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Neonatology

A Novel Unbalanced Chromosome 8 Translocation with Multiple Congenital Malformations

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Abstract **Case Report**

Unbalanced translocation is estimated to be responsible for about 1% of developmental delay and intellectual disabilities. It is inherited from parent with balanced translocation or appears as a new mutation "Denovo". Offsprings of balanced translocation's parents usually display 46 chromosomes including the derivative chromosome and usually partially trisomic and partially monosomic as well. Partial trisomy 8 is responsible for most of the phenotypic features in our case report.

Keywords: Next-generation sequencing (NGS**),** Copy number variance (CNV), Chromosomal microarray (CMA) analysis.

INTRODUCTION

Neonatal unbalanced translocation is a rare diagnosis with a frequency of 0.03% [1]. Unbalanced translocation is responsible for 1% of cases of developmental delay and intellectual disabilities [2]. Among 82% of cases of unbalanced translocation, the derivative chromosome is inherited from a parent with balanced translocation who are phenotypically and functionally ideal [3]. Occasionally, New reciprocal translocation mutation "De-Novo" may develop at gametogenesis or just after fertilization during the early division phases of embryonic development [4]. Progeny of balanced translocation's parent usually display 46 chromosomes including the derivative chromosome, so he/she is partially trisomic and partially monosomic for the translocated chromosome [5]. Patients harbor unbalanced translocation usually display abnormal phenotype with variable severity depending on the dosage effect of the affected genes in translocated chromosome. Clinical presentation ranges from severe insult with miscarriage or intrauterine fetal death or moderate effect with multiple congenital malformation, growth, and developmental disorders and/or characteristic fascial features [6].

THE CASE

A male neonate is born to 29 years old, gravida 4 para 3 plus zero, consanguineous couple at 34 weeks of gestation age, via vaginal delivery with cord around the neck. No fetal scan anomalies or antenatal genetic test performed before delivery. Mother is medically free, and the rest of siblings are alive and well. The neonate infant is vigorous at birth, not required positive pressure ventilation (PPV), with Apgar score of 7 and 8 at 1 and 5 minutes respectively, but soon after developed respiratory distress and spectrum of dysmorphisms observed.

On Physical Examination: Birth weight, head circumference and length are 1500grams, 39cm and 42 cm respectively. The neonate infant looks dysmorphic, prominent forehead, broad nasal bridge, cleft lip, clenched fist with overlapping fingers, deep palmer, planter creases and bilateral cryptorchidism.

Neurologically, looks conscious, large head, wide open anterior fontanelle 6*7cm weak cry, hypotonic, with intact neonatal reflexes. Cardiovascular evaluation revealed normal heart sounds, pansystolic murmur-grade 4/6. Respiratory status: respiratory rate 50 breath per minute, Spo2 was 80% on 2L nasal cannula,

intercostal retraction with diminished bilateral air entry, harsh vesicular sounds. Abdomen was soft, not distended with no palpable organomegaly, normal male genitalia with bilateral empty scrotal sac.

Laboratory Work Up and Imaging:

Full blood count, Electrolytes, kidney and liver panels, CRP all within normal range and blood cultures revealed no growth.

Chest x-ray; showed cardiomegaly with abnormal cardiac configuration (Figure 3). **X ray knee:** showed absent patella (Figure 4).

Pelvi-Abdominal Ultrasound: Normal.

CT brain; was performed that showed, marked dilated supratentorial ventricular system (lateral and third ventricles), with wide separation of the skull sutures, accordingly non-communicating hydrocephalus was suggested. The appearance of widely spaced parallel frontal horns of lateral ventricle suggested agenesis of corpus callosum was also detected on initial CT and order for MRI was issued (Figure 5).

ECHO: Showed, D-TGA, small ASD with left to right shunt, sub-pulmonary VSD with left to right shunt, mild pulmonary stenosis, normal left ventricle function, no pericardial effusion.

Karyotype: Male chromosome complements without numerical or structural chromosomal anomalies (Figure 6). However, as structural chromosomal anomalies below the level of resolution of a light microscope can't be excluded by this study, further evaluation with an array **CGH (comparative genetic hybridization) analysis** to detect submicroscopic chromosomal losses and gains was recommended.

Next-Generation Sequencing (NGS) table 1:

Variant Interpretation: arr[GRCh37] 1q44(244063053_249212725)x1, arr[GRCh37] 8q24.21q24.3(128146073_146292681)x3 . By NGS-based on copy number variance (CNV) analysis, a terminal pathogenic CNV (one copy loss) of approximately 5.1 Mb within the 1q44 chromosomal region including 88 genes and a terminal pathogenic CNV (one copy gain) of approximately 18.7 Mb within the 8q24.21q24.3 chromosomal region, including 199 genes were identified (gene list is attached table 1). These findings are compatible with an unbalanced translocation between chromosomes 1 and 8, with breakpoints in cytobands 1q44 and 8q24.21. An inherited origin from a carrier balanced chromosomal translocation in one of the parents is possible. Chromosomal microarray (CMA) analysis: performed as internal control, confirmed the NGS finding.

Hospital Course:

+ The neonate infant kept in neonatal intensive care unit (NICU) as oxygen dependent.
+ Has been kept on full nasogastric tube feeding due poor sucking coordination
+Developed multiple hospital acquired infection which treated by intravenous antibiotics
+Ventriculoperitoneal (VP)shunt performed as the result of severe hydrocephalus
+A decision of withdrawing of assisted ventilation was taken when the higher cardiac center confirmed the neonate infant is not candidate for surgical intervention.
+ At 18 months of age, the infant demised due to respiratory failure.

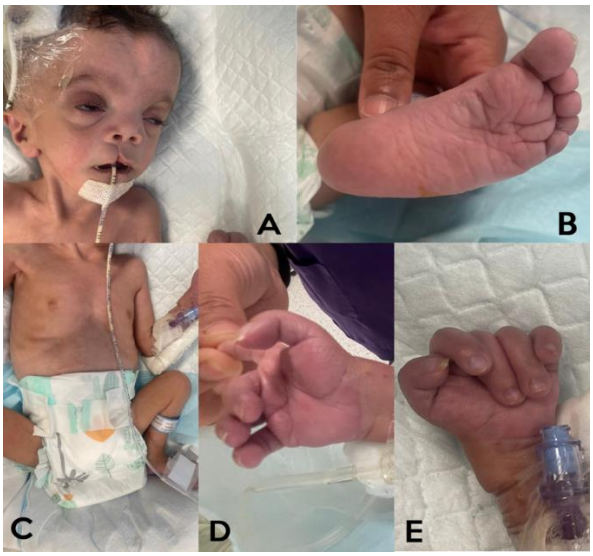

Figure 1: A: Broad nasal bridge, cleft lip, macrocephaly. B: Deep creases in the soles of the feet. C: Elongated narrow chest. D: Deep creases in the soles of the palms of the hand. E: clenched fist with overlapping fingers

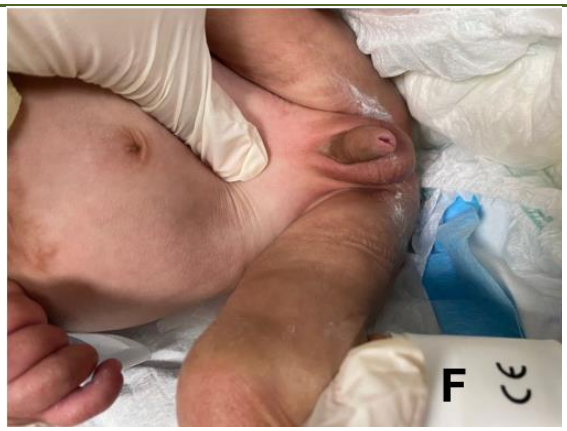

Figure 2:

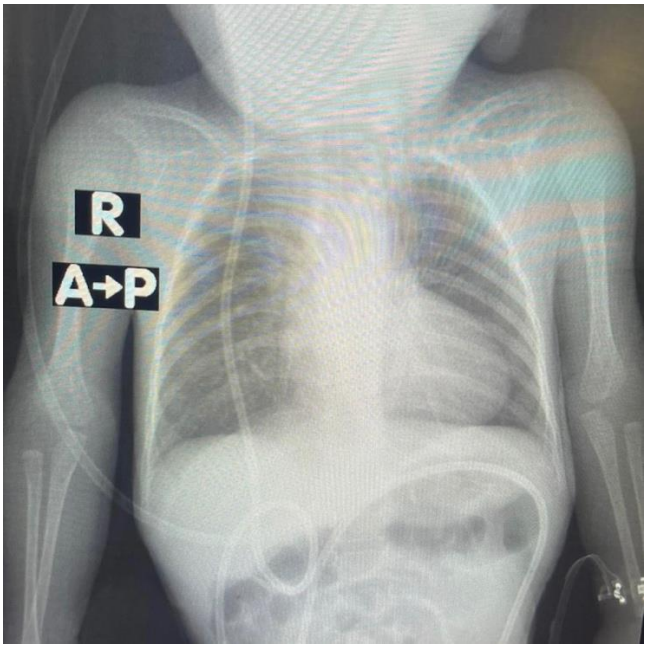

Figure 3: Chest x ray showed cardiomegaly with abnormal cardiac configuration

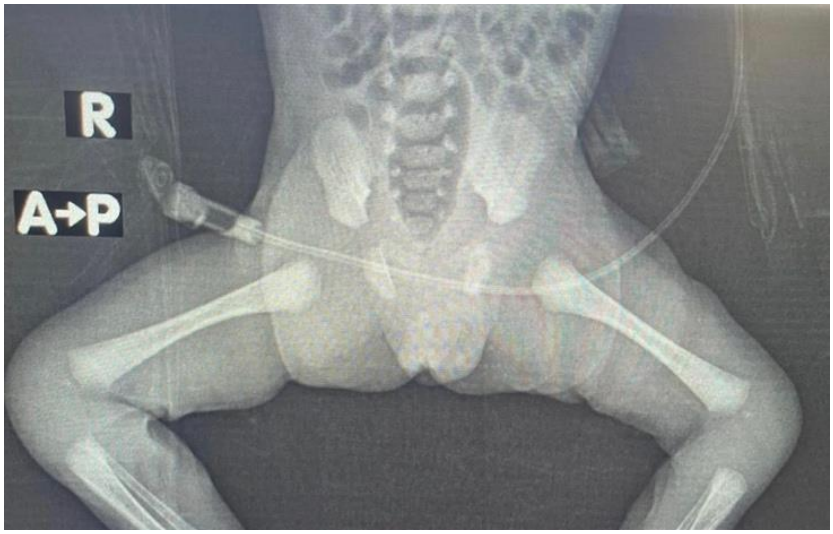

Figure 4: X ray knee showed absent patella

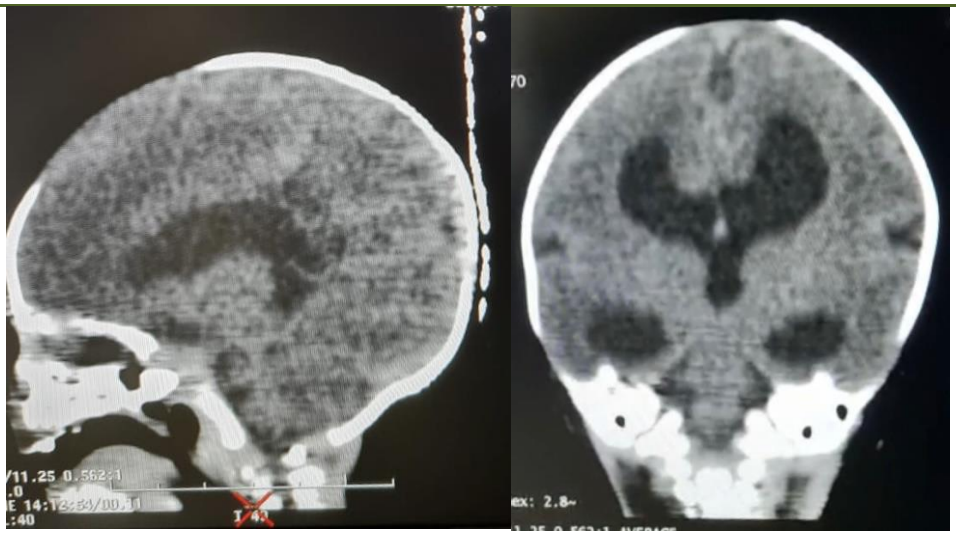

Figure 5: CT brain before external shunt operation, markedly dilated supra tentorial ventricular system (both lateral and third ventricles) with large head feature suggestive non communicating obstructive hydrocephalus. Widening of the lateral ventricles indicated corpus callosum agenesis

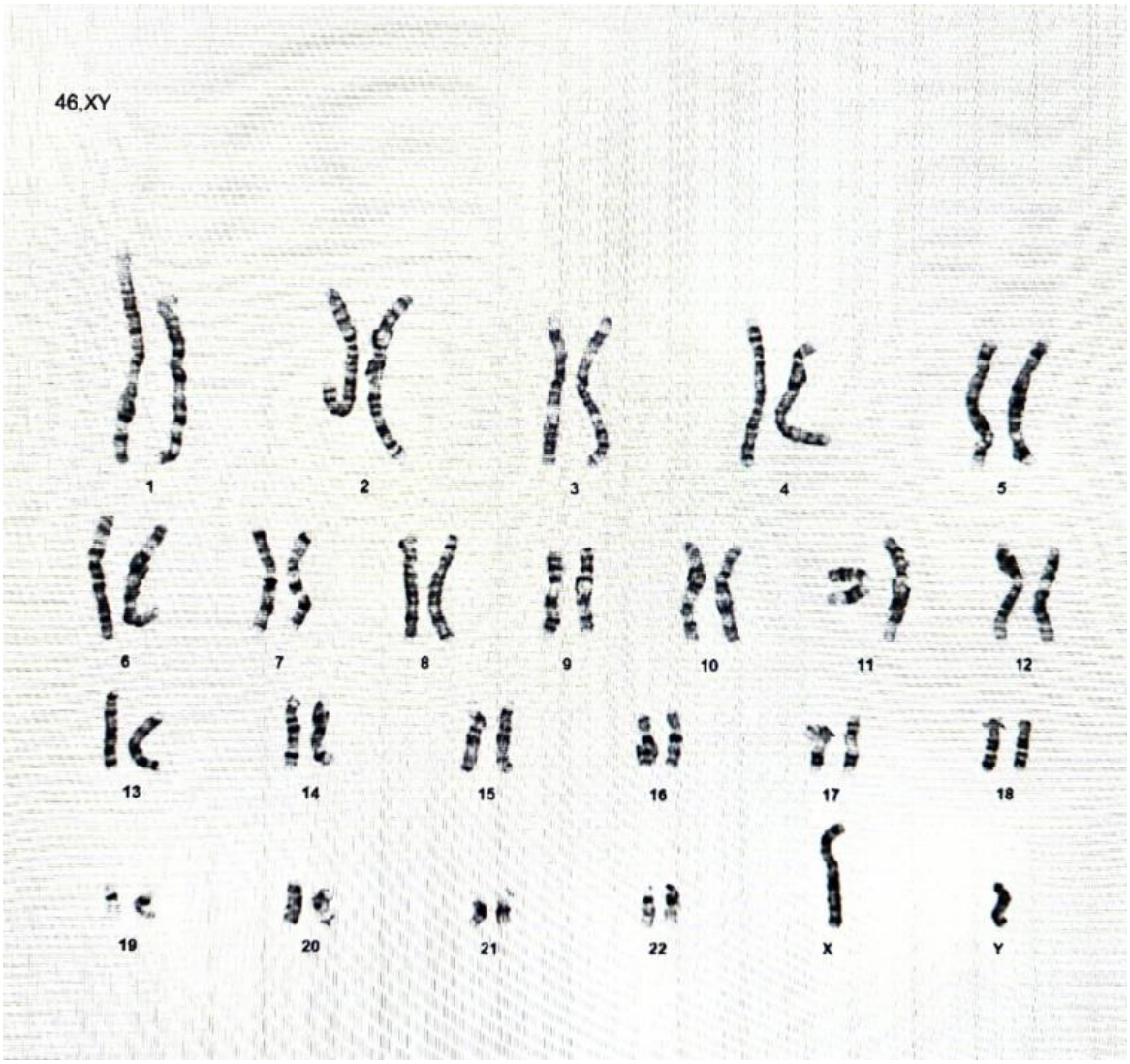

Figure 6: Karyotyping was performed that revealed a male chromosome complement without numerical or structural chromosomal anomalies

Table 1: NGS analysis

MAIN FINDINGS

COPY NUMBER VARIATIONS

CNV DESCRIPTION*	SIZE (KB)	GENE COUNT**	INTERPRETATION***	RELATED DISORDER
arr[GRCh37] 8q24.21q24.3(128146073_146292681)x3	**18747**	**199**	**Pathogenic**	**Distal trisomy 8q**
arr[GRCh37] 1q44(244063053_249212725)x1	**5150**	**88**	**Pathogenic**	**Distal monosomy 1q (ORPHA:36367).**

* according to ISCN 2020; ** genes are listed below; *** according to ACMG 2020, modified

GENES INCLUDED IN THE DETECTED CNVs:

CNV DESCRIPTION*	RefSeq GENES
arr[GRCh37] 8q24.21q24.3(128146073_146292681)x3	CASC19, CCAT1, CASC21, CASC8, CCAT2, POU5F1B, CASC11, MYC, MIR1204, TMEM75, PVT1, MIR1205, MIR1206, MIR1207, MIR1208, LINC00824, LINC00976, LINC00977, MIR3686, CCDC26, GSDMC, CYRIB, MIR5194, ASAP1-IT2, ASAP1, ASAP1-IT1, ADCY8, EFR3A, OC90, HHLA1, KCNQ3, HPYR1, LRRC6, TMEM71, PHF20L1, TG, MIR7848, PTCSC1, SLA, CCN4, NDRG1, ST3GAL1, LOC105375773, LOC101927798, LOC101927822, ZFAT, ZFAT-AS1, MIR30B, MIR30D, NCRNA00250, LOC101927845, LINC01591, KHDRBS3, LINC02055, LOC101927915, LOC401478, FAM135B, COL22A1, KCNK9, TRAPPC9, PEG13, CHRAC1, AGO2, ERICD, MIR151A, PTK2, DENND3, LOC105375787, SLC45A4, LINC01300, GPR20, PTP4A3, MROH5, MIR1302-7, MIR4472-1, LINC00051, TSNARE1, ADGRB1, ARC, LOC101928087, JRK, PSCA, LY6K, LNCOC1, THEM6, SLURP1, LYPD2, SLURP2, LYNX1-SLURP2, LYNX1, LY6D, GML, CYP11B1, CYP11B2, CDC42P3, LY6E-DT, LY6E, C8orf31, LY6L, LY6H, GPIHBP1, ZFP41, GLI4, MINCR, ZNF696, TOP1MT, RHPN1-AS1, RHPN1, MAFA-AS1, MAFA, ZC3H3, SNORD149, LOC100310756, GSDMD, MROH6, NAPRT, EEF1D, TIGD5, PYCR3, GFUS, ZNF623, ZNF707, LINC02878, CCDC166, LOC101928160, MAPK15, FAM83H, MIR4664, LOC105375800, IQANK1, SCRIB, MIR937, PUF60, NRBP2, MIR6845, EPPK1, MIR661, PLEC, PARP10, GRINA, SPATC1, SMPD5, OPLAH, MIR6846, EXOSC4, MIR6847, GPAA1, CYC1, SHARPIN, MAF1, WDR97, HGH1, MROH1, MIR7112, SCX, BOP1, HSF1, MIR6848, DGAT1, SCRT1, TMEM249, FBXL6, SLC52A2, LOC101928902, ADCK5, MIR939, MIR6849, CPSF1, SLC39A4, VPS28, MIR6893, TONSL, TONSL-AS1, CYHR1, MIR10400, KIFC2, FOXH1, PPP1R16A, GPT, MFSD3, RECQL4, LRRC14, LRRC24, C8orf82, ARHGAP39, ZNF251, ZNF34, RPL8, MIR6850, ZNF517, LOC100130027, ZNF7, COMMD5, ZNF250, ZNF16, ZNF252P, TMED10P1, ZNF252P-AS1, C8orf33
arr[GRCh37] 1q44(244063053_249212725)x1	LINC02774, **ZBTB18**, C1orf100, ADSS2, CATSPERE, DESI2, COX20, SNORA100, HNRNPU, LOC101928068, EFCAB2, KIF26B-AS1, KIF26B, SMYD3, LINC01743, TFB2M, CNST, SCCPDH, LINC01341, AHCTF1, ZNF695, ZNF670-ZNF695, ZNF670, ZNF669, FLJ39095, C1orf229, ZNF124, MIR3916, VN1R5, ZNF496, LOC107985115, NLRP3, OR2B11, OR2W5P, GCSAML-AS1, OR2C3, GCSAML, OR2G2, OR2G3, OR13G1, OR6F1, OR14A2, OR14K1, OR1C1, OR14A16, OR11L1, TRIM58, OR2W3, OR2T8, OR2AJ1, OR2L8, OR2AK2, OR2L1P, OR2L5, OR2L13, OR2L2, OR2L3, OR2M1P, OR2M5, OR2M2, OR2M3, OR2M4, OR2T33, OR2T12, OR2M7, OR14C36, OR2T4, OR2T6, OR2T1, OR2T7, OR2T2, OR2T3, OR2T5, OR2G6, OR2T29, OR2T34, OR2T10, OR2T11, OR2T35, OR2T27, OR14I1, LYPD9P, LYPD8, SH3BP5L, MIR3124, ZNF672, ZNF692, PGBD2

* according to ISCN 2020

DISCUSSION

Reciprocal translocation are structural chromosomal abnormalities caused by exchange of parts between non-homologous chromosomes [7]. According to completeness of genetic materials, reciprocal translocation can be balanced or unbalanced. Unbalanced translocation carriers are usually phenotypically abnormal because of deleted or duplicated genes [5]. However, the deleterious effect is widely variable according to dosage of the genes involved on the translocated chromosome [6]. Our reported case diagnosed by using next generation sequencing (NGS)-based copy number variation (CNV) technique and confirmed by chromosomal microarray analysis, is unbalanced translocation between chromosomes 1 and 8, with breakpoints in cytobands 1q44 and 8q24.21**.** Terminal one copy loss on the long arm of chromosome 1 including 88 genes (partial chromosome 1 monosomy) and terminal one copy gain on the long arm of chromosome 8 including 199 genes (partial chromosome 8 trisomy) were documented.

Two scenarios are proposed for the mechanism of unbalanced translocation in our patient, either to be inherited from balanced carrier parent or to develop as deNovo mutation during early embryonic life [3].

Balanced reciprocal translocation is common in human with frequency of 1/500(8). Carrier parents of balanced reciprocal translocation are phenotypically normal but have a significant risk of having siblings with unbalanced translocation in about 19.2% of them [5] . At meiosis, the derivative chromosomes and their homologous chromosomes form a quadrivalent figure (adjacent 1 and 2:2, 3:1, 4:0) segregation models that yield mostly unbalanced gametes [9]. Progeny of balanced translocation carriers are usually 46 chromosomes with partial trisomy and partial monosomy for the translocated chromosome [5]. This scenario is highly accepted, as most cases of unbalanced translocation are inherited (82%) plus the positive consanguinity between the parents. However, new mutation development during early embryonic phases can't be excluded as the cause of unbalanced translocation and supported by the absence of any history

of abortion or still births and the previous production of three phenotypically and functionally healthy siblings. FISH technique for the index case [10] plus karyotyping of the parents and other siblings are needed to solve this issue but unfortunately refused by the family and represents limitation to our case report.

In our reported case, partial trisomy of chromosome 8 appeared to be responsible for most of the presented phenotypic abnormalities including, congenital heart defect, characteristic fascial features, congenital hydrocephalus, absent corpus callosum, deep palmer and planter creases, elongated narrow chest, global developmental delay, bilateral cryptorchidism, and failure to thrive. This constellation of clinical manifestations is quite like trisomy 8 mosaicism syndrome, also known as Warkany syndrome which is a rare chromosomal disorder characterized by the presence of an extra copy of chromosome 8 in some cells of the body [11]. Similarly, partial trisomy due to unbalance translocation between chromosome 8 and 9 has been reported by Kayhan and colleagues, also produced phenotypic findings like Warkany syndrome [5]. Recent case report by Netto and his team presenting a twelve-year-old girl with full clinical and karyotyping diagnosis of trisomy 8 (Warkany syndrome), who is finally diagnosed as partial trisomy 8 associated with non-balanced translocation between chromosome 8 and 6 when she developed type 1 diabetes mellitus and underwent molecular study at the age of 12 years [10]. No case has been reported in Saudi Arbia.

Distal monosomy of chromosome 1 (1q43-q44 deletion syndrome) is characterized by moderate to severely impaired intellectual development, limited or no speech, and characteristic facial features, including round face, prominent forehead, flat nasal bridge, hypertelorism, epicanthal folds, and low-set ears. Other presentations may include hypotonia, poor growth, microcephaly, agenesis of the corpus callosum, and seizures. The phenotype is variable, and not all features are observed in all patients, which may be explained in some cases by incomplete penetrance or variable expressivity [12].

Common findings between partial trisomy 8 and distal monosomy 1 include distorted corpus callosum, broad nasal bridge, cardiac anomalies plus the deleterious effect on growth, development and behavior. Predominant of chromosome 8 trisomy clinical presentations among cases with partial trisomy for chromosome 8 and monosomy of other chromosome may be attributed to the large number of critical genes involved as it represents between 4.5 and 5 percent of the total DNA in cells. In our case 199 genes have been duplicated and have significant effect on the clinical presentation. Several hereditary and acquired disorders have been described in association with chromosome 8 trisomy including 8p11 myeloproliferative syndrome, recombinant 8 syndrome, inversion duplication 8p syndrome and increased risk of myeloid leukemia [13].

Despite the cornerstone role of karyotyping in diagnosis of chromosomal disorders, it still has limitation. Structural chromosomal anomalies below the level of resolution of a light microscope is difficult to be excluded by this modality. In our case karyotyping results revealed a male chromosome complement without numerical or structural chromosomal anomalies. unbalanced translocation between chromosomes 1 and 8, with breakpoints in cytobands 1q44 and 8q24.21 can be detected only by next generation sequencing -based CNV (copy number variance) analysis. Similar scenario is experienced by other researchers that refined and reviewed previous diagnosis after the advancement of molecular studies including FISH technique, microarray, multiplex ligation -dependent probe amplification among others [10]. It is important to note that accurate diagnosis is crucial for appropriate management and genetic counseling of the family.

To our knowledge, and after searching in common electronic research engine, this case has not been reported previously. Further research is needed to improve our understanding of unbalanced translocation associated with partial trisomy 8/ monosomy 1 including the identification of genes and molecular pathways involved. Collaboration among researchers, clinicians, and families is crucial to facilitate the collection of more cases and the establishment of genotype-phenotype correlations. Long-term studies with larger sample sizes are necessary to determine the prognosis and evaluate the effectiveness of various management approaches.

CONCLUSION

Unbalanced translocation is rarely diagnosed perinatally but should be suspected in dysmorphic infant with multiple congenital malformations. Karyotyping, despite being the gold standard of diagnosis in chromosomal abnormalities, but still has limitations. Further techniques including next generation sequencing (NGS)-based CNV, and microarray are recommended in phenotypically suspected cases especially in the setting of normal karyotyping. t(1;8) unbalanced translocation is characterized by constellation of findings like trisomy 8 mosaic, Warkany syndrome.

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