Case report

1q21.1 Microdeletion and Microduplication in a Patient with Coarctation of Aorta, Seizure and Dismorphic Features

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Abstract:

1q21.1 duplication is a rare copy number variant accompanied with multiple congenital malformations, including developmental delay, autism spectrum disorder, dysmorphic features and congenital heart anomalies. The present study described an Iranian 6-month-old infant with coarctation of aorta, seizure and dismorphic features. The parents and the sibling of the patient, were physically and psychologically normal. Whole genome oligo array CGH revealed a deletion 314.2 Kb on 1q21.1q21.1 and duplication of 1.25 Mb on 1q21.1q21.2. Up to date, few evidence are available for the cardiac abnormalities of the patients with micro deletion and microduplication on 1q21 have also coarctation of aorta.

Key words: 1q21.1 Deletion, 1q21.1 Duplication, Congenital Heart Disease, Coarctation Of Aorta

Introduction:

Congenital heart diseases (CHD) are considered as the most common prenataly diagnosed anomalies, with prevalence of 6 per 1000 live births. This includes a heterogeneous group of defects including cardiac malformations, cardiomyopathies, and cardiac arrhythmias with genetic and/or environmental causes (1). In the most CHD cases, the underlying causes are unknown; however, technical advances in genetics leads to the identification of a greater proportion of chromosomal microdeletions, and single gene mutations (2). Genes that are known to play a role in normal heart function are increasingly being investigated for mutations that may be associated with alterations in heart development. Recently, by the new technologies such as comparative genomic hybridization (CGH), the routine detection of submicroscopic deletions and duplications has been facilitated (3).

1q21.1 chromosome region contains extensive and complex low-copy repeats. Copy number variants (CNVs) in this region are associated with neurodevelopmental delay, neuropsychiatric abnormalities, dysmorphic features and a variety of congenital malformations (3). Various types of cardiac anatomic anomalies have been found in syndromic patients with 1q21.1

deletion (4), including left-sided obstructions, conotruncal and septal defects (5). On the other hand, 1q21.1 duplication (OMIM no. 612475) leads to mental impairment, autism, macrocephaly and dysmorphic features (4). In addition, a 1q21.1 deletion, beside the 1q21.1 duplication, have been found in patients with apparently non-syndromic CHD. An association between Tetralogy of Fallot (TOF) and 1q21.1 duplication or variants in GJA5 gene mapping in 1q21.1 were documented recently (6). Recurrent reciprocal 1q21.1 deletions and duplications have been associated with variable phenotypes. Phenotypic features in combination with 1q21.1 microdeletions are neurodevelopmental delay, craniofacial dysmorphism and congenital anomalies. Dysmorphic features are common findings; they may include microcephaly (almost 50% of patients), frontal bossing, deep-set eyes, epicanthal folds, large nasal bridge, long philtrum and highly arched palate. Congenital Heart Disease (CHD), eye abnormalities (microphthalmia, chorioretinal and iris colobomas, strabism, various type of cataracts), skeletal and genitourinary malformations are known as the congenital anomalies related to the deletion; moreover, in some cases, seizure is reported (15%) (3, 5, 7, 8). Clearly, high variability of the 1q21.1 microdeletion phenotype makes it impossible to define a clinically recognizable syndrome. Individuals with 1q21.1 copy number variations (CNVs) may also have a normal phenotype. The 1q21.1 critical region spans approximately 1.35 Mb (from 145 to 146.35 Mb) (8) ,including at least 12 genes, which PRKAB2, FMO5, CHD1L, BCL9, ACP6, GJA5, GJA8, GPR89B Deletions and duplications can be inherited in an autosomal dominant manner or de novo.

The present case report presented an Iranian male patient with a micro deletion of 314.2 Kb on 1q21. 1q21.1 and microduplication of 1.25 Mb on 1q21.1. The patient had a normal karyotype and presented with clinical phenotypes comprising coarctation of aorta, seizure and dysmorphic feature.

Case presentation:

A 6-month-old Iranian male infant was admitted in our institution due to a history of heart murmur, with unrelated parents and no family history of genetic diseases. Facial abnormalities of the patient were microcephaly, frontal bossing, deep-set eyes, low set ear, epicanthal folds, large nasal bridge, long philtrum and highly arched palate (figure 1). There was two episodes of feverless seizures reported at the age of 2 and 4 months, without any familial history.

No birth history of events was detected and all stature indics were within the normal ranges. Our physical examinations revealed a height of 66 cm, weight of 6800 g and head circumference of 40 cm, a Mongolian spot, normal limbs, without other skin lesion and neurodevelopmental delay. The electrocardiogram (figure 2) showed a left bundle branch block with superior axis. Transthoracic echocardiogram showed a discrete coarctation of aorta with gradient of 55 mmHg, small ASD secundum, and tricuspid Aortic valve without significant Aortic stenosis.

Whole genome oligo array CGH was performed using sureprint G3 ISCA V2 8X60K whole genome oligo array version 2, analyzed with aglient cytogenomic software v4. The array consists of 60000 spots with overall median probe spacing of 60 KB and higher in close to 500 targeted disease regions. The sample was hybridized twice against male samples. In both hybridizations, loss of 314.2 Kb on 1q21.1q21.1 from nucleotide 145415190 to 145729384 of uncertain significance. Gain of 1.25 Mb on 1q21.1q21.2 were reported.

Discussion:

To date, a few studies have indicated micro deletion and micro duplication of 1q21 accompanied with coarctation of aorta. The chromosome 1q21.1 locus is a complex region with multiple low-copy repeats that make the region susceptible for recurrent deletions and duplications. Large rare copy number variants (CNVs) at this locus ,as well as microdeletions and micro duplications, found to be associated with genomic disorders (OMIM nos. 612474 and 612475), characterized by neurodevelopmental delay, neuropsychiatric abnormalities, dysmorphic features and a variety of congenital malformations (9, 10). Congenital heart defect is a major feature of 1q21.1 deletion (5), reported to be associated with 1q21.1 duplication (11). The prevalence of CHD was approximately 30%, in a reported series of 1q21.1 deletions (8). The anatomic types were heterogeneous, mainly comprising left-sided obstructions (40%), including aortic coarctation, bicuspid aortic valve and subaortic stenosis, plus septal defects (27%) and conotruncal anomalies (20%) (3). Of note, 1q21.1 duplication was more common in patients with tetralogy of fallot (12).

The genes GJA5 (13), CHD1 L (12) and PRKAB2 (14), located on 1q21.1 locus, were reported to be closely related to CHD. None of them were included in the base sequence of the proban, this implies that there may be other genes, responsible for the occurrence of CHD. In the present study, some genes were not detected in the identified chromosome, including HFE2 A, PEX 14 B, PEX 11 B ,CD 160 , POLR3C , NBPF 10,19,20 , HJA ;on the other hand, some others have been detected, such as GJP, ALPHA-8 , ALPHA-5 ,GJA-8, GJA-5 , ATFB 11 ,ATRST 1. Up to now, only few studies indicated deletion and duplications of the mentioned genes with CHD. According to our findings, it can be deducted that the duplication of these genes caused increased expression of the coded proteins, leading to CHD. HFE2, locating in this locus, encodes hemojuvelin (HJV), a protein involved in the activation of Hepcidin and iron metabolism. HJV found to be expressed in the skeletal muscles, furthermore in the heart and the liver, but at lower levels. A soluble form of HJV circulates in the plasma, as well. Mutations of this gene, were found in hereditary juvenile hemochromatosis (15). In this case, patient had compound heterozygosity for a null mutation, involving the RBM8A gene. Deletion/mutation of RBM8A cause TAR syndrome, characterized by a series of phenotypes, as coarctation of the aorta, left ventricular hypertrophy and sub-endocardial fibrosis (16); however, it has remained elusive whether duplication of this gene results in congenital heart defects or not. To

identify this hypothesis, further clinical and molecular studies are required.

Considering that 1q21.1 duplication may not be well known for clinical cardiologists, the present study facilitates the clinical recognition of 1q21.1 duplication. The results of the genome oligo array CGH, in combination with the detailed phenotype analysis would provide further evidences for the identification of causative genes for CHD, especially the 1q21.1 duplication and deletion. Our study may be useful for the early diagnosis, genetic counseling and effective long-term management of 1q21.1 duplication and deletion.

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Figures:

Figure 1: The patient had facial abnormalities, including microcephaly, frontal bossing, deep-set eyes, epicanthal folds, large nasal bridge, long philtrum and highly arched palate

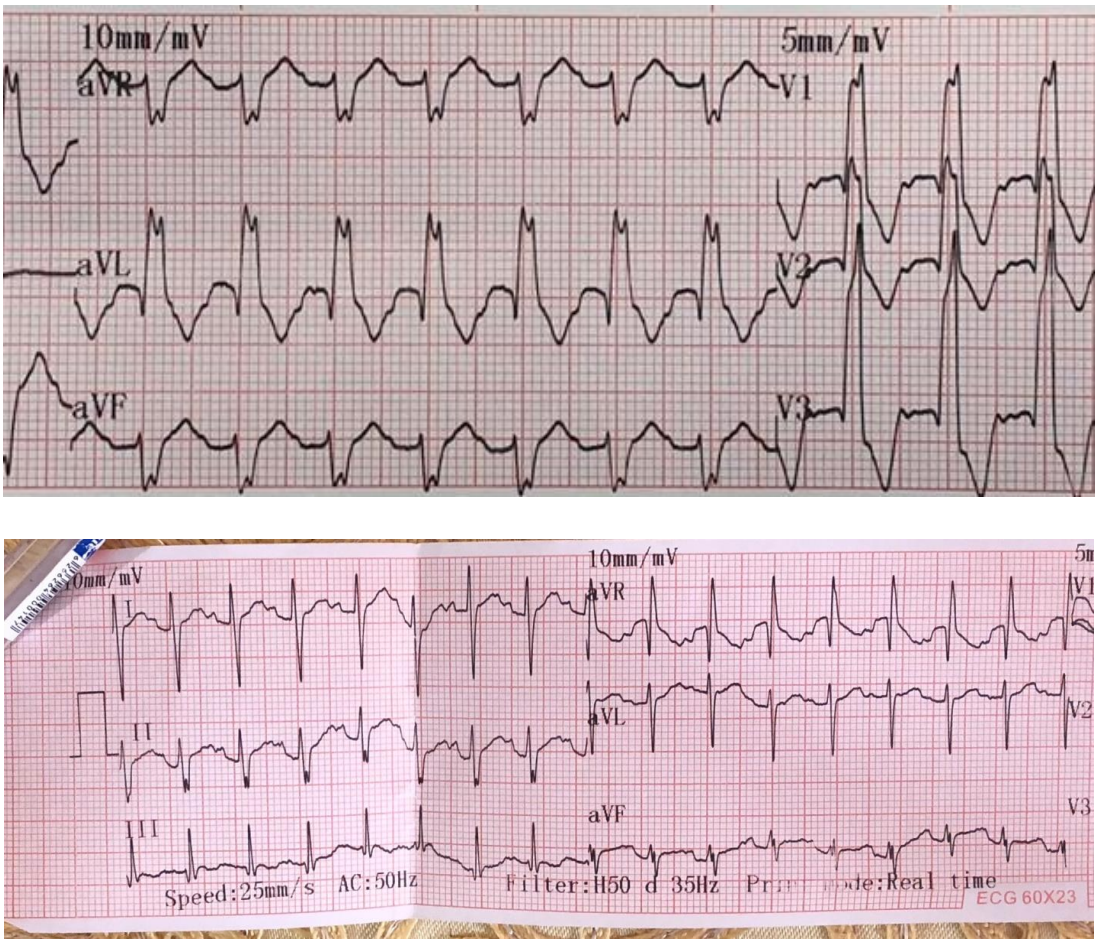

Figure 2: Electrocardiogram shows: left bundle branch block with superior axis.