Pattern of cardiac affection among Down Syndrome pediatric patients attending Assiut University Children Hospital

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Abstract

Aim: The study aims to evaluate the pattern of cardiac affection among Down Syndrome pediatric patients.

Methods: A case series study included 102 children was conducted in tertiary University Hospital between Feburary 2022 and June 2023. The questionnaire was used including the socio-demographic characteristics, nutritional history, motor development, mental and social development and examination.

Results: The current study recruited a total of 102 children with Down syndrome. A total of (45.1%) patients had clinically cardiac affection and (54.90%) without cardiac affection. The participiants majority were < 1 years old (63.7%), males (58.8%) and majority of patients came from rural areas (87.3%). Majority of mothers were multiparous (27.45%) The current study found that advanced age of the mother not a risk factor for occurrence of Down syndrome as the study reveal median maternal age 35.5(18-50) and had Down syndrome child. In the current study was found that Breast Feeding was fairly common in those children (31.4%) but with no significant difference between those with cardiac affection and those without cardiac affection. Both groups had insignificant differences as regard demographic, obstetric and comorbidities with exception of residence where majority of both groups came from rural areas with higher frequency of rural residency among those without cardiac affection (94.65 vs. 78.3%; p= 0.01). In the current study found that the most frequency cardiac lesions were ASD with VSD that present in (45.7%) children, isolated ASD (15.2%), isolated VSD (6.5%) and VSD& PFO (6.5%).

Conclusions: Both cardiac and non cardiac DS children had insignificant differences as regard demographic, nutritional and anthropometric measurements. Primary health care has become essential to help these persons have longer, more productive lives with more attention to growth is recommended.

Trial registration: ASMPCOSP, NCT05056285. Registered 24 August 2022, https://classic.clinicaltrials.gov/ct2/show/NCT05056285.

Introduction

Down syndrome (DS) is the most common genomic disorder of intellectual disability and is caused by trisomy of *Homo sapiens* chromosome 21 (HSA21). The eponym of the syndrome is from Down, who described the clinical aspects of the syndrome in 1866[1]. CHDs occur in ~50% of individuals with DS, most commonly AVSD (42% of CHDs in individuals with DS), ventricular septal defect (22%) and atrial septal defect (16%) [6]. Although the frequency of the specific type of CHD depends on age and ethnicity, the primary point is that CHDs have a severe effect on the quality of life of the individual [3].

During pregnancy, a fetal echocardiography examination is recommended. A cardiology examination should take place postnatally, and another echocardiography examination should be performed within the first month after birth. Management is the same as for the general population, including surgical repair.[3]. The mortality rate after surgery in children with DS is equal to or lower than that in the general population. All individuals with DS should have annual screening throughout life for signs of acquired valve disease and heart failure [4].

Children with Down syndrome (DS) have lower birth weights and grow more slowly than children without DS. Advances in and increased access to medical care have improved the health and well-being of individuals with DS; however, it is unknown whether their growth has also improved [5].

During the first two years of life, children with DS are characterized by reduced body weight [5], which may result from suction/swallowing disorders associated with muscle hypotonia and dysfunctions in the oral motor system. In underweight children the weight for the height it’s a good measurement tool for controlling them. After the second year of life, the occurrence of overweight and obesity in children with DS is more frequent than in the general population (the prevalence of obesity at the level of 30-50%), thereby increased BMI is common in DS [6].

Statural growth, as an indicator of development, often represents a child's health status. The growth retardation of children with DS commences prenatally. Morris et al. [7]. After birth, the growth velocity is most reduced between 6 months and 3 years of age. Short stature is a phenotype of DS and can be influenced by genetic components and other factors, such as comorbidities. Styles et al. [8]

Material and methods

A case series study was conducted in Assiut university children hospital and Assiut University Cardiology Hospital. This study was conducted in the period from February 2022 to June 2023.

(The Inclusion criteria) were All Down Syndrome children attended Assiut University Hospital and Assiut University Cardiology Hospital aged less than four years were included in the study.

Ethical considerations:

The study adhered to the regulations of Assiut University's Ethical Committee and approved by the committee with approval number (IRB No :17101640).

Data collection:

The data were collected by a semistructured questitionnaire that was divided into six sections: **The first section:** included the demographic data of the child as: name, age, sex, residence, birth order, telephone number. **The second section:** included questitions about marital history as: Educational level, mother`s work, age at the patient birth, antenatal care and folic acid supplementation, , history of chronic illness before or during pregnancy, history of rubella infection during pregnancy, consanguainity, passive smoking during the first trimester, weight of the mother before pregnancy.

The third section: included questition about nutritional history: **At first year of life:** Breast feeding, formula feeding, how much is given, number of meals per day, when the solid food or cereals are introduced, content of food, any food allergy, history of

chronic illness. **After first year of life:** Animal protein source (milk, milk product, egg, meat, fish), Legumes and cereals (beans, lentils, peas, wheat, rice), Vegetables and fruits (carrots, potatoes, tomatoes, orange, pear). **The fourth section:** included: **General examination** was done including vital signs (pulse, blood pressure, respiratory rate, temperature), skin color (pallor, cyanosis) and any skin abnormalities (scars, pigmentation)and the charactertistic features(flattened face especially the bridge of the nose, almond-shaped eyes that slant up, short neck, small ears, tongue that tend to stick out of the mouth, small hands and feet, a single line across the palm of the hand(palmar crease)small pinky fingers that sometimes curve toward the thumb). Local examination included chest, heart, abdominal examination, neurological examination and anthropometric measurments; weight, height\length, head circumference, weight for height, BMI and mid arm circumference [5].

Statistical analysis:

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). The Shapiro test was used to determine compliance of the data to normal distribution.

Quantitative data with normal distribution are expressed as mean ± standard deviation (SD) and compared with Student t test. Quantitative data with abnormal distribution expressed as median (minimum-maximum) and compared by Mann-Whitney U test was used. Nominal data are given as number (n) and percentage (%). Chi^2 test was implemented on such data. Level of confidence was kept at 95% and hence, *P* value was considered significant if < 0.05

Results:

102 Down syndrome children were included in the study. The mean age of enrolled patients was 1.03 years with range between 0.10 and 3.8 years old. Majority of patients (63.7%) were < 1 years old, More than half 58.8% were males and 87.3% came from rural areas. 44.1% of mothers were illiterate while 47.1% and 9.8% mothers had primary and

secondary/university educational level, respectively. Only five patients had family history of Down syndrome. **(**Table 1)

Regarding nutritional data, the total of 26.47% children weren't breast fed while 31.37 % and 42.15 % children were exclusive breast feeding and non-exclusive breast feeding, respectively. Also, 69.60% children received formula feeding. Frequency of formula feeding was 1-3, 3-4, 4-5 and > 5 meals/day in 21.12 %, 32.39 %, 18.30 % and 28.16% children, respectively. (Table 2)

The majority were normal except mid arm circumference 50.72% were classified as under nutrition and 47.82% were normal. (Table 3 Figure 1-4)

Based on clinical evaluation; 45.1% patients had clinically cardiac affection (cardiac group) and 54.9% patients had clinically free cardiac examination (non-cardiac group). (Figure 5)

Both groups of patients had insignificant differences as regard baseline data (p> 0.05) with exception of residence where majority of both groups came from rural areas with higher frequency of rural residency among those without cardiac affection (94.65 vs. 78.3%; p= 0.01). (Table 4)

Both groups of patients had insignificant differences as regard nutritional data (p> 0.05) (Table 5)

Both of patients had insignificant differences as regard anthropometric measurements (p> 0.05) (Table6)

The majority of cardiac children had atrial septal defect and ventricular septal defect 21(45.65%) (Table7)

Discussion

Down syndrome (DS) is an autosomal trisomy 21 and is one of the most frequently occurring chromosomal abnormalities. DS occurs once in every 600 to 800 live births and is frequently associated with congenital heart disease (CHD). The incidence of CHDs increases from 0.8% in the general population to approximately 40%-65% in patients with DS. At the same time, children with DS comprise approximately 10% of all children with CHD [9] [10].

In our study the majority of patients was < 1 years old (63.7%), males (58.8%) and came from rural areas (87.3%). Majority of mothers were multiparous (27.45%) this agree with previous studies from Egypt, Iran and India reported the birth order of children with Down Syndrome ranged from 1 to 9 [11].

As regard mother's educational level; 44 (44.1%) mothers were illiterate while 48 (47.1%) and 10 (9.8%) mothers had primary and secondary/university educational level, respectively. Only five patients had family history of Down syndrome.

Shalaby et al.,2011 [12]. reported that consanguineous marriage, parental residence location (rural\urban) parental educational status, father`s behaviors and mother`s reproductive success are probable risk factors for Down syndrome.

The current study found that advanced age of the mother not a risk factor for occurrence of Down syndrome as the study reveal median maternal age 35.5(18-50) and had Down syndrome child partially agree with this study [13].

The possible explanation of younger mothers having child with Down Syndrome are likely to be sleep deprived, had imbalanced diet in order not to too much weight and often unintended pregnancies which are all leading to bad pregnancy habits [14].

In the current study was found that Breast Feeding was fairly common in those children (31.4%) but of no significant value between those with cardiac affection and those without cardiac affection. de Oliveira Agostini et al found a high prevalence of breastfeeding in children with Down syndrome and congenital heart disease, since 80.6% received breast milk [15].

Results similar to these data are already described in previous studies carried out with children with Down syndrome, but without heart disease [16] [17].

DS is associated with intellectual disability, congenital malformations (especially of the heart), dysmorphic features, and dysfunction of several other organs. Short stature is a characteristic feature of DS. Growth retardation of DS individuals starts prenatally. After birth, the growth velocity is most reduced between 6 months to 3 years. Growth charts specific for children with DS are important tools for routine medical follow-up, as well as early identification of pathological causes of growth retardation, and monitoring of growth promoting treatments [18].

Children with DS tend to have lower levels of physical activity practice compared to their healthy peers and, consequently, are at a higher risk to become overweight obese and suffer from detrimental effects on health-related outcomes. Sedentary behavior and excessive fat mass exacerbated the risk of developing co-morbidities and mortality. In children with DS, lower physical activity levels and overweight/obesity conditions contribute to a decrease in the acquisition of motor skills [19].

Meguid et al.,2004 published a report on growth curves of 350 patients with DS, 90 of them had congenital heart disorders. Their study was carried out between January 1999 and July 2001 and their charts were plotted as 3rd, 50th, and 97th centiles from 0–36 months for male and female patients. In comparison with Meguid et al.,2004 there was a statistically non-significant increase in all anthropometric measurements in most age groups [20].

The current study recruited a total of 102 children with Down syndrome. The main findings in the current study were; 1) a total of 46 (45.1%) patients had clinically cardiac affection and 56 (54.90%) without cardiac affection, 2) both groups had insignificant differences as regard demographic, obstetric and comorbidities with exception of residence where majority of both groups came from rural areas with higher frequency of rural residency among those without cardiac affection (94.65 vs. 78.3%; p= 0.01).

The effect of maternal age on the association of CHD and DS is unclear; some studies reported a greater risk for CHDs in young mothers, whereas others observed no maternal age effect [21] [22]. The current study did not find any association between maternal age and the CHDs in our DS children.

A total of 16 (29.4%) children had positive consanguinity but the current study observed no effect of consanguineous mating on the occurrence of CHDs in DS in disagreement with the previous Egyptian Studies. The low frequency of consanguineous mating in urban compared to rural areas, and the decline of consanguineous mating during the past decades may be possible explanations [23] [24] [25].

In the current study there were only 5 (4.90%) children had positive family history of DS with no significant difference between both subgroups. Chéhab et al previously showed that the risk of congenital cardiac anomalies in children with DS was not associated with the parents' consanguinity; instead, having a maternal age above 32 years was more associated with a lesser occurrence of congenital cardiac anomalies in children with DS [26].

With regard to food, the current study found insignificant nutritional history in both subgroups of patients. Down syndrome alone causes anatomical, physiological and behavioral conditions that can hamper the eating process, making it a tiring and unsuccessful act. In addition, these children tend to show aversion and refusal to eat, as well as delayed motor development and often swallowing disorders, making parents more insecure in relation to the supply of solid foods [27] [28].

The most frequently lesions were ASD/ VSD (45.65%) and ASD alone (15.21%). A previous study conducted among 722 with DS reported that; 93.6% were standard trisomy, 4.7% carried a Robertsonian translocation, and 1.7% were mosaics. The age ranged from 2 days to 18 years. The male/female ratio was 1.2. A CHD was present in 426 cases representing 59% of the total [29].

Previous Egyptian studies have reported lower values from DS with CHDs ranging from 36.9% to 40% [23] [24]. Although the frequency of CHDs in DS is lower in the current study compared to previous from Lebanon (54.2%), Saudi Arabia (58.6%), Iraq (53%), Norway (58%), and Mexico (58%) [26] [30] [31].

In the current study found that the most frequant cardiac lesions were ASD with VSD that present in 21 (45.7%) children, isolated ASD (15.2%), isolated VSD (6.5%) and VSD& PFO (6.5%). Geographical differences in the pattern of CHDs in DS have been reported; AVSD is more common in Western countries [30] [21] [32].

In Egypt, ASD, VSD, and AVSD were reported to be the most prevalent CHD in 3 different studies [23] [24] [33].

Other studies from Saudi Arabia, Algeria, and Morocco, reporting AVSD was the most prevalent CHD in their DS patients and research from Iraq where VSD was the most common CHD among Iraqi DS patients [9] [34] [35] [31].

Another study by stoll et al 2015, had Cardiac anomalies in44%, with the most common cardiac anomaly was atrioventricular septal defect (30%), followed by ASD (25%), VSD (22%), patent ductus arteriosus (5%), coarctation of aorta (5%), and tetralogy of Fallot (3%) [36] [33].

Such malformations include all structural and functional cardiac defects present at birth, even if discovered later in life. These malformations can be single or multiple and usually lead to significant implications for the children and their families. These children may develop congestive heart failure, pulmonary vascular disease, pneumonia, or failure to thrive. CHDs are the most common cause of death in children with DS during the first two years of life [37].

Atrioventricular septal defects (AVSD; with or without other CHD) and ventricular septal defects (VSD; with or without other CHD) have both been reported as the most common congenital heart defects and make up approximately 45% and 35% of CHD associated with DS, respectively [38] [39].

DS tends to be associated with the more severe forms of endocardial cushion defect, while the inlet VSD is common in trisomy 21. Several cardiac lesions seen in the non-DS population are rarely if ever found in individuals with DS, e.g., heterotaxy, aortic coarctation or transposition of the great arteries [40].

As trisomy 21 is insufficient to cause CHD, factors contributing to the association of CHD and DS are currently being investigated. One proposed contributing factor recently addressed is gender [41] [22]. In agreement with studies from Libya, we observed

a higher frequency of CHD in the female gender (p=0.03, OR: 1.393, IC: 1.032 to 1.880), implying that this gender is more susceptible to CHD in DS patients. In the present study, AVSD and ASD were more prevalent in females. These results are in accordance with previous studies [21] [41] [22]. We did not observe a sex difference in the prevalence of VSD in agreement with a meta-analysis including 12 publications [41] [22] [42].

The mechanism by which gender contributes to the association of CHD and DS remains to be elucidated. One proposed explanation is that gender differences may reflect a different susceptibility of gender to different CHD pathogenetic pathways; AVSD and ASD prevalent in females are an extracellular matrix anomaly whereas TOF more common in males is an ecto-mesenchymal tissue migration anomaly [41].

On the other hand, PDA was the most common cardiac malformation observed in Guatemalan children with DS, followed by VSD, ASD and then AVSD. The most common cardiac malformations in Mexican children with DS were ASD, VSD and PDA, while the AVSDs were less common than the other malformations [43] [44].

While a defect of the atrioventricular canal remains the most common heart malformation in children with DS, the type of associated CHD may be affected by various factors. For example, the parents' consanguinity status could affect the pattern of CHDs [45].

These differences between the types of CHD in DS and non-DS populations could suggest the impact of a third copy of a gene or genes on chromosome 21 on only specific developmental points [46].

Conclusions:

Consanguineous marriage, parental residence (rural\urban) parental educational status, father`s behaviors and mother`s reproductive success are probable risk factors for Down syndrome. Advanced maternal age is associated with DS. Both cardiac and non cardiac DS children had insignificant differences as regard demographic except residence.

Recommendations:

-Provide attention to Down Syndrome children and their associated problems for improvement in growth.

-Maintenance of optimal health is a major factor in the lifelong functioning of children with Down Syndrome.

-Research for development of Growth charts for children with Down Syndrome in Egypt to be a local reference.

List of abbreviations: **ASD**: Atrial septal defect, **AVSDs:** Atrioventricular septal defects **Complete AVCanal**: Complete atrioventricular canal **CHDs:** Congenital heart defects **DS:** Down Syndrome **HSA21:** Homo sapiens chromosome 21**PDA**: Patent ductus arteriosus, **PFO**: Patent foramen oval **VSD**: Ventricular septal defect.

Ethical approval and consent to participate:

The study adhered to the regulations of Assiut University's Ethical Committee and approved by the committee with approval number (IRB No :17101640).

Consent for publications:

not applicable

availability of data and materials:

The data sets generated and or analyzed during the current study are available from the corresponding author on reasonable request.

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the authors declare that they have no competing interests.

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