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# Etiological Factors and Parental Coping in Congenital Heart Malformations

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**Abstract**: *The etiology of congenital heart malformations is still insufficiently known. Many genetic mutations exert their action through various mechanisms on neural crest signaling, acting on neural cell migration and altering bulboconal region formation or resorbtion. Some studies evaluate the role of punctual or noncoding mutations, while others highlight the teratogen effect of retinoic acid or ethanol, or discuss the role of maternal diabetes or pregnancy rubella. The etiology of congenital heart malformations is complex and multifactorial and requires further studies. The impact on the family of a child with a congenital heart malformation is significant and various coping mechanisms are employed by parents to address the issue.*

**Keywords:** *congenital heart malformation, mutation, genetic abnormality, coping.*

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## Introduction

Congenital heart malformations are the most common type of congenital defect and affect 8 out of 1000 live new borns.

The etiology of congenital heart malformations is not yet fully deciphered but there is various data regarding genetic defects, neural crest migration abnormalities, retinoic acid effect, infectious agents of alcohol on normal heart development during the embrionary period (Lupu et al., 2015, Chirita et al., 2012).

The diagnosis of congenital heart malformations received by a child may significantly impact parental mental health, and the consequence of this may be an impact on child behavioral development. 25-50% of the parents of children with severe CHD reported clinical symptoms of anxiety or depression (Woolf-King et al., 2007). Parental coping strategies vary over time, can be different in mothers and fathers and employ social and spiritual support (Dalir et al., 2020).

## Etiological factors of congenital heart malformations

The etiology of congenital heart malformations is diverse and not yet fully understood. The known etiological factors include genetic abnormalities such as mutations, modifier genes, deletions, maternal alcohol or retinoic acid use.

## Genetic abnormalities

Several genetic abnormalities are involved in congenital heart malformation etiology: chromosomal defects such as 21 trisomy (50% of affected individuals suffer from some type of congenital heart defect such as atrio-ventricular septal defect or Fallot tetralogy) or Turner syndrome (frequently associated with aortic coarctation).

A study made on children born by mothers with congenital heart defects showed that 16% of these children had a congenital heart malformation, often identical of that of the mother. This occurrence rate is much higher than 2-3%, the rate that could have been explained by the principals of polygenic transmission (Whittemore et al., 1982). On the other hand, congenital heart malformation transmission rate from the father seems to be much smaller.

## Modifier genes

Modifier genes are incompletely penetrating monogenes. They have heterogeneous phenotypes and are associated with congenital heart defects (CHD). The NKX2.5 mutation is associated with atrial septal defect, conotruncal defects, hypoplastic left heart syndrome and atrioventricular blocks.

Punctiform mutations in the elastin gene have been identified in Williams syndrome, causing aortic pathology and supravalvular stenosis.

COL6A1, COL6A2, CRELD1, FBLN2, FRZB and GATA5 mutations have been identified in Down syndrome patients who had an atrioventricular septal defect, but not in Down syndrome patients with no CHD (Ackerman, 2012).

## Other types of mutations

De novo mutations: SMAD2 mutation causes dextrocardia, pulmonary stenosis and atrioventricular septal defect.

Noncoding (microARN) mutations cause atrial septal defect, ventricular septal defect, atrioventricular septal defect (Gelb & Chung, 2014).

## 22q11.2 deletion syndromes

22q11.2 deletion causes DiGeorge and velocardiofacial syndromes.

Frequently encountered cardiac abnormalities: type B interrupted aortic arch, common arterial trunk, Fallot tetralogy with pulmonary atresia or stenosis, double outlet right ventricle.

Possibly associated cardiac abnormalities: ventricular septal defect, aberrant right subclavian artery origin.

22q11.2 deletion leads to the underexpression of Tbx1 transcriptional factor, thus disturbing signaling between neural crest cells and the surrounding tissues and neural crest cells migration. In the absence of Tbx1, Slit guiding molecule expression is diminished, therefore neural crest cells migrate to arches 3 and 6, but not arch 4, causing interrupted aortic arch (Calmont et al., 2009).

Tbx1 also regulates Fgf8 activity, a molecule richly expressed in the pharyngeal ectoderm and endoderm, but poorly represented in the visceral mesoderm. Fgf8 plays a crucial role in the correct alignment of left ventricle ejection tract (Park et al., 2006).

The 22q11 region also includes the DiGeorge Critical Region Gene 8 (Dgcr8), which codes a protein that is essential for ARNmi synthesis,

without which the embryo is born with a common arterial trunk, a ventricular septal defect, interrupted aortic arch or abnormal right subclavian artery origin (Chapnik et al., 2012).

## CHARGE syndrome

CHARGE syndrome consists of coloboma, congenital heart malformations, chonal atresia, physical and mental retardation, genital hypoplasia and deafness. It is caused by the CHD7 mutation, thalidomide or retinoic acid exposure. CHD7 is necessary for neural crest transcriptional circuits activation.

## Retinoic embriopathy

The retinoic embriopathy was described after pregnant women were exposed to retinoic acid in the past, as an acne treatment.

Associated cardiac malformations include: conotruncal defects (transposition of the great arteries, Fallot tetralogy, double outlet right ventricle, common arterial trunk, ventricular septal defect) and aortic arch abnormalities (type B interrupted aortic arch, retro esophageal right subclavian artery, aortic arch hypoplasia) (Coberly et al., 1996).

On the other hand, vitamin A deficiency during pregnancy also leads to several malformations, such as ventricular septal defect, common arterial trunk or aortic arch defects (Pan & Baker, 2007).

The mechanism of imperfect cardiogenesis in retinoic embropathy consists of excessive apoptosis in the left ventricular ejection tract endocardium, leading to its abnormal septation (Kubalak et al., 2002).

Retinoic acid receptors upregulate TGFB@. TGFB2 reduction in areas that are retinoic acid deficient is accompanied by septal malalignment cardiogenesis defects (Keyte & Hutson, 2012).

## Fetal alcohol syndrome

Fetal alcohol syndrome includes pre- and postnatal growth deficit, microcephaly, psycho-somatic development delay, fine motor dysfunction, a specific facies, palate cleft, articular abnormalities and congenital heart defects. Alcohol consumption by the pregnant woman in the periconceptional period increases the risk of conotruncal defects 2-2.5 times (Carmichael et al., 2003).

The ethanol induced teratogenesis mechanisms consist of microtubule and microfilament dysfunction, cardiac mitochondrial

dysfunction, increased apoptosis of the neural crest cells, Hox genes downregulation and vitamin A antagonism (Yelin et al., 2005).

**Alagille syndrome**

In Alagille syndrome patients several mutations, like NOTCH2 and JAGGED1 have been described. The associated cardiac malformations include Fallot tetralogy and the ventricular septal defect.

The mechanism of abnormal cardiogenesis relies on the fact that NOTCH and JAGGED receptors, widely disseminated in the aortic arch and left ventricular ejection tract have a crucial role in left ventricular ejection tract and semilunar valves development and neural crest derived cells differentiation towards vascular wall muscle cells.

**Waardenburg syndrome**

PAX3 heterozygote mutations diminish neural crest cells migration, causing a patent ductus arteriosus, left ventricular ejection tract septation abnormalities and semilunar valves abnormalities (Conway et al., 2000).

**Leopard and Noonan syndromes**

These syndromes are characterized by phenotypical overlap. They are associated with hypertrophic cardiomyopathy, septal defects, pulmonary stenosis, aortic coarctation, patent ductus arteriosus, great vessels abnormalities. These abnormalities appear because crest cells do not migrate to the left ventricular ejection tract during its formation period (Nakamura et al., 2009).

**Parental coping strategies**

Upon learning the diagnosis, the reactions vary between denial, shock, sadness, isolation and guilt. The moment is perceived as the most difficult in the life of a parent. During the care of a child with congenital heart malformation, parents suffer through permanent self-sacrifice, restrictions, painful waiting, exhausting search or suffer due to the curiosity or judgment of those around them. These children are difficult to care for due to frequent hospitalizations, aggressive procedures required, permanent precautions related to the environment and medication or other associated diseases. These children have a hard time gaining weight, therefore parents are very careful about the number and quality of meals.

Family coping uses approaches that focus either on emotions or on solving problems: denial, avoidance, acceptance, maintaining family stability, spirituality.

Coping methods vary between women and men. A study that exclusively examined maternal coping methods (Sira, 2014) found that understanding the medical situation, obtained through discussions with doctors and other parents in similar situations, as well as using the Internet for documentation, was the most used coping pattern. In the same study, mothers who relied more on spirituality were more optimistic and continued to be well integrated in their families after finding out the diagnosis. On the other hand, fathers seem to need more time to accept the child's chronic illness (Sharma et al., 2018). Compared to mothers, fathers expressed their emotions less often by crying and as part of their coping strategy they included the continuous attempt to find a solution to the problem (Demianczyk et al., 2022) or the use of alcohol (Jackson et al., 2015).

In a hospital-based study that included 142 parents of children diagnosed with congenital heart malformation, 71.8% of them suffered from moderate stress and 28.2% from low stress (Ghimire, 2017), while another study highlighted increased levels of stress at 25% of the participants, moderate levels in 58.3% of them and low levels in 16.7% (Greshik, 1999).

Fear and stress can lead to the development of acute stress disorder (ASD) and post-traumatic stress disorder (PTSD), while social support decreases stress (Abbas, 2019). Children of parents suffering from PTSD are at greater risk of developing sleep and eating disorders with consequent increased numbers of hospital admissions (Simeone et al., 2018)

Another consequence of the CHD child is the transition to spirituality. Parents can see a child's heart disease as a divine test and rely on God to make the child better. In this sense, they engaged in humanitarian activities. Religion can represent a refuge from anxiety.

The support systems described in his study consisted of support within the couple, within the extended family, and support provided by health professionals. Honesty, reassurance and background information help to understand the illness and help parents cope better (Popazu et al., 2022).

At some point during the coping process, parents try to minimize the impact of the child's congenital heart disease on the family. This is achieved in some cases by trying to restore normalcy, without turning the child's condition into a reason to treat him differently. Other parents document the disease extensively, becoming experts, while others demonstrate hyper vigilance in monitoring their child's health, constantly looking for signs of deterioration (Lumsden et al., 2019).

## Conclusion

The etiology of congenital heart malformations is complex and multifactorial, and the diagnosis of congenital heart disease severely affects the patient's family. Parents of children with congenital heart disease are more vulnerable to psychological and social stress, and the disease impacts the family in multiple ways, throughout the child's life. There are multiple coping patterns, and individuals choose the one that suits them based on their own previous experiences, personal characteristics and beliefs, and the social support at hand. Parents try to maintain a level of normality, integrating the disease into their lives as much as possible.

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