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Congenital Heart Disease (CHD) Amongst Children

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Within the US, the #1 cause of death is Congenital Heart Disease (CHD). Its victims range from those in their last days to those experiencing their first. The cause of CHD in adults is almost always known, however, when it comes to children, 8 out of 10 times the cause is completely unknown. This raises a huge concern, considering that just last year in 2022, approximately 1.3 million children were born with CHD (Benjohnson, 2022). As researchers at Mayo Foundation for Medical Education and Research (2022) have written, there's a variety of different defects that children with CHD are born with, as well as different possible causes, preventions, and treatments. Although there's lots of known information about CHD and its effects and implications, the causes still remain mostly unknown. So this leads one to wonder: what is CHD overall and its impact on children? What causes of CHD have been found, and what can be done with that information? How can one then use this information to increase prevention and decrease presence of CHD in children? CHD is a disease that impacts the health of over one million newborns per year by impacting the function of their hearts. Causes that have been found but not widely talked about or discussed are immature neurodevelopment, mutation of the Nkx2-5 gene, maternal hypercholesterolemia, and lack of education of CHD from children's caregivers.

This paper will be approached from a medical and biological standpoint. As a pre-medical student, planning on pursuing a career in medicine, this topic is of great interest, as I will be seeing this issue within my line of care in the future. The explanation of CHD and its impact on the human body will be from the medical standpoint using information from peer

reviewed sources such as Mayo Clinic and Canadian Journal of Cardiology. For the biological standpoint, possible mutations of genes that could be causing CHD will be looked into.

When looking into CHD, there are different heart defects that present at birth. Colleen Story (2018) defines some of these heart defects and diseases. These heart defects are heart valve disorders which is the restriction of blood flow due to the aortic valve of the heart narrowing, hypoplastic left heart syndrome meaning the underdevelopment of the left side of the heart, holes in the walls of the heart, which can be seen in ventricular septal defect, atrial septal defect, and patent ductus arteriosus, and lastly tetralogy of fallot, four defects that come as a "set" as follows: hole in ventricular septum, narrowing of the passageway between the right ventricle and pulmonary artery, thickened right side of the heart and a displaced aorta. CHD can have long term effects on the child. However there are current treatment options that exist, such as surgery, catheter procedures, medication, and heart transplants in more urgent and severe cases. Other heart diseases that are not as common amongst children but are still seen are atherosclerosis, arrhythmias, Kawasaki disease, heart murmurs, pericarditis, and rheumatic heart disease (Story, 2018).

The Mayo Foundation for Medical Education and Research (Mayo Clinic, 2022) explains how the heart works and develops, in order to enhance the understanding of heart defects and their impact on the heart. The heart has four chambers, two on each side. In order to get blood throughout the body, the heart uses its sides for different tasks. The right side of the heart carries blood to the lungs through the pulmonary arteries. Once the blood is inside of the lungs, it gains oxygen and returns to the heart through the left side via pulmonary veins. The left side of the heart then uses the aorta to pump the blood out to the whole body. Now let's look into how these heart defects develop. During the first and second trimester of pregnancy, the baby's heart is

beginning to form and starting to beat. So this is the point in development where congenital heart defects develop. Researchers however, aren't sure about what causes the majority of these defects, but some guesses are genetics, certain medical conditions, some medications, and environmental factors. Altered connections within the heart or blood vessels such as holes in the walls between two heart chambers is a common defect. An altered connection such as this can lead to a mix with low oxygen blood with high oxygen blood. This change in blood flow leads to the heart being forced to work harder. Different types of altered connections are atrial septal defect, ventricular septal defect, patent ductus arteriosus and total or partial anomalous pulmonary venous connection. Heart valve problems are another defect problem. Heart valves are the doors of the heart chambers, they open and close to make sure that blood is flowing in the right direction. So if the valves aren't working properly then blood won't flow properly. Valve problems present themselves as narrowed which is stenosis, or valves that don't close which is regurgitation. Aortic stenosis, pulmonary stenosis and ebstein anomaly are usually seen for valve problems.

Now when looking at the main possible causes of these heart defects, MD Shabnam Peyvandi (2022), talks about a possibility. They delve into Fetal brain development in CHD, and how there's a significant connection between brain development and CHD, and how factors that impact immature brain development can furthermore cause CHD. Impairment upon neurodevelopment is something that is commonly seen in patients that have complex congenital heart disease (CHD) throughout their lives. There are multiple factors that impact and contribute to neurodevelopment when it comes to CHD. This includes cardiac, medical, and social factors. Brain magnetic resonance imaging (MRI) has been a very important instrument that's been vital in showing differences in the maturity and structure of the brain amongst CHD patients. What

has been found in newborns with complex CHD is abnormal microstructural and metabolic brain development, which is often seen in premature infants. These abnormalities are in utero, meaning that it takes place while the baby is still in the uterus. The third trimester is the best time to spot these abnormalities using fetal brain MRI and interventions. There are also various things that cause abnormal brain development of fetus' such as cardiovascular physiology, genetic abnormalities, placental impairment and environmental/social factors. During the third trimester, there is an intricate connection between the brain, circulation, and the heart that is vital for normal brain developments. Fetuses and newborns that are born with significant CHD are commonly found to have smaller brains. However there are volumetry techniques that allow for modeling brain tissue, furthermore identifying the areas of decreased brain volume in these fetuses with complex CHD. Other technology has been used as well such as diffusion tensor imaging (DTI) and spectroscopy. Using fetal brain MRI structural abnormalities were found in 23% of fetuses with CHD. Abnormalities that were seen the most were mild unilateral ventriculomegaly and increased extra-axial spaces. There was also a pattern that was specifically found in regions of the brain. Fetuses that have CHD had structures within certain regions that were vulnerable to low oxygen or substrate delivery being more affected.

Now, the factors that contribute to brain development in CHD, Starting with genetics. Kids that have CHD and a genetic syndrome have more significant neurodevelopmental impairments than children that only have CHD. For cardiovascular factors, cerebral blood flow and oxygen delivery are often impaired in children with CHD. Normally, cerebral blood flow is highly-oxygenated. In hypoplastic left heart syndrome, the structures of the left heart are deformed, leading to the blood flow going in the opposite direction, and mixing oxygenated blood with deoxygenated blood. This backflow causes disturbances in in utero growth and brain

development. The connection between cardiovascular physiology and brain development has been looked at using fetal cardiac MRI which also measures oxygen saturations in the blood vessels of the fetus. A correlation was found between fetal cerebral oxygen consumption and brain size. Therefore meaning that backflow impacts the oxygen levels in blood leading to less cerebral oxygen consumption. Environmental factors that contribute is maternal stress especially during the third trimester, as well as maternal fetal environment and placental abnormalities.

Another possible cause of heart defects is explained by researcher Heather L. Bartlett (2007). She explains transient early embryonic expression of the Nkx2-5 gene, and how mutation of this gene is linked to congenital heart defects in humans, furthermore being a cause of it. Nkx2-5 is a genetic sequence that holds a transcription factor that is present and expressed amongst organisms that form hearts during development. Mutations of the Nkx2-5 gene have been shown to cause problems amongst organisms development. For example, in fruit flies that lack this gene, do not form dorsal vessels, and mice that are homozygous null for the gene, meaning that due to mutation it is nonfunctional and does not express, leading to the development of small hearts with deformation. Along with this finding, cardiac defects presented in humans have been linked to mutations of this gene. Nkx2-5 is expressed in the early stages of embryo development. Its expression caters to the heart regions of the embryo. When looking deeper at this gene, the different domains on the amino acid sequence of Nkx2-5 was assessed. There is the TN domain, the homeo domain, the NK domain and the GIRAW domain. When looking at the mutations that took place amongst humans with congenital heart disease, the C-terminal regions were deleted by mutations, Gln170ter and Gln198ter. This ultimately affects the expression of Nkx2-5 therefore affecting heart development.

Maria Elena Capra (2021) speaks on another cause of CHD, in her article on the nutritional approach towards the prevention and treatment of CHD, maternal hypercholesterolemia. This is a condition that can occur during pregnancy, it leads to increased levels of cholesterol, atherosclerosis and increased blood levels of low density lipoprotein receptors (LDLR). Exposure to a high cholesterol environment during early development is found to reprogram the set point for cholesterol homeostasis in organisms. This is a big reason as to why babies are already born with such high levels of cholesterol and clogging of arteries, leading to the development of CHD very early on in their lives. This is why it is vital for mothers who are carrying to avoid a diet composed of foods high in saturated fats, lack of exercise and physical activity, smoking, and certain medications.

Lastly, the lack of education and knowledge of CHD from children's caregivers is a very big contributor. Some studies have been done on whether or no socioeconomics plays a role in this. Which was reviewed by Animasahun et al. (2015), leading to the conclusion that children's caregivers from higher socio economics statuses have heard of CHD and caregivers from a lower socioeconomic status have not heard of it. However, most parents of children with CHD don't know much about it, its indicators, its best type of treatment, preventability, regardless of their socioeconomic status. This conclusion however established the urgency of creating educational programs for caregivers of children with CHD.

So these various sources of information tell us how immature brain development has a connection with the physiology of the cardiovascular system, leading to the development of CHD. How the mutation within the Nkx2-5 gene that is in charge of heart development during the fetal development stage of organisms is another cause. The deletion of certain parts of the homeo domain greatly impacts the function of the heart. How maternal hypercholesterolemia

leads to a high level of cholesterol in newborns with their arteries already partially clogged. Along with it programming the newborns homeostasis set point for cholesterol regulation is distorted leading to their body not knowing when to regulate their cholesterol levels, furthermore leading to CHD. Lastly, how caregivers of children with CHD are not well educated on CHD which establishes the urgency to establish and create education programs on CHD for these children's caregivers.

There are limitations that are present for this paper such as the lack of information on the causes and roots of CHD. There is a limit on research funding and the attention that is being given. The amount of funding that is put into heart disease is much lower than other diseases such as cancer. In the book State of the Heart, Warraich (2020) talks about how breast cancer receives 7x more research funding than heart disease based on every death that it causes. Regardless of heart disease being the #1 cause of death. In regards to attention given to heart disease, there is focus put on people who develop CHD due to diet and lifestyle choices, so in that area the problem is "solved" however, do babies that haven't been able to make diet and lifestyle choices don't deserve the attention and research to find more causes for their problem?

CHD is impacting millions of children around the world, affecting their quality of life. For diseases that impact this many people, the cause is usually known. So raising concern over the unawareness of CHD causes is important, because it will significantly improve the preventions and type of treatment that will be given to each form of CHD. Educational programs need to be established and made aware to the caregivers of children with CHD. This project advances the conversation of CHD and its causes/implications because it opens more conversations about the further development of care plans for women carrying children, nursing children, and raising children that have been affected by CHD. Nutrition and lifestyle choices are

important during pregnancy, but the impact certain things can have on the baby's cardiovascular health are not widely talked about. Checking for familial hypercholesterolemia as well as maternal hypercholesterolemia is very important in protecting the bay's heart health as it develops. More research needs to be done to find more causes on CHD and more importantly how to prevent them from happening.

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