASM activity, measured in the skin fibroblasts of the patient, was about 35% of the average level. This result as well as other clinical signs like the serious feeding problems, a failure to thrive, and muscle-hypotony have partially resembled the ASM-deficient forms of NPD. Hepatosplenomegaly was detected only at the time of the tumor-development. The involvement of the liver and spleen may be subtle in mild NPD cases, and therefore its detection may be delayed into adulthood.[6]

Overlaps between the clinical symptoms of BWS and NPD are hard to assess, mainly because of the wide variety of symptoms in both clinical entities. However, the clinical appearance of BWS patients sometimes resemble storage-disorders, with coarse facies, hepatomegaly and mental retardation. The latter two symptoms are features of NPD as well.

We have not yet found a clinical description similar to this among the publications dealing with NPD. Mutational analysis, to be planned in the future, may provide useful information about the genetic background of these findings.

Three distinct BWS-regions on chromosome 11p15 have been identified by Mannens et al,[12] by the analysis of balanced chromosomal BWS-rearrangements. They have been designated as BWSCR1, at 11p15.5, and as BWSCR2- and BWSCR3, at 11p15.3. Genes of these regions may be involved in the development of BWS, possibly through the control of IGF2 expression.[13]

Several mutations have been identified in Ashkenazi Jews as well as in non-Jewish patients with NPD. The R496L, L302P and fsP330 mutations account for more than 90 percent of the mutant alleles in Ashkenazic Jewish patients with NPD-A. DR608 mutation has been described among Ashkenazic Jewish patients with NPD-B. Its true frequency is unknown, but it is relatively frequent in patients from North Africa as well. Other non-Jewish patients with type A and B NPD have each had unique mutations.[6]

The chromosomal localization of the ASM gene (SMPD1) was refined to a 1 Mb region just distal to BWSCR2.[14] Recently, at the 6th International Workshop on Human Chromosome 11 Mapping, where this clinical observation was also presented, SMPD1 was assigned to 11p15.4.[7]

Stored DNA samples from the patient and from his family-members, isolated from peripherial blood, are the only available sources for further DNA investigation in this case. Thus, negative results can not exclude mosaic states. (Explanation of the possible molecular genetic background is discussed in a hypothesis article in this issue by Réthy LA.) For the future we propose to screen of known BWS patients, especially those with translocational breakpoints at BWSCR-II region, for ASM-deficiency and/or SMPD1 mutations.

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