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The diagnosis of Beckwith-Wiedemann syndrome in a child and psychological implications to parents – A case report

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ABSTRACT

INTRODUCTION: While Beckwith-Wiedemann syndrome is among rare genomic imprinting disorders, its diagnosis still presents challenges in clinical settings. Therefore, the aim of this work is to present different phenotypic features of this syndrome.

CASE PRESENTATION: We reviewed two-month-old patient referred to the genetic unit at Rwanda military hospital, Kigali, Rwanda. Physical examinations indicated severe larger birth length (macrosomia), Overgrowth of the right side of lower limbs (hemihypertrophy/hemihyperplasia), larger tongue (macroglossia) and bigger abdomen. We performed karyotype and revealed a normal male chromosomal formula: 46,XY.

CONCLUSION: Based on the phenotypic clinical features, the patient was diagnosed with Beckwith-Wiedemann Syndrome. However, cytogenetic tests performed were not advanced and should not rule out epigenetic abnormalities that should account for phenotypic features of this syndrome in our patient.

Keywords: Genome, Gene, Macroglossia, Epigenetics, Methylation

INTRODUCTION

The Beckwith–Wiedemann syndrome is a genetic disorder with clinical features linked with severe somatic growth disproportion and is the risk factor for embryonal tumors [1]. This syndrome is associated with genetic or epigenetic mechanisms affecting imprinted genes located within a genomic region of chromosome 11p15, with biallelic rather than monoallelic expression of the insulin-like growth factor 2 (IGF2) gene among 25-50% of BWS patients. Another 50% of patients have an epigenetic mutation resulting in loss of imprinting of a transcript called KCNQ1OT1 [2]. Each of these genes resides in one of the two imprinted domains that appear to be subject to developmental dysregulation in BWS [3].

Clinically, the common manifestations of this

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syndrome include macroglossia, omphalocele, umbilical hernia, visceromegaly, ear lobe grooves, large birth size, facial nevus flammeus, congenital anomalies, body asymmetry, occipital prominence, intestinal malrotation, hypoplastic midface, prognathism, clitoromegaly, inguinal hernia, developmental delay or retardation, prematurity, tydramnios, and cleft uvula or palate [2,4,5]. However, some features may vary among patients, including macrosomia, hepatoblastoma, and neonatal hypoglycemia. Molecular analyses of patients with this syndrome revealed genetic and epigenetic defects, including IC2 hypomethylation, segmental mosaic pUPD11, IC1 hypermethylation, CDKN1c mutation and H19-DMR microdeletion, 11p15 translocation/inversion, and 11p15 Duplication [6].

While this syndrome is classified in genomic imprinting disorders affecting different genes on chromosome 11p15.5, the imprinted regions on this chromosome are classified into two domains. In domain 1, H19 and insulin-like growth factor 2 (1GF2) genes have been found to be imprinted. IGF2 as a growth factor, is paternally expressed, while H19 is a noncoding RNA, usually methylated on the paternal chromosome and not methylated on the maternal chromosome [2]. In domain 2, some genes have been found to be imprinted. The first gene is CDKN1C (p57KIP2), known to be a maternally expressed gene that encodes a cyclin-dependent kinase inhibitor and negatively regulates cell proliferation [2,6]. Rarely, CDKN1C also affected by aberrant methylation associated with cell cycle dysregulation leads to tumors. Additionally, mutations in CDKN1C linked to autosomal dominant inheritance have been found to be responsible for BWS. The second gene is TSSC3. It is maternally expressed, and its features and functions are common among genes responsible for Fas-mediated apoptosis and fatal overgrowth, including Tdag51 [2]. KCNQ1 is a maternally expressed gene involved in the formation of the potassium channel. The literature today suggests that this gene contains translocated regions linked with BWS. Intron 10 of the KCNQ1 gene has KvDMR1 and DMR2[7]. The paternal allele of this gene is non-methylated, permitting the paternal expression of a long transcript called KCNQ1OT1, also known as LIT1. Maternal methylation of DMR2 silences the expression of KCNQ1OT1. As a result, KCNQ1 and CDKN1C genes are expressed hence Beckwith Weidman Syndrome [2,3,8].

Despite its severe clinical features and its associated early or later complications in both physical and cognitive aspects. The diagnosis of this syndrome still presents challenges. This may account for the fact that few cases are reported in clinical settings, specifically in Africa. Thus, this work is to describe the clinical features of this syndrome, therapeutic and follow-up plan for both patient and parents; with the aim of raising its awareness in clinical settings.

CASE PRESENTATION

A 2 months child was referred to the genetic unit at Rwanda Military Hospital for a large tongue. Birth history was consistent with having a larger birth length (macrosomia). On physical examination, we noticed an overgrowth of the right side of the lower limbs (hemihypertrophy/ hemihyperplasia), a larger tongue (macroglossia), and a bigger abdomen with enlarged kidneys, liver, and pancreas (organomegaly) as seen in Figure 1.

These features led to the suspected Beckwith-Wiedemann syndrome and a karyotype test was performed, revealing normal results. Karyotype test itself could not be conclusive while it does not describe the structures of genes.

Other advanced tests including DKN1C mutation analysis, KvDMR1 methylation analysis, UPD analysis and loss of methylation analysis were needed to come up with a conclusive result. Unfortunately, our laboratory has no ability to perform those tests. Therefore, the diagnosis was based on phenotypic features.

The patient was scheduled for a preventive long follow-up plan. Bearing in mind the importance and crucial functions of the tongue for deglutition, phonation, and respiration and, dental occlusion, and the skeletal growth of the facial region, the patient was referred to the Otorhinolaryngology department for further management to undergo partial glossectomy at 6 months of age, and be followed up until 5 years. To prevent the delay in gross motor development milestones caused by hemihypertrophy, the patient was started on 3 sessions/ week of physiotherapy of stimulation and re-education, and a physiotherapist and geneticist will evaluate the progress once every three months. To address additional health problems that may be manifested later as the child grows-up, in addition to a geneticist, Otorhinolaryngology specialists, and physiotherapists, speech therapists

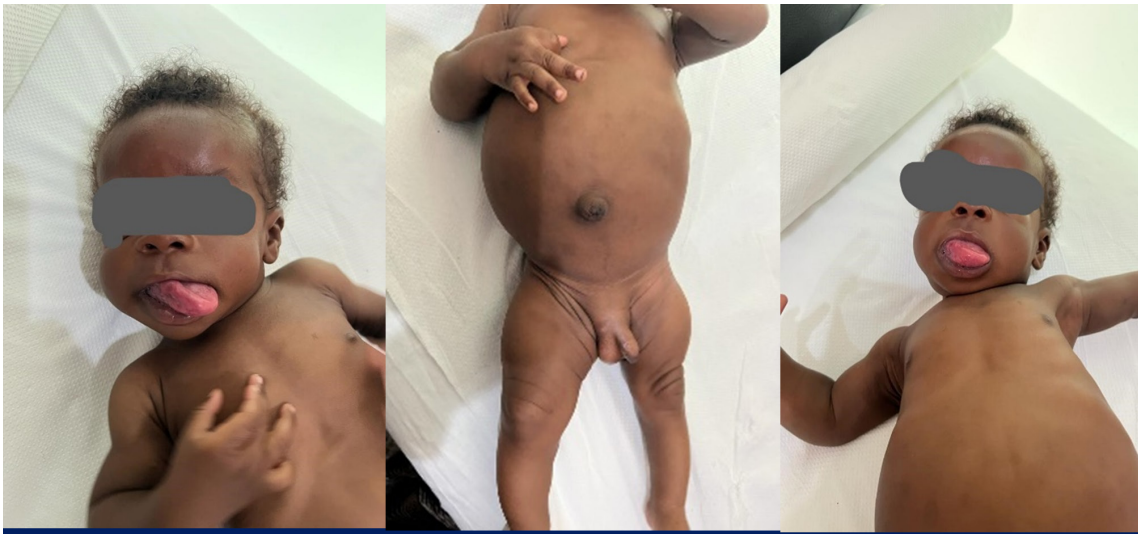

Figure 1: macrosomia, and hemihypertrophy, and macroglossia as clinical features of Beckwith-Wiedemann syndrome

and occupational therapists will be involved. The patient will also be reviewed regularly in internal medicine and nephrology for any cardio-vascular and kidney issues that may emerge later.

The conversation with the mother of the child indicated the presence of anxiety and depressive symptoms. The family consider having a child with Beckwith-Wiedemann Syndrome as the loss of a normal baby they were expecting. In genetic counselling, we provided to the parent the information on Beckwith Wiedemann syndrome. We told the parent the root cause of the syndrome, and the probability to reoccur for the next pregnancies. While the parent seemed discouraged with no hope for the outcome of the patient, we provided related to the available management options with their outcomes. Psychodiagnostics done indicated anger, sadness, sleeping difficulties, fear and self-blame that should be suggestive of symptoms of depression and anxiety in a parent. Therefore, we had sessions with a parent for managing those emotional issues. While we know that emotional issues may emerge and lead to misunderstandings between partners, we told a parent to come with a partner for the next appointments for a family genetic counselling. This family genetic counselling helped both parents understand the syndrome together and strengthened their commitment for the treatment of their child.

DISCUSSION

The aim of the case report was to highlight the clinical phenotypical features of Beckwith-Wiedemann Syndrome. As revealed and highlighted in different studies, our patient presented macrosomia, hemihypertrophy, and macroglossia as common physical features of this syndrome [9]. Advanced laboratory analysis in patients with this syndrome has highlighted different defects on chromosome 11p15.5. Maternal chromosomal rearrangements of 11p15.5, and paternal uniparental disomy (UPD) of chromosome 11, implying that the maternal copy of this chromosome is replaced with an extra paternal copy, have been found in different patients. DNA methylation in different areas of 11p15.5 has also been highlighted, suggesting that normal epigenetic mechanisms that regulate imprinted genes in this region are altered [8]. However, in our analysis were only limited to karyotype and were not able to perform advanced tests. The treatment and management of this syndrome are preventive than curative. While an enlarged tongue leads to both functional and cosmetic abnormalities, that, in turn affect the oral airway, speech, and the development of the jaws [9], the surgical operation designed to reduce the tongue is the most performed treatment option for the patient with this syndrome [10]. The management follow-up of patients with this syndrome must be intensive and long-term and emphasizes disproportionate tongue bulk abnormal tongue

shape, specific speech sound abnormalities, and a short tongue tip, swallowing and taste sensation problems [11]. The brain malformations may occur progressively among patients with this syndrome, especially when the imprinting errors affect genes in domain 2. Therefore , long-term follow-up with brain imaging to evaluate brain growth, malformations and neurodevelopmental problems are crucial [12]. This long-term follow-up of patients with Beckwith Wiedemann Syndrome should be done by the multidisciplinary team and should be combined with supportive and re-education therapies [13].

CONCLUSION

The patient was diagnosed with Beckwith-Wiedemann Syndrome basing on the phenotypic clinical features. The patient was scheduled for a long-term follow-up by a multidisciplinary team of healthcare providers to evaluate, prevent and manage physical and developmental issues that may emerge later as a result of this syndrome. While the family plays a big role in patient treatment processes, genetic counseling was optional to the parents and was designed to provide full information on the pathophysiology, prognosis, reoccurrence probability, and the available patient treatment and follow-up options in addition to emotional management.

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