International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Case Report

Correlation of Assisted Reproduction Techniques with Beckwith - Wiedemann Syndrome

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Received: 16/02//2014 *Revised: 23/03/2014* *Accepted: 03/04/2014*

ABSTRACT

Beckwith–Wiedemann syndrome (BWS) is a rare syndrome and has an estimated incidence of one in 13,700. It is also known as exomphalos-macroglossia-gigantism syndrome. It consist of a combination of congenital abdominal wall defects such as hernias (exomphalos), large tongue (macroglossia), large bodies and/or long limbs (gigantism). There has been an increase observed in the number of cases of BWS in children born by assisted reproduction techniques (ART).

Keywords: Beckwith-Wiedemann Syndrome, assisted reproduction techniques.

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) also known as EMG (Exomphalos, Macroglossia, Gigantism) syndrome was recognized independently by Beckwith in 1963 and Wiedemann in 1964.[1] The incidence of BWS reported is 1 in 13700 live births. This figure is likely an underestimate as milder phenotypes may not be ascertained. The incidence is equal in males and females with the notable exception of monozygotic twins that show a dramatic excess of females.[2] The etiology is unknown but familial cases suggestive of autosomal dominance, autosomal recessive, polygenic inheritance and delayed mutation have been recorded. There has been an increase observed in the number of cases of BWS or alterations in gene expressions in children born by ART(assisted reproduction techniques).[1] A prenatal diagnosis of BWS is possible in pregnancy with uterine sizes incompatible with dates and by use of serial ultrasound monitoring of the uterus of the pregnant woman.[3] Individuals with BWS may grow at an increased rate during the latter half of pregnancy and in the first few years of life. Growth parameters typically show height and weight around the 97th percentile with head size closer to the 50th percentile. Adult heights are generally in the normal range.[2]

CASE REPORT

A 36 weeks preterm male child (Fig.1) born to unrelated Indian parents by normal vaginal delivery was referred to our NICU for omphalocele (Fig.2). The infant's mother was a 32 year old second gravida. She had previously had a spontaneous

abortion. This child was conceived with the help of assisted reproduction technique (ART). Her serial antenatal ultrasound scans had revealed an omphalocele with loops of bowel. The birth weight was 2200 gms, length was 52 cm and head circumference was 34cm. On examination baby had dysmorphic features like bilateral nevus flammeus over eyelids (Fig.3), macroglossia, omphalocele, hepatomegaly and undescended testes. The child was investigated for complete blood count and serum electrolytes which were within normal limits but the blood sugar level was low. The thyroid profile was normal. The baby was put on glucose infusion drip and also required steroids to remain euglycemic. Baby was operated successfully for the omphalocele on day 5 of life. He later developed respiratory distress and a grade II/IV murmur was heard on auscultation. Echocardiography was suggestive of bilateral ventricular dilatation and a small sized ventricular defect. The child was further investigated for inborn errors of metabolism but no defect was detected. Abdominal ultrasonography showed a right adrenal cyst (Fig.4) and mid jejunal atresia. Neuro sonography was suggestive of ischemia in the watershed areas of the brain. displayed areas of calcification. Chromosomal analysis revealed normal male karyotype. Baby developed respiratory distress on day 10 of life. He was put on assisted ventilation care but his condition kept deteriorating progressively. Baby died of respiratory failure on day 22nd of life. Autopsy finding showed evidence of intra-abdominal testis, kidney with increased foetal lobulations, disorganization of the parenchyma, glomerular neogenesis and an increased number of immature collecting tubule. Pancreas revealed an increased number of acini, Adrenals showed cytomegaly and a right Adrenal cyst.

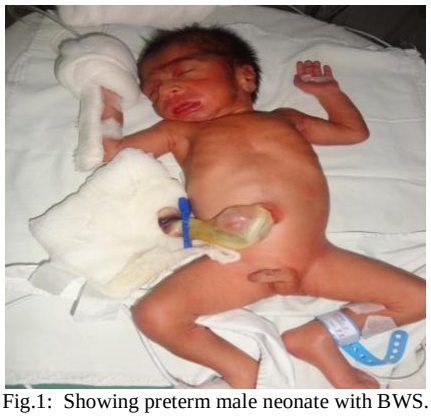
Fig.1: Showing preterm male neonate with BWS.

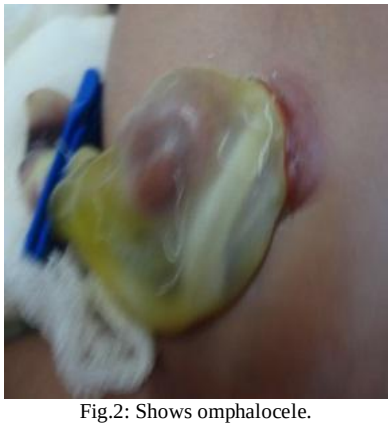
Fig.2: Shows omphalocele.

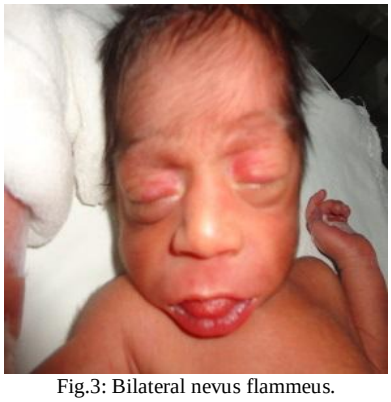
Fig.3: Bilateral nevus flammeus.

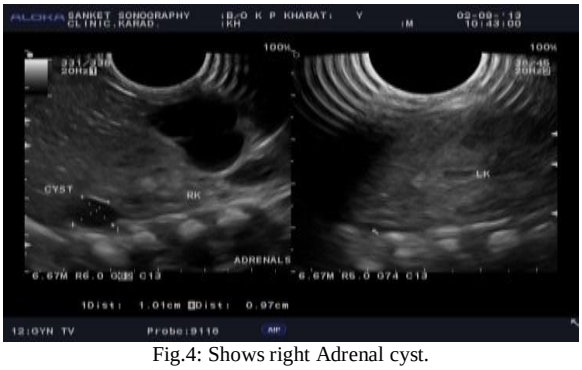

Fig.4: Shows right Adrenal cyst.

DISCUSSION

BWS is a pediatric overgrowth disorder involving a predisposition to tumor development. The characteristic features of BWS are variable, but mainly consist of macroglossia, fusion defects of the abdominal wall, somatic gigantism, midface hypoplasia, ear creases and/or pits, nevus flammeus, visceromegaly, cryptochidism and hemihypertrophy. The acronym EMG syndrome was used earlier to describe exomphalos, macroglossia and gigantism.[4] Hypoglycemia is reported in 30–50% of babies with BWS, likely caused by islet cell hyperplasia and hyperinsulinemia.[2] Abnormalities involving genes on chromosome 11 that undergo genomic imprinting are responsible for most cases of BWS. Many patients have abnormal DNA methylation in different areas of 11p15. Imprinting control regions (ICRS) control the methylation of several genes that are involved in normal growth, including the *CDKN1C, H19, IGF2,* and *KCNQ1OT*.[5] *Individuals with BWS may grow at an increased rate during the latter half of pregnancy and in the first few years of life, but adult heights are generally in the normal range. Abnormal growth may also manifest as hemihypertrophy and or macroglossia. There is an increased frequency of malformations and medical complications, including abdominal wall defects (omplalocele, umbilical hernia, and diastasis recti) and visceromegaly involving liver, spleen, pancreas, kidneys or adrenals. Fetal adrenocortical cytomegaly is a pathognomonic finding. Renal anomalies may include primary malformations, renal medullary dysplasia, nephrocacinosis, and nephrolithiasis.* Most of the tumors associated with BWS occur in the first 8–10 years of life with very few being reported beyond this age, most common are Wilms tumor and hepatoblastoma. Other embryonal tumors include rhabdomyosarcoma, adrenocortical carcinoma, and neuroblastoma. Clinical findings associated with higher risks of tumor development include hemihyperplasia, nephromegaly, and nephrogenic rests.[2] *BWS has also been associated with congenital hypothyroidism in preterm neonates in a few reports.* It has been postulated that the gene governing the production of thyroxin-binding globulin might be in close proximity with the one that governs the production of thyroxin and may well be linked closely to the gene that suppresses the manifestations of BWS.[4] *However we did not find any such association.* Differential diagnosis of BWS can be Sotos syndrome (Mutations in the NSD1 gene on chromosome 5q35), Silver-Russell syndrome (Hypo methylation defects at 11p15), Fragile X syndrome, Berardinelli lip dystrophy syndrome, Marshall-smith syndrome, Weaver-smith syndrome.[6] Diagnosis is based on clinical findings.[2] The criteria for diagnosis is the presence of 3 major findings (macroglossia, pre- or postnatal growth greater than the 90th centile, and abdominal wall defects) or 2 major findings plus minor manifestations.[6] A careful cytogenetic analysis of the 11p15 region is recommended. Prenatal diagnosis by ultrasonography is also possible. When the pregnancy is not terminated, the prenatal diagnosis helps to prevent neonatal complications.[2] The prenatal diagnosis helps because it allows two situations. On one hand, to prepare the parents, motivate them to have a periodic follow-up because of the increasing possibilities of developing tumors, and genetic counseling in case of the desire to have more children. The second situation is that it allows the planification of the surgical interventions necessary for the correction of defects present in the child.[1] The management of BWS patients typically involves standard supportive medical and surgical strategies (e.g. surgical repair of omphalocele). In addition, anticipatory

medical management for certain findings should be invoked if the diagnosis of BWS is established or even suspected. If there are prenatal findings suggestive of or diagnostic for BWS screening for hypoglycemia should be undertaken in the first few days of life. As well, parents should be advised of the typical clinical manifestations of hypoglycemia in the event that it manifests after discharge from hospital. The management of BWS is according to the clinical features associated with it. The abdominal wall defects are treated by surgical repair. Hypoglycemia is treated as per standard protocols. Other features do not require any specific treatment. We have described an apparent increased frequency in children born with the aid of assisted reproductive technology (ART) in patients with the BWS imprinting disorder.[7] As both IVF and ICSI procedures were associated with BWS, loss of maternal allelic methylation at differentially methylated regions within imprinted gene clusters associated with in vitro embryo culture may be an important factor in the pathogenesis of ART associated imprinting disorders.[7]

CONCLUSION

In children born with ART frequent antenatal ultrasound scan should be undertaken to establish the anticipatory medical management to prevent associated complications. Further studies are required to determine the precise relationship between human imprinting disorders and ART.

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How to cite this article: Kumar J, Basu S, Jeswani D et. al. Correlation of assisted reproduction techniques with beckwith - wiedemann syndrome. Int J Health Sci Res. 2014;4(4):229-232.

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