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The Effects of Congenital Heart Disease on the Development of Autism Spectrum Disorder in Pediatric Patients

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ABSTRACT

It is a well-known fact that congenital heart disease (CHD) can cause life-long health complications, especially if it impairs other bodily functions early in life. One of these complications is the risk of developing a serious neurodevelopmental disorder known as autism spectrum disorder (AuSD). With some case studies identifying the linkage of CHD and AuSD, it has been successfully established that being diagnosed with CHD does increase a child's chances of developing AuSD later in life. There is not a simple answer for why this occurs. However, there are several factors that can contribute to why CHD increases the risk of developing autism. Some possible explanations may include synthetic factors such as the alteration of blood flow in genetic pathways due to early cardiac surgery. These explanations can also include uncontrollable factors such as demographics, maternal conditions, and viral infections, all of which are just as likely as synthetic factors. This research, based on case studies conducted recently, further reinforces the conclusion that the diagnosis of certain lesions of CHD results in an elevated risk of developing AuSD.

Introduction

Overcoming neurodevelopmental challenges has been a long-term goal for researchers, scientists, and medical professionals. As research devoted to the field of cardiac surgery greatly contributes to the decrease in mortality rates of children born with congenital heart disease (CHD), consequent concern is now turning to a prominent result of CHD. Despite the incredible surgical care offered to those affected by CHD, another looming outcome of CHD is autism spectrum disorder (AuSD). Children diagnosed with CHD are at increased risk of developing AuSD, a disease with no singular cause and no cure. Neurodevelopmental disorders (NDDs) like AuSD heavily impact executive functioning deficits such as cognition, adaptation, behavior, and communication.

A probable connection between CHD and AuSD is the alteration of the shared connection pathways between the brain and the heart. Infants with severe forms of CHD who require cardiac surgery within the first few crucial years of their lives are extremely vulnerable to developing brain injuries due to altered blood flow within the body.

Cerebral blood flow (CBF) is vital for brain maturation as it ensures the adequate delivery of necessary nutrients and oxygen to the brain. Altered/Decreased CBF may result in unstable blood vessels in the brain that prevent the white matter fibers from effectively connecting regions of the brain and delivering nutrition/oxygen. The reduced connectivity between regions of the brain can subsequently impair the infant/child from its executive functions. Undergoing cardiac surgeries that expose an infant to everything causes concern for that child's current health and future health. Exposing the heart to certain viruses that change cerebral blood flow can subsequently result in severe neurodevelopmental issues like autism. CBF can be compromised by any early-life surgeries, especially ones that are complicated or risky.

Roots of Congenital Heart Disease

Cardiac surgery, a surgical procedure that involves the heart itself or the blood vessels responsible for carrying blood, was first established in the mid-1950s with the invention of the heart-lung machine. Congenital heart disease is extremely common as a newborn is diagnosed with some form of CHD every 15 minutes across the United States. Annually, an average of 40,000 children (about twice the seating capacity of Madison Square Garden) are affected. There is no definitive cause of CHD which broadens the probable causes of it. Broadly speaking, CHD can be caused by a variety of factors like genetic mutations/pathways, environmental exposures, maternal conditions, or even a combination of all three. This means if the parent has a heart condition, it is likely their biological child will also have the same condition. Having any congenital heart defect increases the patient's risk of developing other complications such as heart failure, endocarditis, atrial fibrillation, and heart valve problems.

Branches of CHD: Non-Cyanotic (Acyanotic) Heart Defects

The first of the two main types of congenital heart disease are more complex than the other due to its process for diagnosing. In non-cyanotic (or acyanotic) CHD, babies are visually assessed by the pediatrician, typically within the first few hours of life. Non-cyanotic congenital heart disease implies the baby has sufficient blood carried in its blood flow. Typically, non-cyanotic CHD includes heart defects like aortic stenosis, atrial septal defect, and ventricular septal defect.

Atrial Septal Defect (ASD)

Atrial Septal Defect (ASD) is an extremely serious heart defect that consists of being born with a hole in the septum, the wall that separates the atria of the heart, and keeping the hole after the first few months after birth. To be clear, every infant is born with a hole in its septum, but ASD patients' septum hole does not close after a few months of life. With ASD, the patient has a surplus of blood flowing through the unwanted opening in the septum that connects the two upper chambers of the heart. The individual chambers of the heart only contain one type of blood in each (either oxygen-rich or oxygen-poor blood), but the hole/passageway between the two collecting chambers results in contamination of the oxygen-rich blood. ASD causes extra blood to flow through the hole into the right side of the heart, resulting in a stretching/elongation of the right side of the patient's heart.

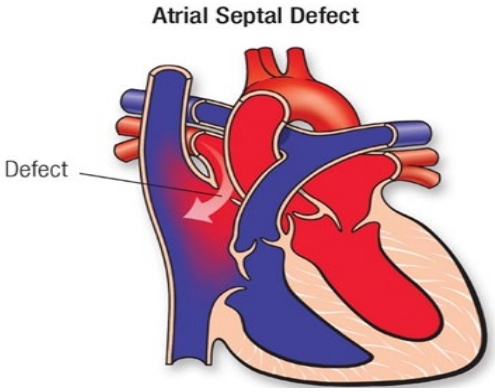

Figure 1. This graphic of the heart shows the location of the atrial septal defect and how this hole in the heart alters blood flow, resulting in an expansion of the right side of the heart. Created in BioRender, copyrighted by Dhriti Shah.

Ventricular Septal Defect (VSD)

Ventricular septal defect (VSD) is another form of congenital heart disease that involves a hole in the septum, but in VSD patients, the hole is in the septum separating the 2 *pumping* chambers of the heart (both left and right ventricles) rather than the 2 receiving chambers. An opening between the ventricles leads to a surplus of blood flowing from the left ventricle to the right ventricle, resulting in a high pressure in the lungs and stretching of the left ventricle. Small openings do not make the lungs and heart work harder, so they do not require interventional cardiac surgery and will likely not affect the blood flow of the patient. On the contrary, large holes in the heart must be closed with either open-heart surgery or cardiac catheterization where a device is inserted in the opening to plug it in and prevent any further symptoms or related congenital issues from developing.

Aortic Valve Stenosis

An extremely detrimental form of congenital heart disease is aortic valve stenosis. This disease is when the aortic valve, the valve that controls the blood flow between the left ventricle of the heart and the aorta (the body's main artery), is narrowed and blood cannot flow freely in and out the aortic valve. Because the left ventricle must work harder to pump oxygen-rich blood from the heart to the rest of the body, the left ventricle thickens as it is a muscular chamber. The thickened left ventricle results in a swelled heart, and the blood cannot enter the patient's circulatory system as quickly as the organs need it to.

Aortic valve stenosis is often caused by calcium buildup on the aortic valve where the calcium deposits come with age. These deposits can easily narrow and stiffen the valve tissue. Aortic valve replacement is the #1 option when treating aortic valve stenosis because it gives the patient three options for their replacement aortic valve. Patients can choose a new valve made from cow, pig, or biological (human) heart tissue, or they can pick a mechanical valve which lasts longer but is made from synthetic materials.

Branches of CHD: Cyanotic Heart Defects

Secondly, cyanotic CHD refers to the lack of oxygen flowing through the blood and body. This form of CHD is simple to diagnose as the skin, fingernails, and lips turn a shade of blue in the first few hours of life. It is easily noticeable and can be treated immediately after cyanotic CHD is diagnosed.

Hypoplastic Left Heart Syndrome

A rare form of congenital heart disease is hypoplastic left heart syndrome (HLHS), where the left side of the heart is underdeveloped and is not large enough to support the amount of oxygenated blood needed. A child typically develops HLHS when the left side of the heart remains underdeveloped after the first 8 weeks (about 2 months) of fetal development. Detection and diagnosis of HLHS can be as early as 16 weeks' (about 3 and a half months) gestation by getting a fetal echocardiogram. Infants with HLHS typically do not live past the 8th day mark without any surgical intervention. HLHS is treated through a series of reconstructive surgical procedures which can sometimes include a heart transplant and can be administered as early as the first hour of birth.

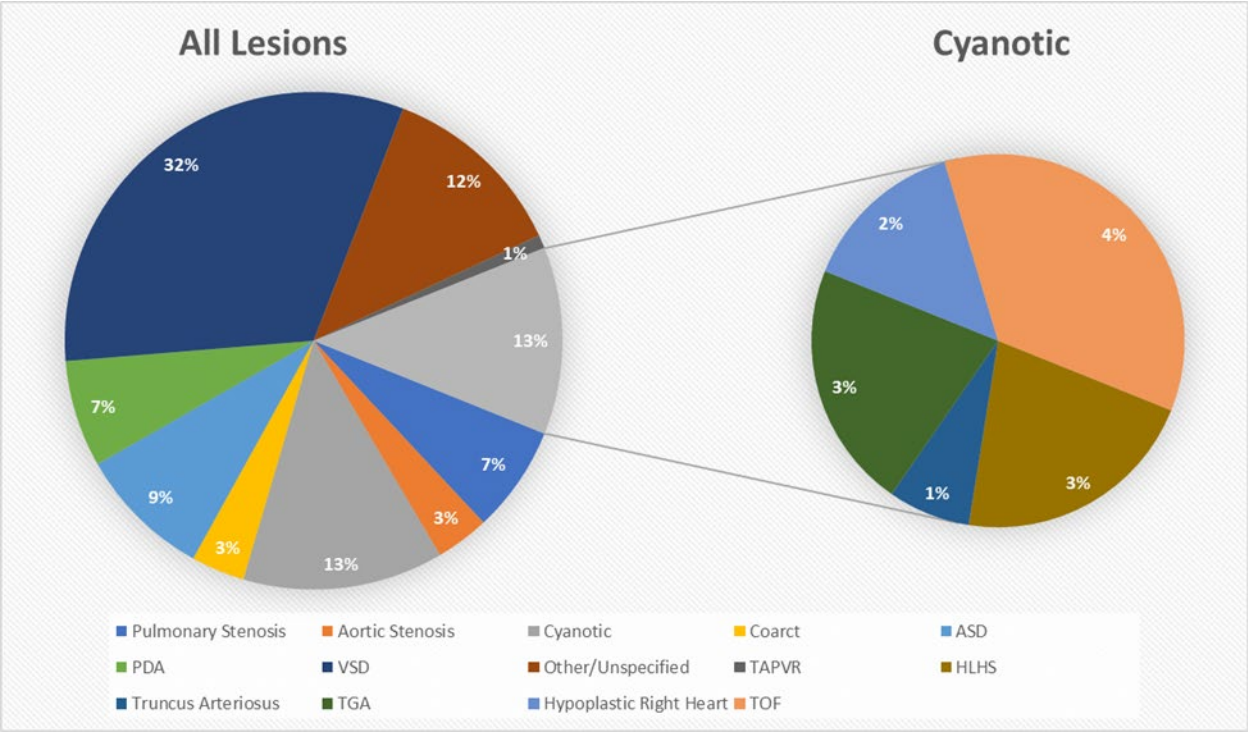

Figure 2. Prevalence of congenital heart lesions. The left pi chart contains demographics of relative prevalence of all possible lesions of congenital heart disease, and the right pi chart contains demographics specifically of cyanotic congenital heart disease legions. Created and copyrighted by Dhriti Shah.

Diagnosis of CHD

What technology is used to diagnose CHD in infants and children both before and after birth? Before birth, the diagnosis of a child can be determined in two ways. One way is through a fetal echocardiogram which can be used when the baby is unborn. It is an ultrasound test that provides pictures detailing the structure and condition of the developing heart through sound waves. Once the baby is born, CHD can be diagnosed by several observational methods. Visually observing/using a pulse oximeter for realizing cyanosis (a bluish skin tone/fingernails), listening for any abnormal heart murmurs, and screening the infant before and after it goes home. The screening process for serious cases of CHD of an infant's thoracic cavity is a simple, non-invasive procedure involving a pulse oximetry. The pulse oximetry tests the oxygen level (oxygen saturation) in the baby's blood flow by placing sensors on the baby's skin. If the pulse oximeter produces a low level of oxygen, it indicates a sign of heart defect.

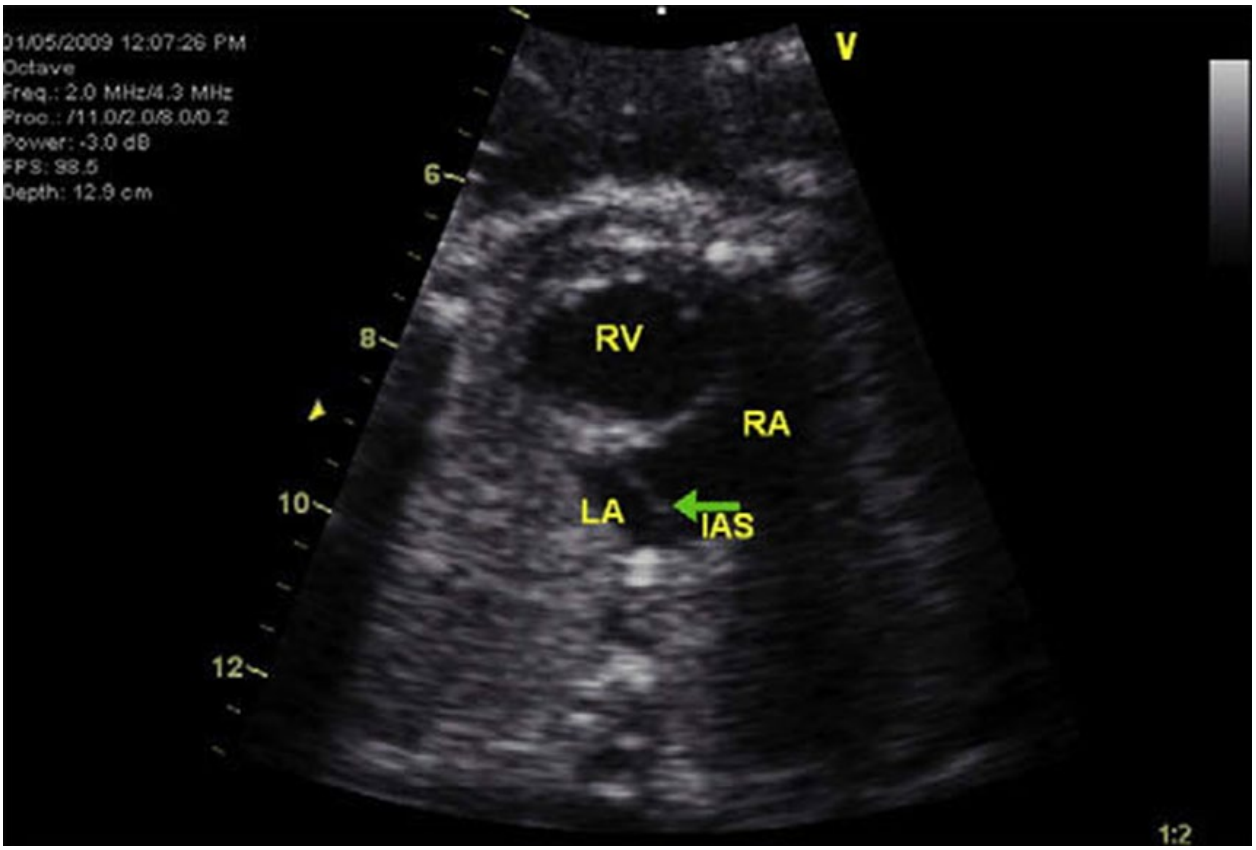

Figure 3. Example of a Fetal Echocardiogram. The fetus demonstrates hypoplastic left heart syndrome where the right atrium (RA) and right ventricle (RV) is enlarged. The left atrium (LA) and left ventricle (LV) are small with no cavity. IAS is the interatrial septum (indicated by the green arrow).

Autism Spectrum Disorder (AuSD)

Autism spectrum disorder is a pervasive neurodevelopmental disorder that can result in compromised communication and motor skills, social interaction, behavioral instincts, and behavioral patterns. Though autism can be diagnosed at any age, the symptoms typically appear in the first two years of life. Patients who are diagnosed with autism spectrum disorder can express hundreds of symptoms, hence the condition is called a spectrum disorder. The symptoms noticeably affect motor skills and physical behavior, but autism can also result in impaired processing and retention rates of the child since autism is categorized as a neurodevelopmental disorder. Autistic children tend to experience certain sensory hypo sensitivities as well as hypersensitivities, the heightened sensitivity to simulation of sight, hearing, touch, taste, and smell. Their hyper and hypo sensitivities often quickly result in the unfortunate alteration of their perception of the environment around them and can cause anxiety within the child due to overstimulation of the brain. Children with any autism spectrum disorder often exhibit difficulty with communicating/interacting with people, engaging in activities, and living a quality social and familial life due to their repetitive behaviors. Some repetitive behaviors may include:

1. Not maintaining consistent eye contact
2. Showing little emotion, interest, and facial expressions in the environment surrounding them
3. Having trouble conversing with others
4. Having difficulty adjusting their behaviors for different social interactions
5. Expressing an unusual tone of voice unfit for the situation

Deficits in motor development and physical activity behavior can significantly limit the opportunities children have to participate in exercise and children become inactive. This can easily result in obesity, a sometimes-irreversible condition due to mobility issues in autistic children. Early life mobilization issues complicate the child's situation by increasing the number of resources parents and caregivers need to spend as well as the amount of time devoted to rehabilitation help. Autism is overall an expensive and time-consuming treatment process as there is no definitive cure.

Potential Causes of AuSD

The primary causes of AuSD are not certain, but many studies point towards the child's genetics combined with other environmental factors which play a key role in the child's developmental issues, leading to AuSD. The factors that are often associated with elevated risk of developing AuSD include having other genetic disorders like Down Syndrome or having a blood relation with an autistic person (i.e., a sibling or older parents).

Diagnosis of Autism

Autism, a neurodevelopmental disorder, is diagnosed through three main methods. First, the parent/guardian of the child under observation can report to the pediatrician slight behavioral changes, any difficulty with speech and cognitive retention, and deficit attention span. This method does not guarantee any condition, but it gives way to the possibility of expanding efficiency of diagnosis. Caregivers and people that spend more time around the child should easily be able to identify any changes in the child's behavior, vocabulary, expression of echolalia (repetition of words and phrases), or episodes of hyper focus on certain aspects of an object. Since the part of the nervous system that regulates heart rate and breather is affected in autism, autistic kids tend to have noticeably elevated resting heart rates. For older kids, having trouble socializing or making friends in a social environment can be a sign of autism as autistic children often cannot comprehend other people's feelings, establishing them as social outcasts. A lack of productive interaction within the child's age group can quickly lead to a multitude of mental health issues, so addressing this symptom as quickly as possible is an integral part of the recovery process. Luckily, there are a few assessments that an undiagnosed autistic patient may participate in to determine the level of severity of their disease in addition to confirming the presence of their conditions. Today's gold-standard technology has significantly simplified the process required to diagnose autism spectrum disorder while minimizing any stress placed on the patient and their families.

Autism Diagnostic Observation Assessment Scales (ADOS)

The first assessment, Autism Diagnostic Observation Assessment Scales (ADOS), specifically focuses on assessing the child itself. It is a standardized test that aims to produce results which serve as evidence for the physician's previous findings. ADOS consists of 4 modules, each of which is specifically designed to fit individual situations/conditions. The first two modules are designed for children who struggle with demonstrating consistent verbal communication and interpersonal communication skills (impaired cognitive communication), respectively. Module 3 tests children who can communicate verbally and can interact with the environment and objects around them. This module is a safety test for children who may have a slim chance of being affected by ASD, but it is not likely (just a method of reassurance for the guardians). The last module is designed specifically for children who can effectively communicate both verbally and interpersonally but fail to interact with objects that surround them. All four modules included in the ADOS test are carefully crafted to match any child's current symptom situation, but if this test truly does not fit a patient's needs, another type of assessment to diagnose autism is also available.

Autism Diagnostic Interview-Revised (ADI-R)

The second assessment is much like an interview that only focuses on the child's parents and caregivers rather than the patient itself. Autism Diagnostic Interview-Revised (ADI-R) strives to provide some insight on how a patient's behavior is perceived by the people actually living with that patient. This simplifies the diagnosis process as ADI-R does not actively test the child in question; it observes the child's summarized developmental past. Since this interview can only ask so many questions, it does not produce live data that can be analyzed with a percentage error. ADI-R certainly cannot be the only indicator for diagnosing autism for a child since the interviews are conducted solely based on personal observations rather than concrete evidence found upon analyzing the child's tendencies itself. The same behavior can be perceived in hundreds of ways by different people which makes this test subjective without working with another assessment. Therefore, ADI-R must work together with ADOS and other test options to ensure accurate results and conclusions for both the patients and the guardians.

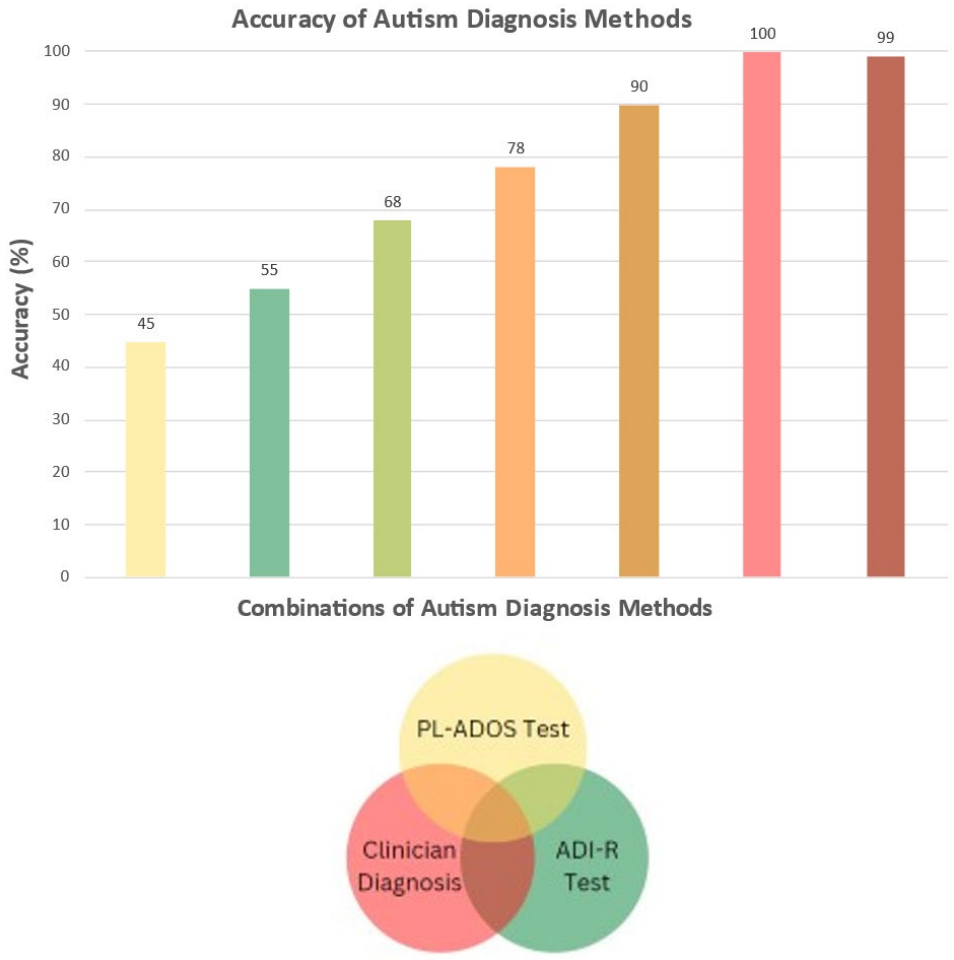

Figure 4. Autism Diagnosis Correctness. This bar graph details the accuracy of different methods used to diagnose autism spectrum disorder including ADOS, ADI-R, and clinician diagnosis with percentages. Note that the Venn diagram including the three methods is not an analysis tool; it is simply a legend for the colors used in the bar graph above. The overall prevalence of autism in the subjects tested upon is 58%. Created and copyrighted by Dhriti Shah.

Association Between Congenital Heart Disease and Autism Spectrum Disorder: Case Study

As early diagnosis of autism has proven benefits that can tremendously improve the quality of life, researchers are constantly finding new methods to diagnose AuSD. Improving methods to diagnose autism is an important priority for researchers and scientists because the quicker a patient can be diagnosed the earlier grave symptoms and results can be prevented. It is also just as important to get accurate results as an incorrect diagnosis or severity can do more harm than good. A study from 2001-2013, led by Juergen Hahn and Daniel Howsmon, meticulously collected data from the analysis of blood samples of the children chosen to participate in this study. Non-cyanotic congenital heart disease implies the baby has sufficient blood carried in its blood flow. Typically, non-cyanotic CHD includes heart defects like aortic stenosis, atrial septal defect, and ventricular septal defect. The 1:3 ratio of children were all enrolled in the US Military Health System.

This 12-year case study consisted of dividing a pool of children on the basis of sex, date of birth, and time frame of enrollment with a 95% confidence level of division. With 26,280 controls and 8,760 cases of ASD included in the study, "there were increased odds of AuSD in patients with CHD. Specific lesions with significant OR included atrial septal defects and ventricular septal defects" (Sigmon et al., 2019). The initial/previous conditions of the subjects in the study are expressed in Figure 5.

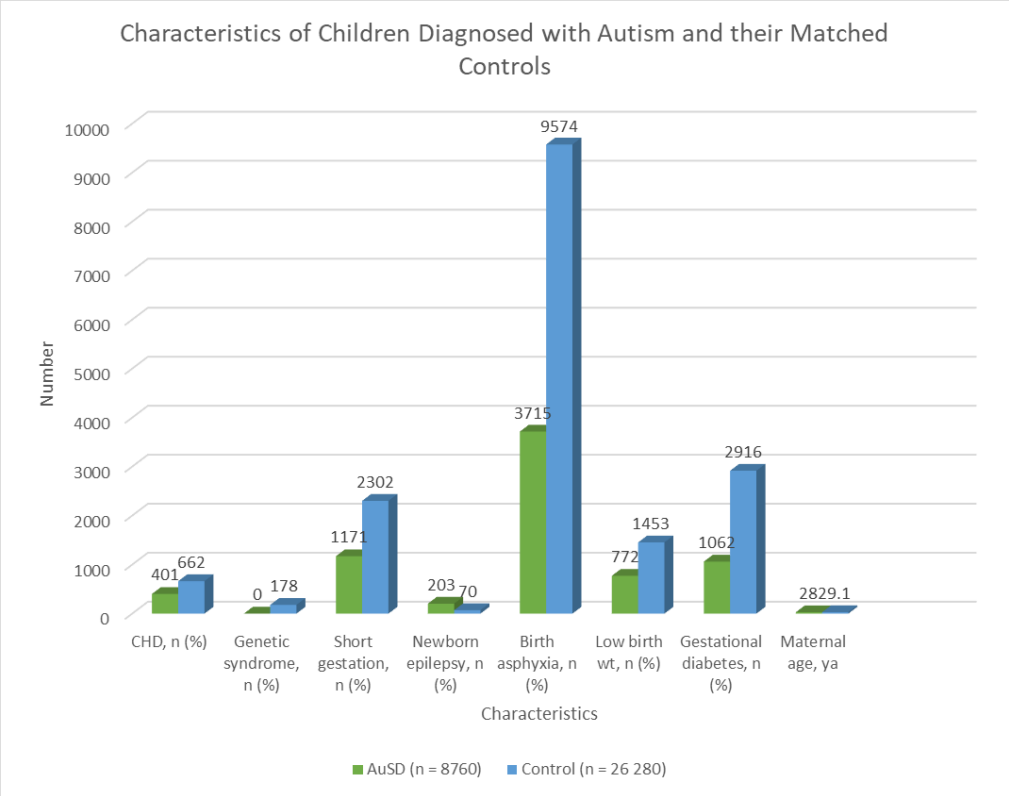

Figure 5. Characteristics of Children Diagnosed with AuSD and Various Categories of Congenital Heart Disease adjusted for certain matched controls. This detailed chart summarizes what characteristics the pool of children was distinguished between as well as what number of these children were diagnosed with factors of CHD. Matched controls include maternal age, gestational diabetes, genetic syndrome, short gestation, newborn epilepsy, birth asphyxia, and low birth weight. Created and copyrighted by Dhriti Shah.

Results

Based on these case study results, Figure 5 safely concludes that children who were compromised with varying lesions of CHD did indeed have increased odds of developing autism with a 95% confidence level. Atrial Septal defects and ventricular septal defects were the two specific CHD lesions with significantly higher odds of the child developing autism spectrum disorder (AuSD). Statistically speaking, they found that a total of 4.6% of children were affected by both CHD and AuSD compared to 2.5% of those just diagnosed with CHD. There is a difference of 2.1% between the two categories which approximates to 552 more children in reference to this specific case study's pool of children.

It has previously been established that CHD has been associated with certain neurodevelopmental delays. With this case study, however, it is now possible that single, more commonly found CHD lesions (such as atrial and ventricular septal defects) can also result in the same neurodevelopmental delays. This conclusion can assist medical professionals in tracking down a patient's condition and its origination by becoming more aware of what can arise from preexisting conditions like congenital heart disease. The "how" aspect of connections between congenital heart disease and autism, however, mostly remains unclear to scientists because of the wide range of factors as well as coincidental aspects.

Possible Connections Between CHD and AuSD

The "how" aspect of linking CHD to autism remains unclear. However, there are several educated theories behind the relationship between the two conditions. Genetic pathways reveal that there are a multitude of cardiovascular pathways that overlap with certain cognitive functions, a key factor of AuSD. Cardiovascular diseases such as atrial fibrillation and atrial septal defect have been prone to lead to serious psychological impairments. These pathways are extremely fragile and can easily be altered with early cardiac surgeries. Infants born with congenital heart disease often require cardiac surgery within the first hours of life. As dangerous as a procedure this can be, it is necessary to carry out these surgeries. These procedures can jeopardize and alter the blood flow of the infant and later result in brain injuries like the diagnosis of autism spectrum disorder. Demographics and other uncontrollable environmental factors may also affect the medical conditions an infant is born with.

Conclusion

There has been considerable progress made in the fields of congenital heart disease and autism spectrum disorder. Specifically, by Hahn and Howsmon, their case study can be used to help parents with affected children become aware of what to expect of their child's developmental course. Regarding AuSD, there is no singular cause or cure, but preventative measures can be taken well in advance. Recognizing certain cognitive shortcomings early on can significantly impact and reduce the severity of the child's condition later in life. Both ADI-R and ADOS are credible assessments that contribute to reducing the condition's negative effects on the patient.

With Hahn's and Howsmon's successful case study, they have concluded that children diagnosed with congenital heart disease (CHD) face increased odds of developing autism spectrum disorder (AuSD), particularly with ASD and VSD diagnosis. As discussed previously, this may be due to several distinct reasons such as environmental factors, demographics, the alteration of genetic pathways, or even a combination of all. The connection between congenital heart disease (CHD) and autism spectrum disorder (AuSD) is truly a medical mystery.

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