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Beckwith-Wiedemann Syndrome: deciphering the genetic and clinical complexity - A case report with literature review

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a rare and heterogeneous genetic condition characterized by overgrowth, organomegaly, and increased vulnerability to embryonal tumors. This review investigates the complex genetic and epigenetic pathways underlying Beckwith-Wiedemann syndrome, focusing on the 11p15.5 region on chromosome 11. Abnormalities in the 11p15.5 area, such as imprinting control region dysregulation and CDKN1C gene mutations, contribute to disrupted growth regulation. This content also provides an overview of the incidence and pathophysiology of this syndrome. Clinical manifestations include macrosomia, macroglossia, and abdominal wall abnormalities. The increased risk of embryonal malignancies, such as Wilms tumor and hepatoblastoma, emphasises the importance of diligent medical observation. Early diagnosis through genetic testing is crucial for tailored management and genetic counseling. This detailed discussion of Beckwith-Wiedemann syndrome sheds light on the molecular complexities of the condition, emphasizing the significance of genetic testing, early detection, and multidisciplinary management for affected infants.

Keywords: Beckwith-Wiedemann syndrome, epigenetic, macroglossia, macrosomia, abdominal wall defects, embryonal tumors

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is a rare genetic condition that mostly affects the growth and development of the foetus [1]. This condition is caused by genetic and epigenetic alterations that damage a region of chromosome 11 [2]. It is characterized by a variety of signs and symptoms, which might vary in severity amongst affected foetuses. This syndrome consists of a classical trio that includes macroglossia, macrosomia, and midline abdominal wall abnormalities such as omphalocele/exomphalos and umbilical hernia.

Many cases with Backwith-Wiedemann syndrome are not manifested with this tipic triad, but show up with other features, with different incidences, summarized in major/minor findings. Major findings include macroglossia, macrosomia, omphalocele, hemihyperplasia or hemihypertrophy (asymmetric growth of the body), visceromegaly (liver, spleen, kidneys, adrenal glands, and pancreas growing), embryonal tumors (e.g. Wilms tumor, hepatoblastoma, rhabdomyosarcoma, etc.), anterior linear ear lobe creases and/or posterior helical ear pits, renal abnormalities, cardiomyopathy, positive family history and cytomegaly of the foetal adrenal cortex. And minor findings such as neonatal hypoglycemia, structural cardiac anomalies, diastasis recti, vascular lesions including nevus simplex or hemangiomas, and findings during pregnancy including polyhydramnios and prematurity [3].

INCIDENCE

Beckwith-Wiedemann syndrome (BWS) is a rare genetic condition with varying incidence among populations. The reported incidence of Beckwith-Wiedemann syndrome ranges from 1 in 10,340 to 1 in 13,700 live births. It is crucial to note that these

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figures are general estimates, and the incidence may vary depending on factors such as ethnicity and geographic region [4]. The incidence is 1:4000 to with IVF children.

BWS affects both men and women, and it can arise sporadically (85% of patients have no family history) or be inherited autosomally dominantly (15% of familial cases). In cases sporadic, the syndrome may result from de novo genetic or epigenetic changes. In familial cases, there is a chance of recurrence in subsequent pregnancies, and the risk may depend on the underlying genetic cause within the family.

AETIOLOGY

Beckwith-Wiedemann syndrome (BWS) is caused by genetic and epigenetic changes that affect a specific region of chromosome 11, notably the 11p15.5 region [5]. The most common genetic mechanisms leading to BWS include:

Imprinting Abnormalities: The 11p15.5 areas are affected by genomic imprinting, a process in which the activity of genes depends on their parental origin. This can result in over expression or under expression of certain genes, contributing to the features of BWS.

Uniparental Disomy (UPD) occurs when both copies of a chromosome or chromosomal region are inherited from the same parent, rather than one copy from each. In BWS, there may be instances of UPD for chromosome 11, leading to abnormal gene expression in the 11p15.5 region.

Alterations in the CDKN1C Gene: The CDKN1C gene, which is found on chromosome 11p15.5, may be mutated or aberrant. These gene alterations have an impact on the development of BWS. The CDKN1C gene normally acts as a tumor suppressor, regulating cell growth and division.

Abnormalities of ICR1 and ICR2: Imprinting control regions 1 (ICR1) and 2 (ICR2) are regulatory areas on chromosome 11p15.5 that influence the expression of neighboring genes. Abnormalities in these regions can disrupt the normal imprinting patterns, leading to BWS.

The genetic pathway underlying BWS can differ between foetuses and the syndrome can occur sporadically or be inherited in an autosomal dominant fashion. Approximately 85% of instances are sporadic, meaning they occur for the first time in a family. In familial cases, the risk of recurrence in future pregnancies may be influenced by the underlying genetic cause.

Diagnosis of BWS often involves genetic testing, including molecular investigation of the 11p15.5 region and the CDKN1C gene. The identification of the specific genetic mechanism can help in understanding the risk of recurrence and guide appropriate genetic counseling for affected families.

PATHOPHYSIOLOGY

Beckwith-Wiedemann syndrome (BWS) is predominantly caused by genetic and epigenetic anomalies in the 11p15.5 region on chromosome 11. This area is subject to genomic imprinting, a process in which the activity of genes is determined by their parental origin. The 11p15.5 region contains imprinted genes that regulate growth and development.

Beckwith-Wiedemann syndrome pathogenesis includes the following major aspects [6]:

- Abnormalities in Imprinting Control Regions (ICRs): The 11p15.5 region comprises two imprinting control regions, ICR1 and ICR2. These areas control the expression of neighboring imprinted genes. Abnormalities in the methylation status of these ICRs can disrupt normal imprinting patterns, resulting in aberrant expression of imprinted genes. This dysregulation contributes to the characteristic features of Beckwith-Wiedemann syndrome.
- CDKN1C Gene Abnormalities: The CDKN1C gene, located on chromosome 11p15.5, is an important regulator of cell growth and division. Mutations or alterations in the CDKN1C gene can result in decreased expression of this tumour suppressor gene, contributing to the macrosomia observed in Beckwith-Wiedemann syndrome.
- Uniparental Disomy (UPD): In some cases of Beckwith-Wiedemann syndrome, individuals may inherit both copies of chromosome 11 or a chromosomal region from one parent, resulting in uniparental disomy (UPD). This can result in aberrant gene expression due to the absence of genetic contribution from the other parent.
- Increased Growth Factors: Imprinted genes in the 11p15.5 region can be dysregulated, affecting the generation of growth factors and other signalling molecules important in foetal development. This dysregulation contributes to overgrowth, including macrosomia (larger-than-average size) and organomegaly (enlarged internal organs).
- Tumor Predisposition: Beckwith-Wiedemann syndrome is linked to an elevated risk of some cancers, including Wilms tumor (a kidney tumor) and hepatoblastoma (a liver tumor). The precise processes that relate genetic and epigenetic anomalies in BWS to cancer formation are unknown, however, they are assumed to include disruptions in normal cell growth control.

Understanding the underlying genetic and epigenetic factors in BWS is crucial for diagnosis, genetic counseling, and management.

CLINICAL FINDINGS

Beckwith-Wiedemann Syndrome (BWS) is a rare genetic condition characterized by excessive growth and an elevated risk of certain tumors. The clinical findings of Beckwith-Wiedemann Syndrome can vary, but common features include [7]:

Macroglossia (enlarged tongue): Infants with BWS often have a large tongue, which may protrude from the mouth.

Exomphalos (omphalocele): This condition where the abdominal organs protrude through the belly button due to a weakness in the abdominal wall.

Visceromegaly: Enlargement of internal organs, such as the liver and kidneys, may occur.

Hemihyperplasia: Asymmetrical growth on one side of the body compared to the other.

Ear creases or ear pits: Distinctive creases or small pits in the skin near the ear.

Neonatal hypoglycemia is defined as low blood sugar levels during the newborn period. Children with Beckwith-Wiedemann syndrome are more likely to develop specific tumors, such as Wilms tumor (a kidney tumor), hepatoblastoma (a liver tumor), and adrenal tumours.

Organomegaly: Enlargement of various organs, including the liver, kidneys, and pancreas.

Children with Beckwith-Wiedemann syndrome may have rapid skeletal maturation. Some infants with Beckwith-Wiedemann Syndrome may exhibit distinctive facial features, such as a high forehead and a pointed chin.

It's important to note that not everyone with Beckwith-Wiedemann Syndrome will have all of these characteristics, and the degree of symptoms can vary greatly. Beckwith-Wiedemann syndrome is usually confirmed by genetic testing, which may identify abnormalities in a region of chromosome 11 called 11p15.5. Early diagnosis and management are crucial to providing optimal medical care.

PRESENTATIONS

A 27-year-old, primigravida, presents at 35+4 weeks of pregnancy with little flow of amniotic fluid from premature rupture of amnion and regular contractions for a premature labor in the Obstetrics and Gynecology clinic in Pristine, Kosovo. The vital parameters (blood pressure, pulse, and breathing) of the mother were normal. The woman declares that she had only two antenatal visits, one in the first trimester to confirm the pregnancy and an ultrasonographic examination two weeks ago; she reasons this approach with low economic conditions and family beliefs. The medical documentation of the previous antenatal visits does not show any specific findings to be distinguished for maternal. The patient had no medical or family history of any congenital malformations, and there was also no antenatal history of infection, radiation, or toxin exposure. The data from an ultrasonographic examination two weeks earlier indicated polyhydramnios (AFI: 28cm) and a baby with greater growth than the gestational age (3900 g) but without any feature in fetal morphology. Diabetes mellitus had been excluded by normal glucose tolerance tests and HbA1C levels. A report of serological investigations of the first trimester (for toxoplasmosis, listeriosis, hepatitis A and B, herpes simplex, cytomegalovirus) had negative results. The maternal pelvis has been clinically assessed and declared to be adequate for a foetus of this estimated weight. The cervix is 9 cm dilated and 75% effaced, with the foetal head at -1 station. After an hour, the woman gave birth to a boy baby weighing 4100 grammes and having an Apgar score of 5/6. The macroscopically placenta was normal, whereas the umbilical cord had an edema of the Wharton's jelly. Postpartum, the baby there was moderate hypoglycemia (1.9 mmol/1) and polycythemia (Hb: 13 mmol/1; HCT: 59%; leukocytes: 15600/ccm; platelets: 149000/ccm). A thorough

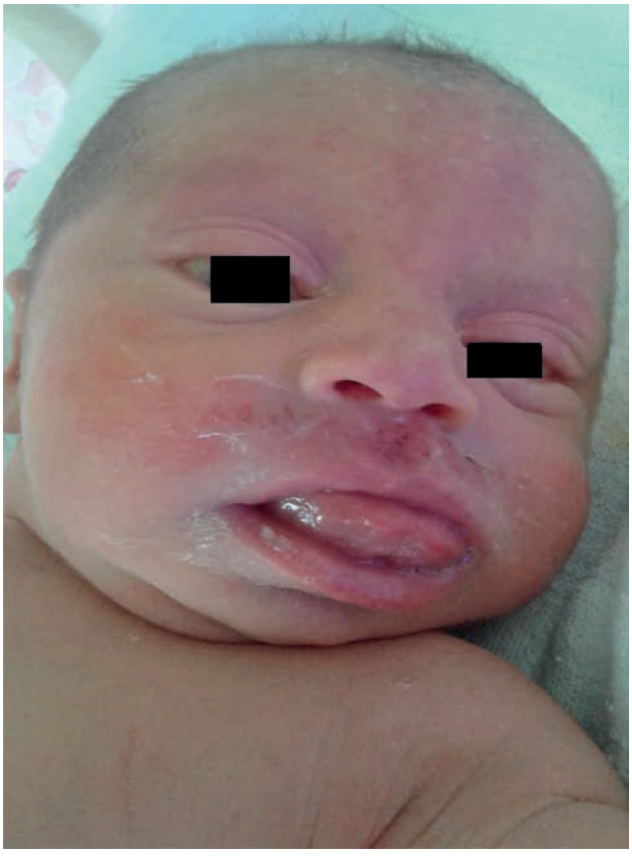

FIGURE 1. Macroglossia and Capillary malformation or port-wine stain, below nose

examination of the foetus revealed several anomalies, including macrosomia (large body size), macroglossia (enlarged tongue), capillary malformation or port-wine stain beneath the nose, anterior linear earlobe creases, and nevus simplex on the glabella and eyelids as faint pink patches with feathery borders. We diagnosed the Wiedemann-Beckwith syndrome based on the following features: polyhydramnios, macrosomia, macroglossia, capillary malformation or port-wine stain, below the nose, anterior linear earlobe creases, nevus simplex on the glabella, and eyelids as faint pink patches with feathery borders. Due to macroglossia, there were initially problems with feeding, but an emergency surgical intervention was not necessary. The infant was released in stable condition from the clinic with an individual plan for monitoring and treatments.

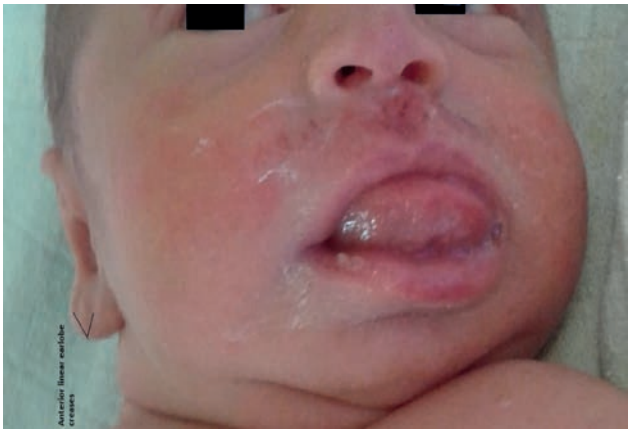

FIGURE 2. Anterior linear earlobe creases and Macroglossia

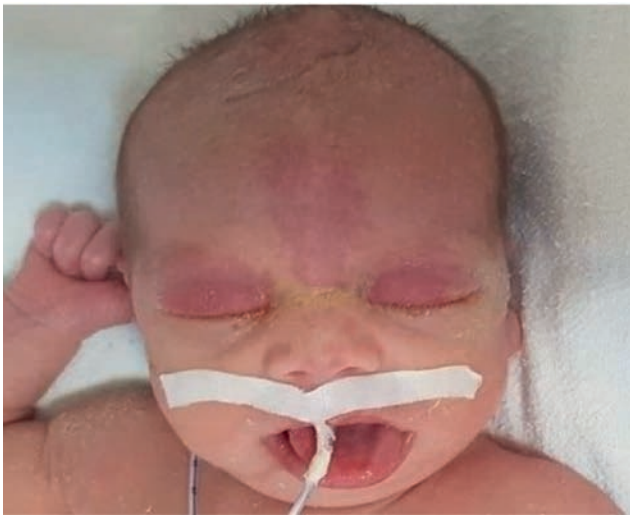

FIGURE 3. The glabella has nevus simplex, and the eyelids are pale pink with feathery margins

DISCUSSION

Beckwith-Wiedemann syndrome (BWS) is a complex genetic condition with a variety of clinical symptoms.

Beckwith-Wiedemann Syndrome is primarily linked to genetic and epigenetic changes in a specific region of chromosome 11, known as 11p15.5 [8,9]. This area has imprinted genes that play an important role in growth regulation. The syndrome can be sporadic or inherited, and it may result from abnormalities in the maternal or paternal copy of chromosome 11.

Beckwith-Wiedemann syndrome clinical presentation varies significantly. Not all infants with BWS will exhibit the same features, and the severity of symptoms can vary widely. This makes diagnosis and management challenging, as clinicians need to be vigilant for a diverse set of signs [10].

One of the hallmark features of Beckwith-Wiedemann syndrome is overgrowth, which can manifest as macrosomia (large body size), macroglossia (enlarged tongue), and hemihyperplasia (asymmetric growth). Overgrowth is most noticeable during the first few years of life.

Individuals with Beckwith-Wiedemann syndrome are more likely to develop certain tumours, including Wilms tumor (a kidney tumor), hepatoblastoma (a liver tumor), and adrenal tumors. Regular screening and surveillance for these cancers are necessary for early detection and management [11,12].

Beckwith-Wiedemann syndrome is diagnosed through clinical evaluations, imaging tests, and genetic testing. Molecular testing, such as methylation analysis of 11p15.5, is often used to confirm the diagnosis and identify specific genetic or epigenetic abnormalities [13].

Management of Beckwith-Wiedemann syndrome involves a multidisciplinary approach. Early intervention for certain features, such as macroglossia, may be necessary. Regular monitoring for tumour development is critical, and surgical removal of tumors may be required. Genetic counseling is also an important aspect of the management, especially for families with a history of this disease [14].

Beckwith-Wiedemann syndrome has a considerable psychosocial impact on affected persons and their families [15]. Coping with the challenges of overgrowth, potential surgeries, and tumor surveillance can be emotionally challenging. Support from healthcare experts, support groups and mental health services are essential.

Ongoing research is focused on understanding the underlying molecular mechanisms of Beckwith-Wiedemann syndrome and developing targeted therapies. Advances in genetic technologies and personalized medicine may contribute to improved diagnostic accuracy and tailored treatment approaches in the future.

In summary, the discussion of Beckwith-Wiedemann syndrome should encompass its genetic basis,

clinical variability, associated features, diagnostic approaches, multidisciplinary management, psychosocial impact, and ongoing research efforts aimed at better understanding and treating this rare genetic disorder [16].

CONCLUSION

To summaries, Beckwith-Wiedemann Syndrome (BWS) is a rare and genetically complex condition marked by overgrowth and higher vulnerability to certain tumors. The clinical presentation of BWS is diverse, encompassing features such as macroglossia, macrosomia, hemihyperplasia, and organomegaly. The condition is connected with genetic and epigenetic changes in imprinted genes on chromosome 11p15.5.

Timely diagnosis, which combines clinical assessment and molecular testing, is critical for optimal care. Genetic counselling is critical in providing families with a thorough understanding of the condition, including probable inheritance patterns and related risks.

The heightened risk of tumor development, particularly Wilms tumor and hepatoblastoma, underscores the importance of vigilant surveillance and regular medical follow-up throughout an individual's life. Surgical interventions may be required to address specific features, and a multidisciplinary approach is typically employed to manage the complex array of clinical manifestations.

Beyond the medical aspects, BWS has a significant psychosocial impact on affected individuals and their families.

Continued research efforts aimed at unravelling the molecular mechanisms underlying BWS hold promise for further advancements in diagnosis, treatment, and potential targeted therapies.

In summary, a holistic and collaborative approach, involving medical professionals, genetic counsellors, support services, and ongoing research initiatives, is essential to address the multifaceted aspects of Beckwith-Wiedemann syndrome and enhance the quality of life for affected individuals.

Informed consent: the patient has given informed consent for the publication of this case report and its accompanying photographs.

Ethics approval: this study is both a case report and a literature review. It was carried out utilizing simply the case description following the patient's approval and collection of data from the literature. Institutional review board permission was not required.

Conflict of interest: the authors declare that they there is no financial or conflict of interest in this case study.

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