Congenital heart disease in Down syndrome

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Children with DS are at an increased risk of multiorgan comorbidities. Congenital heart defects occur in over 60% of infants with Down Syndrome (particularly septal defects). The 5-34% of infants develop persistent pulmonary hypertension of the new-born irrespective of a diagnosis of congenital heart disease. This review aims to expose the latest scientific evidence on the molecular and genetic mechanisms that underlie congenital heart disease in Down syndrome.

Down syndrome (DS) or Trisomy 21 is the most common chromosomal abnormality accounting for 8% of all registered cases, with an incidence of 1 in 700 live births. DS is caused by the presence of a third copy of chromosome 21, or part of it. This extra genetic material is responsible for the classical facial characteristics, multiple malformations, intellectual disability (ID), immune and endocrine dysfunction associated with DS like Autoimmune thyroid disease (ATD). ATD is a multifactorial disease in which autoimmunity against thyroid antigens develops against a genetic background facilitated by exposure to environmental factors (1).

DS has a variable phenotype, but there are many common physical manifestations: hypotonia, epicanthic folds, flat nasal bridge, single palmar crease and sandal toe gap (2). Children with DS have an increased risk of congenital anomalies including congenital heart defects, increased risk of hearing loss, Recurrent Respiratory Infections (3). ophthalmological problems, obstructive sleep apnoea as well as hip dysplasia and pes planus (2-5) and obesity. The hormone, leptin, may contribute to the known higher risk of obesity among children and adults with Down syndrome. Leptin is responsible from long term regulation of metabolism and ghrelin functions as an appetite stimulatory signal. (6) and it is also synthesised and secreted in breast milk, especially in colostrum (7).

In Children with DS is known that immune function is abnormal. They have a higher incidence of autoimmune disorder (8). The increased

Key words: Down syndrome (DS), Congenital heart disease (CHD), Atrioventricular septal defects (AVSD), pulmonary hypertension (PH)

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0393-974X (2020)

susceptibility to infections is due to atypical immune function associated with various non-immune related medical and anatomical co-morbidities (4-8). The prevalence of leukaemia is 20 times more frequent in children with DS, and it is still a major cause of mortality in children with DS (9).

The implementation of medical guidelines with preventative health care programmes screening for associated multiorgan involvement continue to help improve life expectancy and quality of life (2). These guidelines have been well established internationally via the Down Syndrome Medical Interest Group (DSMIG) and American Association of Paediatrics (AAP) (10-11).

Cardiac involvement

Congenital heart disease (CHD) is frequently diagnosed in infants born affected by DS, with significant impact on morbidity and mortality. The 54-66% of infants born with DS will have a diagnosis of CHD (12). The AAP's guidelines include cardiology review and echocardiogram in the first 6 weeks of life, however in most centres this occurs within the first few days of life (10, 11). Early surgical correction is necessary to prevent the development of Eisenmenger syndrome and pulmonary hypertension. In unselected populations, septal defects are mostly associated with DS, particularly atrioventricular septal defects (AVSD), followed by ventricular septal defects (VSD), and atrial septal defect (ASD) (Table I).

Patent Ductus Arteriosus and Tetralogy of Fallot are common in children with DS but the rate of conotruncal defects are overlapping compared to the general population (13). CHD in DS is more commonly associated with females particularly AVSD and VSD (14). In children affected by DS and CHD is present the five-year survival rates of 92% compared to 94.2% in children with structurally normal hearts. Mortality is highest if CHD was associated with other extra-cardiac malformations, 93% of deaths occurring in the first year of life. Mortality of children with DS and CHD compared to children with normal chromosomes and CHD was similar (13).

Persistent pulmonary hypertension of a new-born (PPHN) has an incidence of 5-34% in the DS population, in comparison to 0.1% in the general population; pulmonary hypertension (PH) is associated with increased morbidity and mortality (15). Oxidative stress is important in the pathogenesis of PPHN. (16) High mobility group box 1(HMGB1) is a useful marker of oxidative stress (17-21).

Children with uncorrected septal defects will develop shunt of systemic blood to the pulmonary circulation, so there is increased exposure to left to right shunt flow which can cause a sheer stress on the endothelium, induce endothelial dysfunction and, in conclusion, lead to pulmonary arterial hypertension.

Cardiac involvement	Management
- Septal defect AVSD 42% VSD 22% ASD 16% - Pulmonary Hypertension CHD in 45% Respiratory causes in 18%	- Cardiovascular examination with in 24 hours of birth and pulse oximetry - ECG - Ecocardiography as soon as possible (within 6 weeks of age) - If corrective cardiac surgery is required a long cardiological follow-up - Regular cardiological follow-up is necessary for young people and adults to exclude valvular dysfunction

Children with DS and CHD have a greater risk of developing PH than children with CHD, but without DS. Adults with DS, with and without CHD, are at an increased risk of valvular disease. Adults who have previously had a surgical repair for AVSD, have an increased risk of Eisengmenger syndrome and/or left ventricular outflow obstruction with Aortic valve dysfunction, so serial cardiology follow up post corrective surgery is essential (22).

Molecular mechanisms of congenital heart disease

In DS two hypotheses are used for explaining the DS associated CHD:

- Gene dosage amplification hypothesis claims that an increased dosage of genes on human chromosome 21 in DS may increase the level of gene expression (23).
- Gene mutation hypothesis holds that in the trisomy 21 background, certain locus mutations can cause CHD (24).

Genes on chromosome 21

Different genes have been considered as candidate genes for the increased CHD risk in children with DS. DSCAM, located on 21q22.2, is a member of the immunoglobulin superfamily of cell adhesion molecules (Ig-CAMs) and it is important in the nervous system development. Several studies have suggested that, due to the gene dosage multiplier in trisomy 21, the expression of intercellular mucoprotein increases abnormally before endocardial cushion development, so enhanced the adhesion between cells and affected the fusion of endocardial and causing AVSD (25). Collagen VI is expressed in fetal hearts (5-18 weeks of development) and involved in the formation of the original atrioventricular septum.

Also including the middle and lower part of the atrioventricular septal valve and the membrane. Overexpression of type VI collagen (COL6A1, COL6A2) plays a critical role in the pathogenesis of AVSD in DS. It is an interesting phenomenon that AVSD, VSD, PS and TOF could be observed if both DSCAM and COL6A1 were co-expressed, while only DSCAM was copied, just TOF was seen. It indicates that DSCAM and COL6A1 may have a synergistic effect on the overall cardiac defects (26).

Genes on another chromosome

Other genes, not localized on chromosome 21, may play an important role in the development of these cardiac anomalies. The genes CRELD1, CRELD2 and ALK2 seem to increase susceptibility to DS-CHD (27, 28). The CRELD family of proteins have two members: CRELD1 and CRELD2. CRELD1, located on 3p25, is the first find to be involved in the pathogenesis of isolated AVSD (with or without DS).

Congenital Heart Disease (CHD)[13]	**%**
Atrioventricular septal defects (AVSD)	**45%**
Ventricular septal defects (VSD)	**35%**
Isolated secundum atrial septal defects (ASD)	**8%**
Isolated persistent patent ductus arteriosus (PDA)	**7%**
Tetralogy of Fallot (TOF)	**4%**
Other	**1%**

It is expressed during endocardiac cushion development and encodes a cell surface protein that acts as cell adhesion molecule. Studies have found missense mutations in CRELD1 in DS patients with AVSD, these several results indicate that mutations in CRELD1 may contribute to the pathogenesis of AVSD in the context of trisomy 21 (29, 31).

MicroRNA might participate in AVSD in DS patients by negatively regulating AUTS2 and KIAA2022 gene expression. Overexpression of the miR-99a/let-7c cluster subsequently decreased their targets in fetal DS heart tissue. SNP and CNVs probably contributes to the different predisposition to specific CHDs in the various ethnicities.

In this review, we summarized the possible molecular mechanism of DS associated CHD. Gene dosage imbalance hypothesis and gene mutation hypothesis are the main pathogenesis. Different genes are related to CHD in children DS: DSCAM, COL6A1w2, CRELD1, CRELD2. Among these genes, DSCAM, COL6A1w2, located on CHR 21 cause abnormal heart development through different mechanisms by gene dosage effect. CRELD1, CRELD2 lied in other chromosome results in CHD, due to gene locus mutation.

In addition to the factors mentioned above, there may be other new mechanisms that have not yet been discovered, and we believe that the CHD phenotype in DS patients is a combination of multiple factors that interact with each other synergistically or antagonistically and participate in the occurrence of DS-CHD. Our comprehension of the molecular pathogenesis of DS associated with CHD is significantly insufficienct. Many important future research goals need to be achieved.

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