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t(6;8)(q21;q24.1),+21 in newborn with Down Syndrome having cardiac, pulmonary and thyroid anomalies- A first case report

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Abstract:

Trisomy 21 characterizing Down syndrome has often been reported with underlying translocation involving additional chromosome 21, especially Robertsonian translocations with D and G group chromosomes or mosaicism. There are very few reports on additional chromosomal abnormalities like translocation between chromosomes other that chromosome 21 along with trisomy 21. To the best of our knowledge, we report the first case of translocation between chromosomes 6 and 8 t(6;8)(q21;q24.1) along with trisomy 21. Further the report highlights the association of pulmonary and thyroid anomalies in Down syndrome in addition to cardiac abnormalities which are well known. The report also reiterates the importance of karyotyping in Down syndrome as compared to targeted techniques like Fluorescence in situ hybridization (FISH). Even in the present case, FISH technique only reflected on the status of numerical change (trisomy 21) and not underlying structural chromosomal abnormalities.

Key words: additional translocation, chromosome, trisomy, ASD, PDA, PAH, hypothyroidism

Introduction

Down syndrome is a well-established and well-characterized syndrome with characteristic phenotypic 'Mongoloid features' including flat nasal bridge, epicanthal folds, protruding tongue, sandal gap between toes, Simian crease etc. [1,2]. The association of many clinical conditions like cardiovascular abnormalities, gastrointestinal problems, hypertension, leukemias and Alzheimer's disease is also well-established [3].

The chromosomal abnormality well-established as the hallmark of the disease is trisomy 21 (three copies of chromosome 21). Free trisomy 21 is the most prevalent cytogenetic anomaly observed in Down syndrome (>90-95%). The other cytogenetic anomalies observed include mosaicism, translocation (mostly Robertsonian translocation involving D and G group chromosomes) or duplication. However there is very limited literature available on the additional chromosomal abnormalities present in addition to trisomy 21 [1,3,4]. Cytogenetic analysis or karyotyping is recommended investigation to rule out these underlying chromosomal changes especially involving the chromosomes other than chromosome 21. Many clinicians opt for Fluorescence *in situ* hybridization (FISH) for analysis of trisomy 21 using specific locus-specific probes for chromosome 21. Although FISH analysis provides rapid and reliable results on numerical anomalies of chromosome 21, it does not reflect on underlying structural chromosomal changes, if any.

To the best of our knowledge, we present the first case of translocation between chromosomes 6 and 8 [t(6;8)(q21;q24.1)] along with trisomy 21 in a child with ASD, PDA with mild PAH and hypothyroidism. The

case highlights the importance of karyotyping in newborns with similar abnormalities and need to report these variants for further clinico-genomic correlation.

Case Report

A male child born to a 39 years old G4L1A2 mother at 38 weeks of gestation after 8 years of marriage appeared to have Mongoloid features. The father's age at the time of his birth was 44 years and had an elder male sibling [9 years old] who was normal. The findings of various investigations at different phases are detailed as follows:

Antenatal period- The mother had regular antenatal checkups and two doses of Td vaccine was administered along with regular folic acid, calcium and iron. Triple test revealed a risk factor for Trisomy 21 of 1:1, trisomy 18 of 1:266 and neural tube defect <1:10000. Repeated ultrasounds done during pregnancy were normal except ultrasound at 26 weeks which showed mild polyhydramnios of 21. Fetal echocardiography was done which showed small echogenic focus in left ventricle.

Delivery- The male baby cried immediately after delivery. The Apgar score was 8/10, 9/10, birth weight was 3.1 kg saturation was 88%. On physical examination, the baby revealed low set ears, flat nasal bridge, large protruding tongue, sandal gap in both feet and simian crease. The phenotype as well as suspected congenital heart disease raised the suspicion of Down syndrome. Considering the same, a venous blood sample in sodium heparin was referred for cytogenetic analysis (karyotyping) on third day of life to Department of Cytogenetics, Clinical Reference Lab, Agilus Diagnostics Ltd., Gurgaon.

Cytogenetic analysis was performed using standard protocols wherein chromosome preparations were obtained from 72 hours peripheral blood lymphocyte cultures [5]. These chromosomal preparations were then subjected to GTG-banding after which karyotyping was done at 550-band resolution according to the standard ISCN nomenclature [6] using Zeiss Axioscope microscope equipped with *ikaros* software [Metasystems]. The karyotype observed was 47,XY,t(6;8)(q21;q24.1),+21 in all the 20 cells analyzed. It was recommended to do parental karyotyping but the parents denied the same citing socio-religious reasons due to which familial nature of the chromosomal finding could not be established.

FISH analysis was also performed on interphase nuclei and metaphases using standard protocols and Spectrum Orange labelled locus-specific DNA probe for chromosome 21 & Sepctrum Green locus-specific DNA probe for chromosome 13 [Abbott Molecular]. The analysis was done using Zeiss fluorescence microscope with appropriate filters and *isis* software [Metasystems] in accordance with latest ISCN guidelines [5,6]. The cut off of this probe was 2% in normal individuals. All 200 cells revealed three signals (copies) for chromosome 21 i.e. trisomy 21 and 2 signals for chromosome 13.

Postnatal period- The baby was transferred to nursery and kept under oxygen for desaturation. There was no murmur, no signs of respiratory distress and no features of congestive cardiac failure. Septic screening was negative. Echocardiography revealed atrial septal defect (ASD) and Patent ductus arteriosus (PDA) with severe pulmonary arterial hypertension (PAH). The baby was started on furosemide and spironolactone. The echocardiography repeated after 3 days showed no improvement so the baby was started on Sildenafil. The repeat echocardiography after 7 days revealed ASD and PDA with moderate PAH. The baby maintained saturation without oxygen. The thyroid function test was also done at 3 days, 10 days and 17 days which showed borderline TSH but at 24 days showed high TSH so was started on Thyroxine 15 ugm/kg/day revealing hypothyroidism.

The baby was administered lasilactone, sildenafil and thyroxine and the final diagnosis of Down syndrome with ASD, PDA with moderate PAH and hypothyroidism was established.

Discussion

Down syndrome is characterized with presence of an extra copy of chromosome 21 (trisomy 21) usually as free *de novo* trisomy with parents having normal karyotype. In 5-10% cases, the extra chromosome 21 originates due to errors in paternal meiosis or non-disjunction of chromosomes during a post-zygotic mitosis in early development. Around 4-5% cases involve Robertsonian translocation where chromosome 21 is translocated onto any other acrocentric chromosome. These translocations may be *de novo* or inherited from phenotypically normal parents [3,4]. Around 95% of these *de novo* cases originate during maternal meiosis. About 3-5% of Down syndrome cases may reveal mosaicism that usually arises as a result of non-disjunction in postzygotic stage. Another 1-2% cases reveal autosomal translocation with chromosome 21 most of which are familial [7,8].

Less than1% cases have been reported with additional chromosomal abnormalities along with Down syndrome. The present case falls under the same category. However, to the best of our knowledge, none of the reported cases included translocation of either chromosome 6 or 8. The reported translocations involved chromosome 1,2 ,15, 18 etc. [4,7,8,9]. The reported translocations were either familial or *de novo*. In the present case, the nature of the translocation i.e. familial or not could not be established as the parents denied for karyotyping citing socio-economic-religious reasons.

Moreover the increasing prevalence of Down syndrome with increase in maternal age (>35 years) is also well reported though the underlying mechanism of this is still not very well understood. Some studies propose increasing rate of meiotic errors due to ageing process of ovary as a possible reason with long arrest of oocytes in prophase I of meiosis as a possible mechanism [1,8,10]. In the present case also the maternal age was 39 years which probably increased the risk of prevalence of having a child with Down syndrome.

Apart from characteristic phenotypic features, Down syndrome is accompanied usually with caries clinical presentations e.g. cardiovascular, neurological, respiratory and gastrointestinal abnormalities along with an increased risk of developing leukemias [1,8,9,10,11]. In the present case there were rare clinical findings of PDA with moderate PAH and hypothyroidism along with the common finding of ASD. It is not clear whether these findings are due to trisomy 21 or due to the additional translocation t(6;8)(q21;q24.1).

It is challenging to establish the same in view of the limited information available. Both the loci involved in the additional translocation 6q21 and 8q24.1 harbor the tumor suppressor genes known to play a role in leukemia [12, 13]. Further a gene for autism has also been reported on 6q21 [13,14]. However it is too early to comment on the same at present as neither autism nor any hematological malignancy was diagnosed in the present case. Further follow-up and evaluations would be necessary to confirm any of these preliminary hypothesis.

Nevertheless, the present case highlights the importance of cytogenetic analysis (karyotyping) in a newborn with any phenotypic or clinical findings in comparison to use of other targeted genomic techniques that would only establish the numerical abnormality trisomy 21 and miss any balanced rearrangements involving chromosome 21 or not. Even in the present case, FISH analysis revealed trisomy 21 only while cytogenetic analysis (karyotyping) revealed a balanced translocation between chromosomes 6 and 8. Further the case reiterates the importance of extensive clinical examination and clinico-pathological correlation which like similar case could bring forth some rare clinical findings even in well-known diseases or syndromes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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FIGURES WITH LEGENDS:

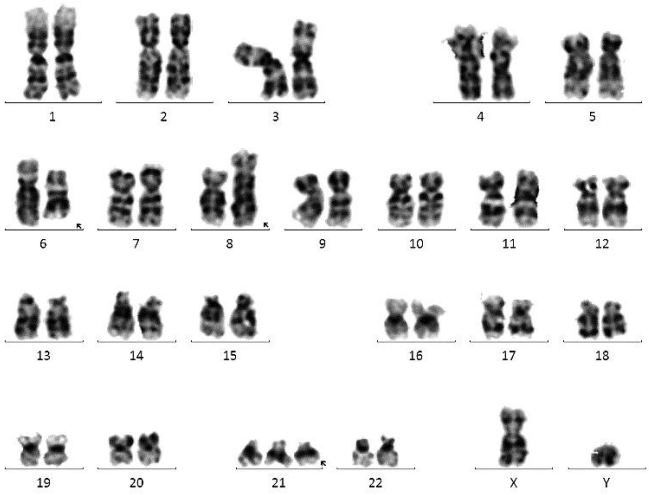

Figure 1. G-banded karyotype of the child revealing 47,XY,t(6;8)(q21;q24.1),+21

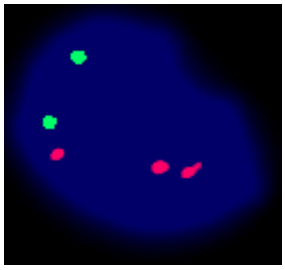

Figure 2. FISH image revealing three orange signals for chromosome 21 and two signals for chromosome 13 using probes specific for chromosome 21 & 13