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Article

Causes of Hospitalization in Children with Down Syndrome

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Abstract: *Background and Objectives:* Down syndrome (DS) is the most common chromosomal disorder in the world. It is caused by the imbalance of the chromosomal constitution of 21, by free trisomy, translocation or mosaicism. Children and adolescents with Down syndrome have immune dysregulation and are more susceptible to infections. This study aims to evaluate hospitalizations of children and adolescents with DS in the pediatric ward of Botucatu Clinics Hospital (HCFMB), to classify the population of children included in the study regarding age, diagnosis, outpatient follow-up, length of stay and need for Intensive Care Unit (ICU). Thus, it will be possible to improve care for these children, aiming to reduce these hospitalizations. *Materials and Methods:* It was an observational, cross-sectional study, with retrospective data collection from the last 10 years of hospitalization, from January 2013 to December 2021, of children and adolescents with DS, in the pediatric ward, emergency room and ICU of HCFMB. Children hospitalized in this period in the pediatric ward and ICU, in the age range of 30 days to 15 years (age of acceptance for admission to this service) were included in this study. Those who at some point had the exclusion of the diagnosis of DS were excluded. The evaluation of comorbidities that culminated in the need for hospitalization in this population can be the focus of actions to improve diagnoses and conducts for this population, to prevent worsening and hospitalizations in future populations. *Results:* The statistical analysis of the data was performed. In this analysis, 80 children with DS were evaluated, with a total of 283 hospitalizations and it was noticed that 46 of them had more than one hospitalization in this period. The most prevalent age group was 1 to 3 years, and the main cause was due to problems in respiratory system (99 cases). Among respiratory causes, the main cause of hospitalization was due to pneumonia, in 50% of cases, followed by acute respiratory failure, in 14%. The average hospitalization time was 8 days and in 49 hospitalizations the children required the ICU. The main cause of hospitalization in the ICU was due to respiratory causes (36%), followed by cardiac malformations (14%). During the ICU hospitalizations, there were 13 deaths, and we observed a higher prevalence of heart conditions and, in some cases, positive urine cultures in these children. *Conclusions:* preventive actions, such as vaccinations and improved monitoring of these children, without outpatient follow-up or during hospitalization, should be carried out. Thus, it has been developed a proposal for a risk score for mortality in children and adolescents with DS admitted to the ICU, and those patients with five or more points should be monitored more closely. A meeting will be held with the genetics, cardiology, and pediatric ICU teams to discuss this score and propose a surveillance plan for these patients at the HCFMB and potentially for the pediatric community in the future.

Keywords: down syndrome; children; hospitalization; health evaluation

1. Introduction

Down syndrome (DS) is the most common chromosomal abnormality in the population with an estimated incidence of 1 in 700 live births. Children who have the condition are predisposed to have several comorbidities that interfere with their growth and development [1–3].

DS is a genetic anomaly characterized by an extra chromosome at position 21 in 92 to 95% of patients. In addition, DS may also be the result of mosaicism in 2 to 4% of patients or translocations in 3 to 4% of cases [1]. According to data from the Brazilian Ministry of Health, a child is born with DS in every 600 to 800 births, regardless of ethnicity, sex, or social class [4].

Children and adolescents with DS present with cardiovascular, endocrine, respiratory, and musculoskeletal disorders. Patients with Down syndrome is more predisposed to autoimmune diseases, including type 1 diabetes mellitus, alopecia areata, vitiligo, and celiac disease [5]. Therefore, they should have multidisciplinary and multiprofessional outpatient follow-up.

In children and adolescents with Down syndrome, the maturation of T cells in the thymus is aberrant. They exhibit a reduced response to antigens since they produce fewer molecules essential for the recognition of T cell-specific antigens [6]. It is observed that during the early years of life in a child with Down syndrome, there is a lesser increase in B and T lymphocytes, suggesting a disturbance of the adaptive immune system [7]. In these children, there is a decrease in the production of active oxygen derivatives, which affects the ability of leukocytes to destroy harmful agents. Consequently, they exhibit immune dysregulation and are more susceptible to infections [8].

Among hospitalizations of these children, according to a study by Soares et al., 50% are due to respiratory problems. This occurs due to the multiple comorbidities associated with Down syndrome, such as obstructive sleep apnea syndrome (OSAS), lower airway diseases, congenital heart diseases, relative obesity, hypotonia, pulmonary hypertension, pulmonary hypoplasia, upper airway obstruction, immunodeficiencies, among others. Thus, in addition to being more susceptible to hospitalization, they spend more time in the hospital environment and require ventilatory support disproportionate to the disease [9].

From 2020 to 2022, Brazil and the world experienced the COVID-19 pandemic caused by the SARS-CoV-2 virus [10]. Children with Down syndrome exhibit markers of chronic autoimmunity, including high levels of pro-inflammatory cytokines and chemokines. The additional comorbidities found in these children, such as congenital heart disease and obstructive sleep apnea syndrome (OSAS), combined with this pro-inflammatory condition, may exacerbate the infection by the SARS-CoV-2 virus. Therefore, the pediatric community suggests that these children should be more closely monitored due to their increased risk [11]. Treatment flowcharts have been proposed for children with Down syndrome and COVID-19, including those proposed by Bambino Gesù Children's Hospital in Norway, indicating the need for hospitalization or otherwise [12].

The Botucatu Clinical Hospital (HCFMB), which provides comprehensive care to patients of the Unified Health System (SUS), is an autarchic entity linked to the São Paulo State Department of Health. It serves 68 municipalities within the Regional Health Directorate (DRS VI) – Bauru. The HCFMB's service area is estimated to encompass 2 million people. The Pediatric Ward and the Pediatric Intensive Care Unit (PICU) are responsible for inpatient beds and cater to infants, children, and adolescents.

The present study aimed to identify the main causes of hospitalization in children and adolescents with Down syndrome at the Botucatu Clinical Hospital over the past 9 years, aiming to identify gaps in care that could be improved to prevent some of these admissions and provide comprehensive care for children with DS.

2. Materials and Methods

It was an observational, cross-sectional study, with retrospective data collection from the last nine years of hospitalization, from January 2013 to December 2021, of children and adolescents with DS, in the pediatric wards of HCFMB and other sectors, including emergency room referenced Unesp (ER), pediatric ICU (PICU). The local Research Ethics Committee approved the study under protocol CAAE no. 47934121.2.0000.5411.

2.1. Eligibility Criteria and Sample Size

All hospitalizations of children and adolescents diagnosed with DS at any point during care were included, encompassing infants, children and adolescents aged 30 days up to 15 years of age

(age of acceptance for admission to this service). Children who do not have Down syndrome were excluded.

The consolidated data were provided by a management report in the HCFMB Information System, from January 2013 to December 2021, a total of 80 children with DS were hospitalized, of which 46 had more than one hospitalization, totaling 283 hospitalizations analyzed.

Diagnoses were sought from the International Disease Code (ICD), 10th Revision (ICD-10), as shown in Table S1.

From this database, the information considered in the study was: primary care diagnosis according to the International Code of Diseases (ICD), 10th Revision, 2nd edition [13], recorded in care - Classified according to the 12 chapters of the Tabulation List of Morbidity for the SUS (ICD-10); total length of stay (in days); place of admission - pediatric ward, ICU and pediatric emergency ward. In a single hospitalization, children can stay in more than one different unit, depending on whether intensive care is needed or not. Other information taken into consideration included: patient's age - classifying them according to age groups, as per classification of the Ministry of Health (SUS), being under one year of age (A); between one and three years of age (B); between four and nine years (C) and greater than or equal to ten years (D) [14]; gender; city of origin - distinguishing between Botucatu and the municipalities within the DRS-VI, and the municipalities from other DRS; laboratory tests, including karyotype and requested imaging exams; resources utilized during hospitalization, as laboratory and imaging tests or surgery; need for oxygen support or need for invasive or non-invasive ventilation in the ICU; death or not during hospitalization.

2.2. Statistical Analysis

The database was built directly in an Excel spreadsheet, and statistical analysis was carried out using the Statistical Analysis System (SAS), version 9.2; with descriptive analyzes of the studied population extracting means and standard deviations. Chi-square test and Student's t test were used, with a significance level of 5% ($p < 0.05$) [15].

3. Results

The average length of stay was eight days, with the shortest period being 1 and the longest being 251 days, with a median of four days. These children were analyzed according to sex and age group, with 52% being female and a higher incidence of hospitalizations in the age group between one and three years of age. In age group A (under one year old) there were 54 (19%), in B (one to three years old) 130 (46%), in C (four to nine years old) 88 (31%) and in D (over ten years old) 11 children (4%). The origin of the hospitalized children was 143 (59%) from Botucatu, the municipality in which the HCFMB is located, and from other municipalities belonging to the health region (DRS VI), totaling 85%, with the other 15% coming from other regions.

The causes of hospitalization were grouped according to the ICD-10 Chapters, with the main cause of hospitalization being those related to the respiratory system, as shown in chart S2. The main cause of hospitalization was due to diseases of the respiratory system (35%), followed by other infectious diseases (10%), malformations and congenital anomalies (9%) and digestive system (8%).

Among the diseases classified by ICD-10 of the respiratory system, the most common causes were pneumonia (49 hospitalizations, 50%), followed by acute respiratory failure (14 hospitalizations, 14%). Regarding ICD-10 of other infectious diseases, the most common causes were unspecified bacterial infections (10 hospitalizations, 35%) and acute diarrhea and gastroenterocolitis (8 hospitalizations, 28%). Among the ICD-10 chapter on malformations, the most prevalent were cardiac malformations (12 hospitalizations, 44%) and ectopic testicles (5 hospitalizations, 18%).

Out of the total of 283 hospitalizations analyzed, 82 (29%) of these were in the intensive care unit (ICU). These hospitalizations occurred for 62 children. Of these hospitalizations, 21 children were initially admitted to the PS, totaling 26% of ICU admissions. In data analysis, the number of hospitalizations is considered, not the number of children admitted to the ICU.

The resources used during hospitalization in the emergency room, ward or ICU were classified as: oxygen support (venturi mask, face mask, O₂ catheter), use of antibiotics, chemotherapy or other medications, carrying out laboratory and imaging tests, and are identified in Chart S3.

3.1. Admissions to the pediatric ICU at HCFMB

The average length of stay in the ICU was 24 days. The main cause of hospitalization was respiratory diseases (23 hospitalizations, 28%), with 12% (10 hospitalizations) due to acute respiratory failure and 16% (13 hospitalizations) due to bacterial pneumonia. The second main cause was for cardiac malformation correction (12 hospitalizations, 14%), with 10% (8 hospitalizations) for AVSD correction and 4% (3 hospitalizations) for VSD correction.

Regarding the resources used during ICU admissions, 58 (71%) children had the diagnosis confirmed by karyotype, out of 22 (27%) the karyotype did not appear in the hospital system, and in two (2%) hospitalizations, it was not possible to obtain this data. Of these patients, 65% underwent an echocardiogram, an important test in the diagnosis of cardiac malformations.

Regarding ventilatory support, 35 of the hospitalizations required mechanical ventilation and 29 of them were on non-invasive ventilation. It must be considered that the same patient may use more ventilatory support according to their needs, therefore it is not possible to count this as a percentage (graph S4).

As shown in Table S5, out of the surgeries performed ten (23%) were due to ophthalmological causes. HCFMB is one of the few reference services for the treatment of congenital cataracts in the state of Sao Paulo. Of the other surgeries performed, nine (19%) were for correction of cardiac malformations and five (10%) to correct otorhinolaryngological causes in the DS population.

An unfavorable outcome of hospitalizations is death, with 13 (15,9%) fatalities recorded in this study, all of which occurred during ICU admission.

3.2. Characterization of the Children Who Died

The average age of children who died was 7.8 months (SD=6.6), with no statistically significant difference with those who did not die ($p=0.37$). The median was 7 months, with a maximum age of deaths being 21 months (1 year and 9 months).

The most prevalent comorbidities in these patients were cardiac malformations, followed by thyroid, ophthalmic, pulmonary, and gastrointestinal tract diseases (Table S6). The average length of stay was 33 days, with a median of 10 days, with a minimum of 2 days and a maximum of 224 days.

There was a statistically significant relationship between deaths and urine culture results (Chart S7), with four children who died having positive urine cultures. Blood culture results were not statistically significant.

In the analysis of the distribution of admissions and deaths of children admitted to the pediatric ICU, according to the year of occurrence, a higher concentration of these two events can be observed in the years 2019 to 2021, with 27 ICU admissions (39%), and 54% of deaths ($n=7$), as it shown in Table S8.

4. Discussion

Patients admitted with Down Syndrome (DS) totaled 283 hospitalizations in this study, with 29% of them (82 hospitalizations) requiring intensive care in the ICU. Considering the resources used during hospitalization, 35 of them required mechanical ventilation. Considering that children with DS have other associated comorbidities, such as cardiac and endocrinological malformations, they require greater attention in their care, often requiring intensive care, as shown by the present study [16].

It was found that, regardless of age group, the main causes of hospitalizations were respiratory diseases (5.8 million, 21% of hospitalizations), as seen in this study. In the Ministry's analysis, it is also possible to verify that the age group with the highest number of hospitalizations was those under four years of age, as was also proven in this work. On the other hand, deaths, according to the

SIH/SUS, were more prevalent in children under one year of age (55%), mainly due to conditions originating in the perinatal period. In this study, the mean age at death was seven months, and comorbidities associated with Down syndrome should be considered as responsible for early death in these children [1,2], incompatible with current technologies for monitoring and treating them in Brazil, as this scenario has been undergoing transformations and advances in medicine, especially genetics and cardiology, have contributed to substantially changing the statistics. Specialists linked to the Brazilian Society of Cardiology (SBC) affirm that regarding prognosis, the survival of these children has significantly increased in the last three decades [17].

Among the comorbidities that justified hospitalization and even surgical intervention in the children in this study, congenital cataracts should be highlighted. A child with Down syndrome must undergo an ophthalmological evaluation, and may present numerous alterations, including oblique palpebral fissure, epicanthus, supernumerary vessels, blepharitis, myopia, hyperopia, nystagmus and congenital cataract [18]. Congenital cataracts in DS that require a surgical approach have a low incidence, but an increase in frequency with age can be observed [19]. According to the literature, most patients who require a bilateral ophthalmological approach are over 3 years old and there is an association between cataracts and strabismus and nystagmus, which delays their diagnosis [20]. Furthermore, these children are at greater risk of developing post-surgical complications, such as capsular opacification and retinal detachment [21], which justifies the need for referral to congenital cataract reference centers for ophthalmological and surgical evaluation, as is the case with HCFMB.

According to the literature, children with DS may have multiple organs and systems compromised. However, the most associated congenital malformation is of cardiac origin, with 40% to 60% of individuals with Down syndrome affected [22]. It is the main cause of morbidity and mortality in the first 2 years of these children's lives [23]. Those with congenital heart disease have low weight gain, with longer ICU stay [24]. Furthermore, female sex associated with congenital heart disease is related to a higher risk of death in hospitals [25].

Cardiac malformation was the main comorbidity associated with death and it was the second most prevalent cause of ICU admission. Analyzing the hospitalizations of children and adolescents with congenital heart diseases, it is possible to verify the predominance of those belonging to families with unfavorable socioeconomic conditions, which corroborates the need for public policies to promote health for these children [26]. Echocardiogram is an important test in the diagnosis of cardiac malformations. However, only 65% of patients admitted in this study underwent it. Furthermore, only 58 children (71%) had the diagnosis of DS confirmed by karyotype. Although this number is not the appropriate number expected for these children, it is important to highlight that this study was based on a consolidated database, generated by the Information System, and did not collect the medical records of each child, therefore recording data is important for assistance and also for research.

As observed in this study and confirmed by the literature, the main cause of hospitalization in children with DS is due to respiratory diseases, also in those with congenital heart disease [27]. The main respiratory disorders that affect these children and are associated with hospitalizations are upper airway obstruction, lower respiratory tract diseases, pulmonary hypertension, pulmonary hypoplasia, obstructive sleep apnea, immunodeficiency, relative obesity and hypotonia [9]. Therefore, these patients may present bronchopneumonia and progress to acute respiratory failure, corroborating the main ICD-10 hospitalizations in all sectors of pediatrics at HCFMB in the period from 2013 to 2021.

Considering this, one of the interventions to prevent new hospitalizations is vaccination. The 23-valent pneumococcal vaccine is recommended for children with DS by the Brazilian Society of Immunization and the Brazilian Society of Pediatrics [1,2] bringing scientifically proven benefits to them [28]. Palivizumab in Brazil is currently indicated for children born prematurely, with bronchopulmonary dysplasia and/or congenital heart disease. In Japan, all children with DS are vaccinated with Palivizumab, revealing a drop in Japanese DS hospitalizations due to respiratory syncytial virus – RSV [29]. The adoption of this measure could reduce the inconvenience caused by RSV during seasonal periods in this population [30].

In the present study, it was seen that from the years 2019 to 2021, there were 27 ICU admissions (39%), with a total of 7 deaths (54%), suggesting a temporal correlation with the covid-19 pandemic, with some studies finding a relationship between DS and greater severity and complications such as sepsis, the need for mechanical ventilation and severe acute respiratory distress syndrome (SARS) with covid-19 [31,32]. Therefore, covid-19 is also associated with high mortality in children with DS, even after adjusting the analysis for sociodemographic factors and comorbidities such as cardiovascular diseases present in this population [33,34]. It is described that Down syndrome increases the likelihood of hospitalization by four times and the risk of death from Covid-19 by ten times more than patients without Down syndrome.

Deaths in pediatrics can occur due to various etiologies, including infections. In the study of neonatal deaths occurring at a hospital similar to HCFMB, 66% (207) had at least one positive microbiological culture, isolating microorganisms in tracheal secretions, swabs, blood, urine and liquor [35]. One of the most important complications of cardiac surgery in patients with DS is postoperative infection, mainly associated with low weight and inadequate antibiotic prophylaxis [36].

Children with sepsis and DS have a high risk of death, even after adjusting for potentially confounding factors, such as demographics, pathogens and concomitant conditions [37]. Associations of genitourinary tract malformations with Down syndrome have been described, including glomerulonephritis, renal agenesis, microcysts, ectopic kidneys, hydronephrosis, hydroureter, posterior urethral valve, anterior urethral obstruction, and hypospadias. Some of these are associated with recurrent urinary tract infections [38]. In this study, a statistically significant correlation was observed between positive urine culture and deaths of children with DS.

Limitations of this study include reliance on a consolidated report rather than individual medical records, resulting in the absence of specific diagnoses for sepsis, septic shock, and Covid-19 confirmation. Additionally, none of the ICD-10 diagnostic codes listed in the corresponding chapters precisely matched these conditions, likely due to the temporal relationship between hospitalizations and deaths in the pediatric ICU from 2020 to 2021.

A risk score for death in children and adolescents with Down syndrome who were admitted to the ICU (table A9). According to this scoring system, patients who score five points or more are at a higher risk of mortality.

5. Conclusions

HCFMB serves as a reference for pediatric hospitalizations within its region and beyond, owing to its status as a tertiary hospital with specialized capabilities.

The main causes of hospitalization for children with DS are those related to the respiratory system. Roughly one-third of these children require admission to an intensive care unit, with a high prevalence of cardiac malformations.

It can be concluded that preventive measures, such as vaccinations, and improved monitoring of these children, both in outpatient follow-up and during hospitalizations, are essential.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Informed Consent Statement: Not applicable for these studie. We obtained an exemption from the application of the Free and Informed Consent Form.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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