Clinical Features and Cardiac Anomalies of Children with Down Syndrome. A Literature Report

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Abstract
Background: Clinical diagnosis of Down syndrome is based on the characteristic features and associated malformations. Nonetheless, there is significant individual diversity in the clinical presentation. Not every physical characteristic may be present, particularly in infants. At the same, congenital heart abnormalities (CHD) remain a major predictor of death in children with Down syndrome (DS) despite improvements in surgical therapy for these conditions. The effects of DS vary from person to person, with some people having a significant impact while others are well and capable of living unassisted as adults. So, this study is done to understand the pattern of clinical features and cardiac anomalies in various research reports.

Aim: This scoping review aims to describe the frequency and distribution of clinical features and cardiac anomalies in children with Down syndrome and to consider the clinical implications of this knowledge.

Methods: Medline, CINHAL, and PubMed databases were searched electronically to identify pertinent articles from 2000 to 2023. Children with Down syndrome and cardiac comorbidities aged 18 years or younger met the inclusion criteria. Articles that were not peer-reviewed or written in English were disqualified at the title or abstract level.

Results: Literature revealed that the common physical and dysmorphic features found in individuals with Down syndrome include flat facial profile, epicanthal folds, upward slanting eyes, hypotonia, small ears, short neck, protruding tongue, small hands and feet, brushedfield spots, sandal gap, and short stature. It’s important to note that while these physical features are commonly associated with Down syndrome, not all individuals will exhibit every characteristic, and the severity can vary greatly among individuals. A high prevalence of CHD was reported in DS children from a group where consanguinity was relatively frequent. The prevalence of congenital heart disease in children with Down syndrome is the highest reported, especially when the researchers have used diagnostic ultrasound. VSD and AVSD, followed by persistent ductus arteriosus, and tetralogy of Fallot are the most
common CHD in DS children. Recent research suggests that though the incidence of CHD in DS children has remained stable over time, there may be trends in some forms of CHD, with a rise in isolated, less severe kinds and a reduction in complicated, more severe ones. Individuals with Down syndrome can lead fulfilling lives with appropriate support and resources.

Conclusion: All neonates with a new diagnosis or suspicion of DS must undergo comprehensive screening, which includes clinical examination, ECG, and echocardiography in the second trimester combined with fetal echocardiography when the fetal ultrasonography raises the likelihood of an abnormality. Literature proves that regardless of the existence of DS, early CHD repair is advised for newborns susceptible to biventricular surgery. For the most part, DS is not linked to an increased perioperative risk for CHD.

Understanding DS heterogeneity will help professionals provide better prenatal counseling, assist parents in establishing focused early interventions to improve daily activities and the quality of life for their children, and assist policy-makers in providing and allocating resources for disability services. A sustaining commitment to scientific and clinical research studies is necessary to enhance the quality of life and survival for DS patients from infancy into adulthood.

Introduction
The most common neurodevelopmental disability with a known genetic basis, Down syndrome (Trisomy-21), was initially reported in 1866 by Dr. John Langhan Down [1]. According to reports, the incidence was 1:800 to 1:1000 [1-4]. DS affects 14 out of every 10,000 live births globally, and its frequency rises with rising maternal age. DS is clinically identified by its distinctive dysmorphic characteristics and related abnormalities. The affected children experience various congenital abnormalities, delayed physical growth, and mental impairment. [13,27,49].

Three primary types of Down syndrome exist: [1-4,19,39]

- **Trisomy 21 Due To Non-Dysjunction**
  Non-disjunction is an error during cell division that leads to DS. Non-disjunction prevents the two copies of chromosome 21 from separating.

- **Translocation**
  A second copy of chromosome 21 causes the condition known as DS. Robertsonian translocations, most often t (14;21), account for around 3% of instances of DS; other forms of translocations are extremely uncommon causes of the condition. Translocations between chromosomes 21 and 13, 14, 15, and 22 are possible. Maternal age does not affect translocation DS frequency. The chance of recurrence for carriers of translocation t(21;21) is 100%.

- **Mosaicism**
  When a child has mosaic Down syndrome, it means that:
  - Twenty cells are present; however, only 5 carry 46 chromosomes.
  - Due to an additional chromosome 21, the remaining 15 have 47 chromosomes. These infants may exhibit fewer symptoms of the syndrome than individuals with other forms of DS.

Research on DS is focused not just on HSA21, the smallest autosome, but also on deciphering intricate gene-expression pathways that give rise to characteristic DS characteristics. [4,19,31,39]

It is useful to see how this goal has been achieved. It was evident from the groundbreaking research of Lejeune et al. (1959) and others that DS was typically caused by an extra copy of a complete single chromosome, making it a trisomy. Nevertheless, there have been some fascinating cases of "partial trisomy 21" as reported by Aula et al. (1973), and "incomplete trisomy" as reported by Ilbery et al., (1961), in which a chromosome has only been partially duplicated or translocated and joined to the end of a complete 21. [4,19,39] These first results suggested that phenotypic Down syndrome might be caused by three copies of a small number of chromosome 21 genes. Niebuhr (1974) suggested that one additional copy of band 21q22 was sufficient for DS based on the new chromosomal banding techniques, while Rahmani et al. (1989) reduced the problematic area to a section less than 3 Mb long, which they referred to as the DS "critical region." To aid in identifying the genes most closely linked to the DS symptoms, additional teams joined the search and mapped a significant number of DNA...
markers throughout chromosome 21. Eight persons with partial trisomy 21 had their DNA examined by Sinet et al. (1994). Ohira et al. produced a thorough map of the area around band 21q22 and identified the upper limit of the excess material in a family with partial trisomy in 1996. After combining their findings with information from other research teams, they suggested a tiny area on chromosome 21 with 1.6 million bases (Mb). [4, 19]

After thoroughly examining several investigations, it became obvious that numerous critical areas or essential genes, rather than a single critical region gene, are more likely to be involved in trisomy 21. Understanding the genetic basis of the wide variation in DS phenotypes, according to Ganguly (in Genetics and Neurobiology of Down Syndrome, 2022), would help identify more candidate genes and analyze the effects of individual and/or combinations of alleles on HSA21 and other disomic chromosomes. The interpretation of genotype-phenotype associations would be further complicated by genetic variances at the population or ethnic level. [4,38]

The Down syndrome phenotype exhibits a great degree of intra- and inter-individual heterogeneity. Thus, thinking of DS as only an additional copy of chromosome 21 would be oversimplified, given the wide range of individual characteristics that DS manifests at so many levels. Several more genetic, epigenetic, and environmental variables influence an individual’s expression of the DS phenotype [40]. Thus, making the case that the only method that enables the definition of accurate personal DS profiles is an interdisciplinary one. [14,59]

The typical DS behaviors (facial dysmorphologies, inherited and/or acquired medical disorders, rapid...
aging, early start of Alzheimer's disease in adults, and intellectual disability) are taken from the long-standing norm in DS research, which treats DS afflicted as a homogenous group and compares phenotypic results to physical or neurodevelopmental diseases [4,19,59]. This conventional belief has altered due to recent research showing a wide range of diversity across DS patients regarding the prevalence and severity of symptoms, supporting DS heterogeneity rather than a single "DS profile." [4,19,59] This mini-review offers a succinct update on the body of knowledge about the variability of DS from a full-spectrum physical and cardiac viewpoint.

Understanding DS heterogeneity will help professionals provide better prenatal counseling. It will also assist parents in establishing focused early interventions to further improve their children's daily activities and quality of life [40,59].

Objectives
1. To do a scoping review of Down syndrome's physical features
2. To do a scoping review of Down syndrome's cardiac anomalies.

Clinical Features
As multiple systems are impacted by Down syndrome, many health disorders are linked to it. A wide range of symptoms and indicators are present in these people, including developmental and cognitive difficulties, sensorineural characteristics, congenital heart problems, gastrointestinal (GI) abnormalities, and distinctive facial traits. [4,19,34,39,43,49,64]

- The dramatic drop in the frequency of Down syndrome can be explained by the consistent association between prenatal diagnosis and birthrate that Huete-Garcia et al., (2021), found. Second, their review also found that the increase of reproductive services in healthcare systems and older mother ages were related to a modestly greater prevalence of Down syndrome. Thirdly, they illustrated the ubiquity of using congenital birth defect registries as the primary data source and the murky link between territorial and socio-cultural characteristics.
- Gender ratio: Publications of Down syndrome reveal skewed demographics towards males worldwide. [5, 13,26,38,52]
- Literature proves that most (79%) of patients' hospital stays began before they became one year old. [60] The risk of readmission is higher for children with Down syndrome than for other children as reported by Hughes-McCormack et al., (2020), and hospital admissions become less common as people become older [4,5,13,38,46,55,58,60]. The main causes of hospital admissions were malformations, respiratory illnesses, and illnesses of the neurological system or sensory organs. [5,13,38,46,55,58]
- Maternal age and Down Syndrome [5]: People from various racial and socioeconomic backgrounds can get DS. According to the National Down Syndrome Society, as the mother gets older, the risk rises (1 in 1250 for a woman who is 25 years old, 1 in 1000 at age 31, 1 in 400 at age 35, and around 1 in 100 at age 40). 91.6% of DS infants were born to mothers aged 20 to 35, while 8.4% were delivered to mothers above 35. [5,13,55]. Kava et al. (2004) have stated that the average maternal age at birth of the affected child was 26.8 years [60]; Muthumania P. (2019), reported that the mean maternal age was 28.6 years [38]; Das, et al. (2018), reported that the mean maternal age was 27.6 years [13]; Narayanan et al. reported a mean maternal age of 29.7 years [39]; and Erika et al., (2009) reported the mothers' age as 32.0 ± 8.6 years [55]. However, mothers under 35 give birth to 80% of kids with Down syndrome because they give birth more frequently. In a second pregnancy, there is a significantly increased chance of developing translocation Down syndrome [3,52,58,67].
- Growth: Compared to typical newborns, DS babies have smaller birth weights, lengths, and head circumferences. Newborns with DS frequently weigh 0.18 to 0.37 kg less than their siblings [12,43,49,57]. The mean length at birth is almost 0.5 standard deviations lower than in control infants [12,57]. Growth characteristics were lowered in a study of 105 children with DS compared to controls, and they stayed lower until puberty (age 11 for boys and 9.5 for females) [12,57]. Male growth in height and weight has improved over the first three years of life since the 1980s.
- Short stature: DS children develop more slowly than regular kids do, especially between infancy and puberty. The largest development retardation is seen in children with severe congenital heart dysfunction [4,12,57]. People with DS had average heights of 61.7 and 57 inches (157 and 144 cm), respectively, and average weights of 157 and 140 lb (71 and 64 kg), according to a 1998 study [4,49,57].
- What causes growth retardation in DS patients is still a mystery. It has been demonstrated that certain people have low amounts of growth hormone (GH), and insulin-like growth factor 1 (IGF-1), [3,19] While hypothalamic dysfunction has been associated with inadequate endogenous GH production, children with DS do not exhibit low blood GH levels [5,19,39]. IGF-1 insufficiency has been identified in patients with DS older than two years but not IGF-2 deficiency. IGF-1 receptors are present in the brain tissue of fetuses with trisomy 21 [19].
- Obesity: DS has a greater prevalence of obesity than the general population (defined as a body mass index [BMI] >27.8 kg/m2 for adult men and >27.3 kg/m2 for adult women) (45 vs. 33 percent, 56 vs. 36 percent, respectively, for males and females).
This is thought to be caused by DS children and adults’ decreased resting metabolic rates [13,52]. By the time they are three or four years old, most children with DS are fat. In babies with DS, weight is often lower than expected for length before developing disproportionally [5,12,13,54,57].

- **DYSMORPHIC FEATURES** - Brachycephaly, upslanting palpebral fissures, and epicanthic folds are most commonly present in DS. Each of the other defining dysmorphic characteristics of DS is present between 47 and 82 percent of individuals. Kathryn et al., (2023) report that these characteristics most commonly affect the head, neck, and limbs [52].

  - Characteristic dysmorphic head and neck features of DS include:
    - **Upslanting palpebral fissures:** reported in 86% of the research cohort by Muthumania P., (2019); in 92.9% of the research cohort by Das, et al., (2018); in 93.5% of the research cohort by Erika et. al., (2009); in 83.9% of the research cohort by Kava et al., (2004); and in 83% of the research cohort by Ahmed et al., (2005). [5,13,38,55,60]
    - **Epicanthic folds:** reported in 61% of the research cohort by Muthumania P., (2019); in 91.3% of the research cohort by Das, et al., (2018); in 79% of the research cohort by Erika et. al., (2009); in 56.9% of the research cohort by Kava et al., (2004); and in 63% of the research cohort by Ahmed et al., (2005). [5,13,38,55,60]
    - **Flat facial profile/flat nasal bridge:** reported in 88.5% of the research cohort by Muthumania P., (2019); in 78.6% of the research cohort by Das, et al., (2018) in 98.4% of the research cohort by Erika et al., (2009); and in 50.9% of the research cohort by Ahmed et al., (2005). [13,38,55,60]
    - **Folded or dysplastic ears:** reported in 46% of the research cohort by Das, et al., (2018); in 40.3% of the research cohort by Erika et al., (2009). [13,55]
    - **Low-set small ears:** reported in 83.9% of the research cohort by Muthumania P., (2019); in 44.4% of the research cohort by Das, et.al., (2018); and in 32.3% of the research cohort by Erika et. al., (2009). [13,38,55]
    - **Brachycephaly:** reported in 80.6% of the research cohort by Muthumania P., (2019); in 22.2% of the research cohort by Das, et al., (2018); in 98.2% of the research cohort by Erika et. al., (2009); and in 40% of the research cohort by Ahmed et al., (2005) [13,27,38,55]
    - **Brushfield spots:** reported in 85% of blue or hazel-eyed patients with trisomy 21 by Langan et al., (2002), and in 2.4% of the research cohort by Das, et al., (2018); [5,13]
    - **Open mouth:** reported in 47.85% of the research cohort by Erika et. al., (2009). [55]
    - **Protruding tongue:** reported in 56% of the research cohort by Muthumania P., (2019); in 29.4% of the research cohort by Das, et al., (2018); in 33.9% of the research cohort by Erika et al., (2009); and in 29.9% of the research cohort by Kava et al., (2004). [5,13,38,55,60]
    - **Furrowed tongue:** reported in 19.4% of the research cohort by Erika et al., (2009). [55]
    - **Short neck:** reported in 83.9% of the research cohort by Erika et al., (2009); and in 36.7% of the research cohort by Ahmed et al., (2005). [27,55]
    - **Cleft lip:** reported in 7.1% of the research cohort by Das et al., (2018). [13]
    - **Cleft palate:** reported in 80.6% of the research cohort by Muthumania P., (2019); [38]
    - **Narrow/high palate:** reported in 1.6% of the research cohort by Das et al., (2008). [13]
    - **Downward-oriented corners of the mouth:** reported in 85.5% of the research cohort by Erika et al., (2009). [55]
    - **Micrognathia:** reported in 83.9% of the research cohort by Erika et al., (2009). [55]
    - **Wide neck:** reported in 78.7% of the research cohort by Erika et al., (2009). [55]
    - **Sandal gap sign:** reported in 42.1% of the research cohort by Das et al., (2018); in 64.5% of the research cohort by Erika et al., (2009); 46.2% of the research cohort by Kava et al., (2004); and in 46.4% of the research cohort by Ahmed et al., (2005). [13,27,55,60]
    - **Microcephaly:** reported in 60.7% of the research cohort by Erika et al., (2009); and in 61% of the research cohort by Ahmed et al., (2005). [27,55]
    - **Tooth alterations:** reported in 44.7% of the research cohort by Erika et al., (2009). [55]
Flat occiput: reported in 83.9% of the research cohort by Erika et al., (2009). [55]
Cutis marmorata: reported in 70% of the research cohort by Erika et al., (2009). [55]

Ophthalmic features included
- Hyperelorism was reported in 21.8% of the research cohort by Muthumania P., (2019); in 31.7% of the research cohort by Das, et al., (2018); in 72.6% of the research cohort by Erika et al., (2009); in 33.9% of the research cohort by Kava et al., (2004); and in 62.4 of the research cohort by Ahmed et al., (2005). [13,27,38,55]
- Nystagmus was reported in 5.7% of the research cohort by Muthumania P., (2019); in 3.2% of the research cohort by Das, et al., (2018); and in 24.2% of the research cohort by Erika et al., (2009). [13,38,55]
- Refractory errors were reported in 10.3% of the research cohort by Muthumania P., (2019); [38]
- Strabismus: was reported in 2.4% of the research cohort by Das, et al., (2018); in 16.4% of the research cohort by Erika et al., (2009); in 2.7% of the research cohort by Kava et al., (2004); in 6.4% of the research cohort by Ahmed et al., (2005). [13,27,55,60]

Limbal anomalies included
- Clinodactyly was reported in 57.5% of the research cohort by Muthumania P., (2019); in 36.5% of the research cohort by Das, et al., (2018); in 46.7% of the research cohort by Erika et al., (2009); in 36.1% of the research cohort by Kava et al., (2004); and in 24.7% of the research cohort by Ahmed et al., (2005). [13,27,55,60]
- Simian crease was reported in 71.3% of the research cohort by Muthumania P., (2019); in 33.3% of the research cohort by Das, et al., (2018); in 83.9% of the research cohort by Erika et al., (2009); in 33.2% of the research cohort by Kava et al., 2004; and in 64.7% of the research cohort by Ahmed et al., (2005). [13,27,38,55]
- Brachydactyly was reported in 39.1% of the research cohort by Muthumania P., (2019); in 37.3% of the research cohort by Das, et al., (2018); in 80.6% of the research cohort by Erika et al., (2009); in 11.1% of the research cohort by Kava et al., (2004); and in 23.7% of the research cohort by Ahmed et al., (2005). [13,27,38,55,60]
- Sandal gap sign: was reported in 49.4% of the research cohort by Muthumania P., (2019); and in 64.5% of the research cohort by Erika et. al., (2009). [38,55]
- Kennedy crease was reported in 13.8% of the research cohort by Muthumania P., (2019) and in 53.2% of the research cohort by Das, et al., (2018); [13,38]
- Hypotonia was present in 70.1% of the research cohort as reported by Muthumania P., (2019), in 64.3% of the research cohort by Das, et al., (2018); in 93.4% of the research cohort by Erika et al., (2009); in 76.3% of the research cohort by Kava et al., (2004), in 55.9% of the research cohort by Ahmed et al., (2005). [13,27,38,55,60]
- Short hands: was reported in 68.9% of the research cohort by Erika et. al., (2009). [55]
- Wide feet: was reported in 66.1% of the research cohort by Erika et. al., (2009). [55]
- Plantar crease between first and second toe: was reported in 41.9% of the research cohort by Erika et al., (2009). [55]
- Nail hypoplasia: was reported in 11.5% of the research cohort by Erika et al., (2009). [55]
- Sydney line; reported in 24.6% of the research cohort by Das, et al., (2018); [13]
- Increased ATD angle reported in 40.5% of the research cohort by Das, et al., (2018); [13]

Short, wide hands, an incurved fifth finger with a hypoplastic middle phalanx, a transverse palmar wrinkle, a space between the first and second toes (sandal gap), and hyperflexibility of joints are typical dysmorphic symptoms of DS that affect the extremities including delay in motor development and poor Moro reflex. [4,5,12,13,25,27,38,55,57,

NEONATAL traits: According to Hall’s criteria [5,13,25,38,52], infants with Down syndrome are commonly recognized soon after
Cardiovascular Disease

According to the literature, cardiac abnormalities are frequent in Down syndrome, ranging from 30 to 65% [4,19,39]. In the thirteen mentioned below, the researchers discovered that the overall prevalence of CHD in DS patients born between the early 1970s and 2015 ranged from 20 to 57.9%, with a mean of 44.8%. [4,19,37]

The literature identifies the following main lesions listed below in various studies (see Table 1 in Appendix 1).

Discussion

The probability of CHD is 40–50 times higher in those with DS than in the general population [4,14,30,33,47]. Cardiac anomalies are prevalent in DS, with reported incidences ranging from 23% to 79%, varying in time and place in published research [6,7,14,19,21,33,36,47,49,50,58]. In diagnostic ultrasonography research, CHD is observed in 29% to 56% of DS patients with karyotype-confirmed cases [20,37,42,49,66]. According to research, the prevalence of CHD in DS children hasn’t changed much over time [6,7,14,26,28,53,61-64], however, it does seem to be rising lately [53,66]. In the research where DS patients were exposed to echocardiographic assessment, even without any symptom, physical sign, ECG, or chest X-ray abnormalities to suggest CHD, the incidence has been reported higher. [6,14,19,31,66,68]. This fact is consistent with the hypothesis that the increasing rates of cardiac defects are related to improved ascertainment of these defects in the population, inclusion in studies of minor CHD lesions, such as closing or small patent ductus arteriosus, maternal risk characteristics, and also because of the underreporting of CHD in the neonatal and pediatric surveillance system [6,20,30,32,49,50,66,67-69].

According to Bergström et al., 2016, there has been a shift in the distribution of CHD in DS over time, with a recent trend towards simpler lesions. There may be a bias in favor of higher survival rates for straightforward lesions, but there may also be a correlation between a higher incidence of prenatal diagnosis and a higher chance of pregnancy termination for more complex disorders [65,66,68]. One echocardiogram in adult life is recommended; as literature reports, at an average age of 20, mitral valve prolapse developed in 46% and aortic regurgitation in 6% of 35 patients with DS [6,22,23,63-66]. Compared to primipara, the frequency of CHD was considerably greater in children of women with parities of 2, 3, and 4 and more [6,38,39]. An elevated CHD risk was linked to parental consanguinity, passive mother smoking, prenatal infection, maternal diabetes, maternal obesity, and a lack of folic acid/multivitamin supplementation [2,3,7,33,58]. Low birth weight was the only variable related to children’s demographics linked to an increased risk of CHD. [23]

According to Torfs et al., heart problems made up the largest category of all anomalies, occurring 108 times more frequently in people with Down syndrome than in people without the condition. The Ventricular Septal Defect was the most prevalent overall, occurring 1000 times more frequently in those with Down syndrome than in people without the condition. [56]

CHD in DS varies in kind and character across various geographic regions, locally and globally. Literature proves that the most common isolated CHD defects were VSD, AVSD, and ASD. Patent ductus arteriosus and tetralogy of Fallot were next in frequency. [6,7,13,17,15,20,23,28,36,39,41]. Frequently encountered common multiple anomalies were VSD + PDA and VSD + ASD [6-8,11,13 17-18,15,20,23,28,36,39,41-45,51-52,55]. In the western countries, AVSD and VSD were the most prevalent. [18]

In India, different studies have reported AVSD, VSD, and ASD in varying proportions [36,38,39]. However, PDA was most prevalent in Pakistan and Ethiopia [68], and valvular affections were reported in Pakistan and Mexico. It is confirmed in a study that more than half of the fetuses with Down syndrome bear a CHD, which is an AVSD in 44% of cases. [42]. According to reports, it is linked to a non-Hsa21 CRELD1 gene mutation [4,41]. Most children who underwent echocardiography for heart abnormalities had Trisomy 21 had non-disjunction, followed by mosaicism and translocation karyotypes [2,6,8,28,39,48-51,66]. The DS gene CRELD1 (cysteine-rich EGF-like domain1) is involved in the development of AVSD located on chromosome 3p25 [5,39].
Pulmonary arterial hypertension (PAH), Eisenmenger syndrome, Left Superior vena cava (LSVC), pulmonary stenosis (PS), Coarctation of the aorta (CoA), partial anomalous pulmonary venous connection (PAPVC), double outlet right ventricle (DORV), patent foramen ovale (PFO), mitral valve prolapse (MVP), and cardiomegaly were the other miscellaneous anomalies reported by the researchers in lower frequencies. [6,9,13,15,17,21,23,36,48]. Venugopalan et al. reported that Trisomy 21 has no significant role in the pathogenesis of complex heart diseases. The kind of CHD described in the studies varies widely across the included papers. The location and year of the studies that offered longitudinal data varied, and it was unclear if or how the frequency of particular forms of CHD (severe or complicated) was evolving.

CHD, in Harm Velvis’s opinion, is a risk factor for survival in people with Down syndrome. Between 1973 and 1980, 24% of deaths in Sweden (10-year mortality) were related to CHD, whereas 5% did not. When it came to DS, in Japan in 1997, the 25-year survival rate was 92% for those without CHD, 75% for those with CHD, 88% for those with CHD with surgery, and 41% for those without surgery. The majority of recent investigations show that Down syndrome is not a risk factor for surgical mortality [14,24,28,35,44,47,62,67]. Among 801 AVSD repairs in Down syndrome performed in Sweden between 1973 and 1997, the 5-year survival rate was 65% from 1973–77 and 90% from 1993–97. Of the group of 256 children with DS, 104 (40.6%) had surgical therapy, according to Narayanan et al. (2014), with remarkable intermediate-term results [7, 39]. The kind of CHD, clinical presentation, and comorbidities determined the type and timing of surgery or intervention needed for people with DS and CHD. Assuming adequate hemodynamics and anatomy, CHD was either palliated or ultimately corrected surgically or percutaneously (44%-89% of patients). [10,28,44]. The early primary cardiac reconstruction group had a decreased mortality rate compared to the groups receiving palliation along with reconstruction or only palliative treatment. The findings show that following an early primary reconstructive operation, the life expectancy of children with Down syndrome and congenital heart disease is equal to that of Down syndrome children without cardiac problems. [10,24,28,29,35,44,47,61,62]. Children with and without DS experience similar levels of postoperative morbidity, including the length of intubation, admission to the critical care unit, and overall length of hospital stay. However, compared to those without DS, mortality is greater in those with DS and single ventricle physiology. [11,14,16,18,24,28,35,44,47,62], DS is linked to a high prevalence of imbalanced AVSD, a diagnosis that may call for several procedures (either catheter-driven or surgical), culminating in a Fontan-type procedure to treat the single ventricle. [14,24,65]. Mathew et al. concluded that mortality remains high in patients treated nonsurgically due to the development of pulmonary vascular disease and congestive heart failure. Cardiovascular transplantation and single ventricle palliation were the treatment options for these individuals [14,28,62].

Even though pulmonary hypertension is generally linked with high rates of cardiac and respiratory comorbidities that impact its severity, children with pulmonary hypertension associated with Down syndrome often have a survival rate similar to those of children with pulmonary hypertension without this association. Though less frequently in kids with complicated respiratory comorbidities, pulmonary hypertension frequently settles. [63,65]

Clinical Implications

All neonates with a new diagnosis or suspicion of DS must undergo comprehensive screening, which includes clinical examination, ECG, and echocardiography due to the high risk of CHD. Screening of fetuses with suspected or confirmed Down syndrome must be done in the second trimester in health systems having access to obstetric ultrasonography screening combined with fetal echocardiography when the fetal ultrasonography raises the likelihood of an abnormality.
If DS and CHD are discovered during pregnancy, a delivery strategy should be developed with professional assistance to address the lesions and difficulties related to CHD. The care of all patients with DS and CHD should be sent to an expert center; the kind and timing of repair will depend on the type of CHD, the patient’s clinical presentation, and their risk of developing PH.

Regardless of the existence of DS, early CHD repair is advised for newborns susceptible to biventricular surgery. For the most part, DS is not linked to an increased perioperative risk for CHD. Even though they have a greater perioperative risk than people without DS, people with DS and single ventricle physiology should be administered Fontan-palliation when appropriate. Every person with DS and CHD has to have their PH levels checked, both before and on a recurrent basis following CHD repair. To determine the diagnosis of PH, its causes, and the best course of treatment, expertise is needed.

The clinical care of individuals with DS and CHD requires research, with a particular emphasis on early diagnosis, person-centered follow-up, health-related quality of life evaluation, and when to perform percutaneous or surgical procedures. Research methods should be designed and implemented using a multidisciplinary approach that considers intellectual disability, and individuals with DS should be included with informed permission in randomized trials and other investigations, including national and international registries.

The scoping review may be interpreted with caution, given the study’s confounding variables that emerged during the scoping review:

- The information used in each study varied; some used registration data, while others examined medical records.
- Some studies have classified both the entire atrioventricular canal and endocardial cushion defect as AVSD.
- The methodology used to count CHD varied throughout research; some reported data in terms of patients, while others presented results in terms of defects, some studies categorized CHD according to several criteria, such as the size of the VSD, primary or secondary, isolated or complicated, right- or left-sided, and severity of the condition.
- Studies may contain selection bias; for instance, the prevalence of severe CHD in single-center research from a stipulated clinic may be erroneously high if patients with DS are more likely to visit the clinic.
- The frequency, diagnosis, and treatment of CHD in DS may have changed throughout time due to several causes. E.g., advancements in echocardiography technology and the accessibility of cardiac testing, advancements in cardiac care, and overall surgical results for CHD over time. The number of babies born with DS may be impacted by the number of elective terminations performed, the availability and uptake of prenatal diagnosis of DS, racial and ethnic makeup of the population. To enable comparisons across research, it would be helpful to have a uniform nomenclature or methodology when discussing CHD in DS for some of the confounding factors, such as naming, diagnosing, numbering, grouping, and selecting cases.

Conclusion

A common method of diagnosing DS is prenatal screening. If not, DS is often identified by the newborn’s distinctive phenotypic characteristics. If genetic testing is feasible, it should be used to confirm a clinical diagnosis of DS. The head, neck, and limbs are the main areas affected by the distinctive dysmorphic traits of DS. Newborns with Down syndrome frequently have ten of the typical dysmorphic traits, which are typically identified shortly after birth. Flat facial profile, slanted fissures in the palpebra, abnormal ears, hypotonia, a poor Moro response, hypoplasia of the fifth finger middle phalanx, Simian transverse palmar crease, excess skin around the nape of the neck, hyperflexibility of the joints, pelvic dysplasia.

The prevalence of congenital heart disease in children with Down syndrome is the highest reported. VSD and AVSD are the most common CHD in DS children. A high prevalence of CHD was observed in DS children from a group where consanguinity was relatively frequent. A relative scarcity of a few CHD conditions is observed as AS, CoA, TGA, and complex CHD. However, for many years, CHD has continued to be a frequently existing co-occurring syndrome in DS. While not all studies support it, recent research suggests that there may be trends in some forms of CHD, with a rise in isolated, less severe kinds and a reduction in complicated, more severe ones. Sustaining commitment to scientific and clinical research studies is necessary to enhance the quality of life and survival for DS patients from infancy into adulthood. Future research should ideally be population-based, longitudinal, multinational, adhere to standard nomenclature, and take into consideration variables that affect the prevalence and severity of CHD.

References


Hypertension in Children with Down Syndrome. J and Risk Factors for Developing Pulmonary

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### Table 1: The Most Common Lesions in Down Syndrome

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<tbody>
<tr>
<td>CHD Frequency</td>
<td>44%</td>
<td>60%</td>
<td>58.8%</td>
<td>-</td>
<td>56.9%</td>
<td>-</td>
<td>54%</td>
<td>36.9%</td>
<td>-</td>
<td>70.1%</td>
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<td>52.1%</td>
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<tr>
<td>Complete atrio-ventricular septal defect (CAVSD)</td>
<td>45% (with/without other CHD)</td>
<td>27.7%</td>
<td>8.7%</td>
<td>37%</td>
<td>-</td>
<td>9.4%</td>
<td>24.73%</td>
<td>42%</td>
<td>16.4%</td>
<td>-</td>
<td>-</td>
<td>22.6%</td>
<td>23.4%</td>
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<tr>
<td>Endocardial cushion defect</td>
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<td>7.9%</td>
<td>4.6%</td>
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<tr>
<td>Ventricular septal defect (VSD)</td>
<td>35% (with/without other CHD)</td>
<td>25.9%</td>
<td>22%</td>
<td>31%</td>
<td>28.1%</td>
<td>19.3%</td>
<td>21.5%</td>
<td>22%</td>
<td>39.8%</td>
<td>7.9%</td>
<td>16.1%</td>
<td>50.9%</td>
<td>35%</td>
</tr>
<tr>
<td>Secundum ASD/ASD</td>
<td>8%</td>
<td>33.3%</td>
<td>24%</td>
<td>15%</td>
<td>27.3%</td>
<td>30.5%</td>
<td>19.9%</td>
<td>16%</td>
<td>12.6%</td>
<td>4%</td>
<td>4%</td>
<td>81.1%</td>
<td>31.8%</td>
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<td>Partial atrio-ventricular septal defect (PAVSD)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6%</td>
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<td>7.3%</td>
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<td>4%</td>
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<td>3.2%</td>
<td>9.4%</td>
<td>5%</td>
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<tr>
<td>Tetralogy of Fallot (TOF)</td>
<td>4%</td>
<td>1.9%</td>
<td>-</td>
<td>5%</td>
<td>-</td>
<td>2.5%</td>
<td>5.4%</td>
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<td>4%</td>
<td>3.2%</td>
<td>9.4%</td>
<td>5%</td>
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<tr>
<td>PDA</td>
<td>7%</td>
<td>9.3%</td>
<td>21%</td>
<td>4%</td>
<td>16.8%</td>
<td>17.5%</td>
<td>16.7%</td>
<td>-</td>
<td>4.4%</td>
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<td>10.3%</td>
<td>67.9%</td>
<td>3.6%</td>
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<tr>
<td>Miscellaneus</td>
<td>1%</td>
<td>1.9%</td>
<td>(pulmonary stenosis)</td>
<td>-</td>
<td>2% (including coarctation of</td>
<td>CoA-0.5%, DORV-0.5%, TGA-0.3%</td>
<td>Single ventricle-0.3%</td>
<td>-</td>
<td>PFO-3.6%, CoA-0.5%, PS-0.3%</td>
<td>DORV-0.3%, dextrocardia-0.16</td>
<td>1.6%</td>
<td>(Eisenmenger complex)</td>
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<tr>
<td>Children having more than one anomaly</td>
<td>-</td>
<td>11.1%</td>
<td>26%</td>
<td>23% (commonest additional)</td>
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<td>25.9%</td>
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<td>21.6%</td>
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<td>57.5%</td>
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<td>Diagnoses were ASD and PDA.</td>
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<td>Median age at diagnoses</td>
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<td>One year of age (range, 0-13 years)</td>
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<td>One month (range 0-203 months)</td>
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<td>28.6 months</td>
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**Note:** LSVC- Left Superior vena cava, PS- pulmonary stenosis, CoA-Coarctation of aorta, PAPVC-partial anomalous pulmonary venous connection, DORV-double outlet right ventricle, PFO-patent foramen ovale, MVP-mitral valve prolapse; CMe-cardiomegaly