

**„VICTOR BABEȘ” UNIVERSITY OF MEDICINE
AND PHARMACY
TIMIȘOARA
FACULTY OF MEDICINE
Department XI Pediatrics**

NEAMȚU (OLARIU) G. IOANA-CRISTINA



**CONGENITAL HEART DISEASE
IN PATIENTS WITH DOWN SYNDROM
– FROM DIAGNOSIS TO PROGNOSIS**

ABSTRACT

Scientific advisor

PhD PROF. DOROȘ GABRIELA SIMONA

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KEY WORDS : Down syndrome, congenital heart malformations, conditions associated with Down syndrome, metabolic syndrome.

INTRODUCTION

Down syndrome or Trisomy 21 is one of the most common genetic pathologies, which is associated with an increased risk for the development of a wide range of diseases.

In 1959, the French geneticist Jérôme Lejeune discovered that Down syndrome is caused by the presence of an additional chromosome 21, resulting in a total of 47 chromosomes. The name "Down" comes from the English physician John Langdon Haydon Down, the first to describe this syndrome in 1866, almost 100 years before this additional chromosome was discovered.

The probability of conceiving a child with Down syndrome increases with the mother's age, from less than 0.1% in the case of 20-year-old mothers, and can reach up to 3% in 45-year-old women. In Romania there are no statistics on the number of people with Down syndrome, the incidence worldwide is about 1: 600 - 800 births and taking into account our country's natality rate, it is estimated that each year are born between 235- 313 newborns with Down syndrome.

One of the major causes of morbidity and mortality in Down syndrome is congenital heart malformations. Therefore, it is important that people with Down syndrome be systematically evaluated and have access to specialist healthcare in order to anticipate, prevent or modify any complications.

In 1929 the average life expectancy of a child with trisomy 21 was 10 years, the high mortality being determined by the comorbidities that occur frequently, but also by the passive attitude of society. Today the life expectancy in patients with Down syndrome is over 65 years, mostly due to congenital heart surgery.

In the current study, a significant cohort of patients with Down syndrome was followed prospectively, both in terms of the presence and type of heart malformations and of the associations between Down syndrome and various comorbidities. The temporal relationship between the surgical interventions and the post-operative evolution of these patients was recorded. Aspects regarding the characteristics of growth and development, but also of the change of body composition were analyzed. These aspects are perceived more important as, in recent years, a connection has been made between the presence of the diagnosis of Down syndrome and the occurrence, starting with the pubertal period, of the risk of metabolic disorders that can lead to metabolic syndrome. Also for this purpose, the food intake was analyzed, through a standardized method, in order to be able to assess the degree to which the experts' recommendations regarding the nutrient intake and the macro-element composition of the diet are met.

Congenital heart defects (CHD) are some of the most common birth defects, representing a major cause of mortality and morbidity, especially in the first year of life. The association between Down syndrome and CHD is well known, the incidence of CHD in patients with Down syndrome being between 40-60%. Routine cardiac screening of all DS infants is recommended. Expert groups suggest that the heart condition of all children with DS should be established by the age of 6 weeks to allow for

appropriate and timely treatment, avoiding the onset of irreversible lung vascular disease that would make reparative surgery impossible.

Advances in cardiovascular surgery have resulted in survival in adulthood in approximately 85% of patients with CHD. The increase in the survival rates of patients with heart malformations is determined by early diagnosis, improved medical results, intensified concerns for the quality of life of children with this diagnosis. Given the growing population with such conditions into adulthood, the problems these patients face must be assessed. The quality of life from the perspective of health is a constant concern in medical practice.

CURRENT KNOWLEDGE STATUS

In this chapter, a review of current knowledge status of research on Down syndrome was made, starting from the diagnosis of Down syndrome, with the recognition of all possible conditions that can be associated with the syndrome, from simple characteristic physical features, to cardiac malformations that can be found in over 50 % of these patients. The type of chromosomal abnormality and the genes involved in various manifestations of the syndrome have been extensively researched, thus knowing the *Down syndrome critical region (DSCR)* on chromosome 21. Both the diagnosis of chromosomal abnormality and intrauterine detection of heart malformations can be done, theoretically, to a very large number of pregnancies, through active screening (screening of trimester 1 - double test, screening of trimester 2 - triple test, amniocentesis, cordocentesis, etc.). However, in Romania many pregnancies are not medically followed due to the lack of addressability of pregnant women, either for financial reasons or lack of health education.

In addition to heart malformations, patients with Down syndrome may associate extracardiac malformations, the most common being digestive malformations. A series of endocrinological, hematological, orthopedic, neurological diseases can be encountered during the life of people with Down syndrome, thus being mandatory their permanent monitoring.

Prenatal screening of chromosomal abnormalities and CHD, initiation of a national program for monitoring pregnant women with fetuses diagnosed with Down syndrome with or without CHD, then undertaking these patients to specialized centers of pediatric cardiology and pediatric cardiovascular surgery for optimal surgical treatment in order to improve the evolution and prognosis of patients with CHD leads to improved quality of life by reducing the rate of complications.

Quantitative epidemiological arguments can direct to health programs that intervene in the complexity of the interaction of predictable factors involved in the etiopathogenesis of CHD, leading to a decrease in the number of early deaths by applying specific diagnostic and treatment procedures.

THE RESEARCH PART

The research part is divided into 3 studies. The first study evaluated the epidemiological profile of pediatric patients diagnosed and followed up with Down syndrome. The study included 242 patients with Down syndrome. We evaluated the existence of heart malformations, but at the same time we noted the identified extracardiac malformations, respectively other health problems detected in this group of patients, in an attempt to establish correlations between the existence / type of medical conditions and the evolution of pediatric patients with Down syndrome.

The epidemiological study allowed the assessment of the incidence of CHD in children with Down syndrome, especially in the western part of the country, data that may motivate the introduction of national registers of these abnormalities.

Although Down syndrome is the best known chromosomal abnormality, in our country there are still many deficits in monitoring and treating patients with this diagnosis. Individuals with Down syndrome require continuous medical multidisciplinary follow-up, and are likely to develop various complications of the syndrome lifelong. Each newborn with Down syndrome should have a comprehensive medical evaluation, focusing on all possible medical problems associated with DS. Congenital heart disease may not be evident at the initial clinical examination, and appropriate cardiac screening and evaluation by pediatric cardiology experts should be initiated prior to discharge from the maternity ward. Neonatal screening by complete blood count for transient myeloproliferative disorder, ophthalmologic evaluation, audiological screening and screening of the newborn for hypothyroidism are particularly important, given the increased prevalence of cataracts, hearing loss and hypothyroidism in Down syndrome. Patients with Down syndrome have a high incidence of gastroesophageal reflux with microaspiration, recurrent respiratory infections and sleep apnea. They may present with chronic hypoxia due to upper airway obstruction in the form of tracheobronchomalacia, or subglottic stenosis. From gynecologist, geneticist, neonatologist, pediatrician, cardiologist, gastroenterologist, radiologist, ophthalmologist, ENT specialist, endocrinologist, etc., all medical specialties are involved in monitoring and treating these patients.

Working method: each case was analyzed from an anamnestic, clinical and paraclinical point of view. To establish the diagnosis of CHD the following were performed: clinical examination, electrocardiogram, transthoracic echocardiography, laboratory investigations.

In the studies performed, the data usually collected as part of the patient's clinical care were analyzed. The informed consent of the parents / legal guardians of all pediatric patients included in the study was obtained. The study was conducted in compliance with the rules of ethics set out in the Helsinki Declaration and in compliance with the rules for data protection.

The study population was divided into two groups, depending on the presence or absence of heart malformations. The first group, representing patients with DS and CHD, included 144 cases (59.5%), and the second group (patients with DS, without CHD) included 98 cases (40.5%). Of the 144 patients in group 1, 129 (89.6%) presented non-cyanogenic forms of CHD, and 15 cyanogenic forms, representing 10.4%.

Analyzing the group regarding the type of cardiovascular disease present, we found that patients were diagnosed with the following types of non-cyanogenic lesions: in the first place are the communications at the level of the interatrial septum - atrial septal defect (ASD) ostium secundum, in 44 patients (30.55%), followed by complex malformations of the atrioventricular septal defect (AVSD) - 33 cases (22.9%), defects in the interventricular septum (VSD) - in 27 (18.75%) patients, the persistent

ductus arteriosus (PDA) was viewed in 24 patients (16.6%); into a much smaller number encountered aortic coarctation (in 2 patients). Cyanogenic CHDs were detected in 15 patients (10.4%), of which 12 (8.33%) were Fallot of Tetralogy and 3 double outlet right ventricle (DORV) .

Dysplastic valvular anomalies or valvular malformations were detected in 16 patients. Twelve patients presented other cardiac malformation, rarely encountered in association with Down syndrome, (like double outlet right ventricle, coarctation of the aorta, peripheral stenosis of the branches of the pulmonary artery, left persistent superior vena cava).

Most frequent complications associated with congenital heart defects are represented by heart failure, present in 93 (64.5%) of patients, and pulmonary hypertension (PAH) in 83 (57.6%) of the patients.

High blood pressure was detected in 5 patients with Down syndrome, of which 2 with aortic coarctation, one patient developed hypertension secondary to corticotherapy following the protocol for the treatment of leukemia, and 2 patients were diagnosed with chronic kidney disease. The last 3 children did not associate CHD.

The search of extracardiac malformations and other associated comorbidities revealed a high frequency of digestive malformations (duodenal stenosis, jejunal stenosis, esophageal stenosis, annular pancreas, anal agenesis) and Hirschsprung's disease among patients with Down syndrome. A very large number of patients with DS in our study were diagnosed with thyroid pathology, 45 of them with hypothyroidism and 2 with hyperthyroidism.

Analysis of deaths in the group of children with Down syndrome. Of the 242 patients with Down syndrome, 21 died during the cohort study. Of these, 19 (90.47%) associated cardiac malformations, most with AVSD (9 patients, 44%), 4 (25%) had cyanogenic CHD (3 Tetralogy of Fallot and 1 DORV), and 6 patients presented other types of CHD. Other diseases that led to the death of patients, in much smaller numbers compared to CHD, were malignant pathologies. Neither case was associated with cardiac malformations.

The objective of the second study of this research was to analyze the atrioventricular septal defect (AVSD), the most frequent cardiac malformation described in the literature in children with Down syndrome and comparison with a sample with the same type of cardiac malformation in children without Down. The study included 31 patients with Down syndrome who associated the atrioventricular septal defect as a heart malformation, diagnosed and followed-up in the III Pediatric Clinic of the "Louis Turcanu" Hospital in Timișoara.

The anatomopathological, clinical and evolution of AVSD in children with and without Down syndrome were evaluated to establish the role of early diagnosis and optimal surgical treatment before the onset of irreversible complications.

The complete form of AVSD was more common in the Down syndrome group, with a more unfavorable prognosis, while unbalanced AVSD was predominantly observed in the group without Down. The age at diagnosis varied between 1 day and 15 years. There were no significant differences between age at diagnosis and age at surgery between the two groups, however, postoperative care for children with DS required special attention due to the risk of PAH. The postoperative results were encouraging, however, a large number of children with AVSD did not have surgery. Late diagnosis was an important risk factor for the unfavorable prognosis. Although postoperative mortality has been low, infant mortality before surgery remains high. The early diagnosis of AVSD and the surgical treatment performed at the optimal time, before the appearance of irreversible PAH, lead both to the increase of life expectancy and to the increase of the quality of life for these patients.

In the third part, a case study on the body composition and nutritional status of children with Down syndrome was conducted.

The aim of this study was to assess the nutritional status of patients with Down syndrome, who are prone to eating difficulties and inadequate energy intake, although they are often overweight compared to their peers.

The study aimed, in addition to anthropometric data, laboratory analysis, body composition analysis, investigation of nutrition by telephone interview and analysis of data obtained. According to the growth curves for age and sex, of the 242 patients with Down syndrome, 63 (26%) were underweight, 90 (37.2%) were normal weight, and 89 (37%) they were overweight or obese.

For a number of 18 children with Down syndrome, a case study was performed which analyzed the body composition by electrical bioimpedance and food intake. Of the 18 participants in the study, 7 patients also associated cardiac malformation, 11 being diagnosed with Down syndrome without CHD. It was found that the percentage of adipose tissue was higher in almost all patients evaluated. Lean tissue and muscle mass were not affected. Macronutrient intake is within the limits recommended by the European Food Safety Authority (EFSA) for carbohydrates for 61% (11) of patients and fat for 50% (9) of patients. Protein intake is suitable for the whole sample. Seven (40%) patients consume lipids above the recommended threshold. Saturated and monounsaturated fatty acids have the greatest contributions to food intake. In the analyzed group, 70% of children reach their recommended level of fiber, but none reaches their recommended water intake.

Obesity is a common condition of clinical importance and public health in many countries around the world. The most important cause of overweight and obesity in patients enrolled in the study is eating unhealthy diets (diet rich in fat and / or sugar) and lack of exercise, with the contribution of genetic susceptibility given by trisomy of chromosome 21.

GENERAL CONCLUSIONS

- Down syndrome or trisomy 21 is the most common and best studied chromosomal abnormality. It has major implications both by the association of congenital heart and extracardiac malformations, and by the multiple medical conditions and comorbidities that can occur during the life of these patients.
- Although the diagnosis of trisomy 21 can be established prenatally in 90-95% of cases, in Romania many pregnancies remain un-followed. The most common cause of non-dispensation of pregnant women is the low socio-economic level, but the low level of health education in the population has an important role.
- The diagnosis of heart malformations can be established prenatally, but for this aspect several factors are necessary. Highly trained medical staff and high performance medical equipment can contribute to this goal.
- Between January 2015 and July 2021 we conducted a study at the Emergency Clinical Hospital for Children "Louis Turcanu" Timisoara which included 242 patients aged 0-18 years, diagnosed with Down syndrome, with or without CHD associated.

- Of the 242 children in the group, only 12 had been diagnosed with prenatal Down syndrome, which makes it necessary to increase the diagnosis rate, especially by *non-invasive* methods of maternal venous blood - *non-invasive pretreatment screening (NIPS)* through which, starting with gestational age of 10 weeks of pregnancy, can be detected with an accuracy of 99.9% all fetal aneuploidies. Fetuses diagnosed with Down syndrome *in utero*, which was chosen to terminate the pregnancy, were not included in the study .
- The aim of the study was to analyze children with Down syndrome in terms of the association of heart malformations, but also other medical conditions, extracardiac malformations or comorbidities that may influence the evolution of each case.
- International guidelines recommend cardiological evaluation of all newborns with Down syndrome for screening for heart malformations in the first 2 weeks of life if they show clinical signs suggestive of CHD or have an altered ECG, and no later than 6 weeks of life in the absence of these changes.
- We started from the premise that heart malformations in patients with Down syndrome are diagnosed late by delaying the initial cardiological evaluation. An important conclusion of this study is that the diagnosis of CHD is usually established early enough (89.7% of children in the study group were evaluated cardiologicaly in the first 6 weeks of life), but the optimal operative moment is very often delayed. The age at diagnosis varied between 1 day and 15 years.
- Patients with Down syndrome associate congenital heart defects in 40-60% of cases. Our findings are consistent, and cardiac malformations were detected in 144 patients, representing 59.5% of the 242 patients evaluated.
- Although, in the literature, the most common CHD associated with Down syndrome is AVSD, in the studied group the interatrial septal defect (ASD) was the most common heart malformation, being detected in 44 cases, which represents 30.55% of all CHD diagnosed. AVSD is the second type of malformation in frequency, in 33 cases (22.9%), followed by VSD in 27 patients (18.75%), (PDA) in 24 (16.6%). Cyanogenic CHDs were diagnosed in 15 patients in the group, representing 10.4%.
- Most deaths were in patients who associated heart malformation, so 90% of deaths in the group occurred in patients with CHD (19 of 21 deaths). AVSD remains the most common cardiac malformation causes of deaths among patients with Down syndrome in the study group. A large number of children with AVSD did not receive surgery.
- The comparative analysis of AVSD cases in children with and without Down syndrome showed that the complete form of AVSD was more frequent and with a more unfavorable prognosis in cases that associated Down syndrome. There were no significant differences between the age at diagnosis and the age when surgery was performed in children with Down syndrome compared to the group of AVSD patients without Down syndrome.

- In cases that have received surgical treatment, the postoperative results have been encouraging, but postoperative care for patients with Down syndrome requires special attention due to the risk of persistence of PAH.
- Late diagnosis was an important risk factor for the unfavorable prognosis. Although postoperative mortality has been low, infant mortality before surgery remains high. The early diagnosis of CHD, especially of AVSD, and the surgical treatment performed at the optimal time, before the appearance of irreversible PAH, lead both to the increase of life expectancy and to the increase of the quality of life for these patients.
- Among the associated extracardiac malformations, in the studied group, digestive malformations were the most common. Some of these, such as duodenal stenosis or annular pancreas, required surgery in the neonatal period or in the infant period. The evolution of each patient with Down syndrome and CHD, who associates other medical conditions can be particular.
- For the corrective surgical treatment of CHD, patients are redirected to centers specializing in pediatric cardiovascular surgery in the country or abroad. Because in Romania there are few such centers, crowded by the large number of children born with CHD and requiring intervention, appointments are sometimes obtained late. The conclusion is that, for the optimal evaluation of newborns with Down syndrome, a greater number of specialists in pediatric cardiology is needed both for the diagnosis and for the monitoring of these patients. It would also be of major importance to set up new centers specializing in pediatric cardiovascular surgery or to increase the capacity of existing centers. In Timișoara, at the Institute of Cardio-Vascular Surgery, the foundations of a pediatric department are being laid, but the lack of specialists in the field delays the opening.
- Eating disorders are reported immediately postnatal and continue to negatively affect the growth and development of patients. They are mainly due to hypotonia and protrusion of the tongue through pseudomacroglossia that lead to difficulty chewing and swallowing. Food surveys have highlighted the consumption of blended foods and predominantly soft foods over the age of peers without DS.
- Children achieve the proportions recommended by EFSA for the age group and sex of protein in the diet, but in terms of fat intake, 40% of the group consume hyperlipidic diets (25% in children with CHD and 50% in those without CHD). None, on the other hand, meet the EPA and DHA or water consumption recommendation.
- A small proportion of the children studied, less than 10%, meet the EFSA criteria for the age group and sex for the nutrients involved in the metabolic cycle with a carbon atom, namely choline, betaine, folate, vitamins B6 and B12.

- The degree of compliance of the diet by age and sex with the EFSA criteria is better for children with CHD than for those who do not have these malformations. A possible explanation for this phenomenon would be the increase in mothers' knowledge through contact with health services, during repeated hospitalizations and the greater degree of compliance of families towards a healthy diet in the presence of heart malformations in these children.
- Metabolic syndrome is one of the most serious complications of Down syndrome. If until the prepubertal period, the body mass index remains within normal limits for about 80% of the children investigated, over the age of 14 the proportion of overweight and obesity reaches 40%.
- Data on percentage of fat from the body composition, showed marked changes, which precede the increase in body weight. On average, fat percentages of 43.6 +/- 14.7% were reported in girls and 22.2 +/- 3.8% in boys. For more than 90% of the patients investigated, the percentage of fat exceeds 20% of body weight, ranging from a minimum of 18.3% to a maximum of 65.5%.
- Hypotonia and ligament hyperalgesia negatively influence the level of physical activity reported by children with Down syndrome (only 1 patient being involved in regular physical activities and moderate / high intensity).

PERSPECTIVES

- The establishment of national registries for both children with congenital heart defects and patients with Down syndrome would increase the degree of monitoring and, implicitly, would improve the quality of medical care.
- Creating follow-up networks of patients with Down syndrome, through multidisciplinary, loco-regional teams, which assess the health of these patients according to specific protocols, well established, accessible to any medical specialty.
- Active prevention of metabolic syndrome through integrated nutrition counseling in follow-up. Integration of the measurement of body composition and nutritional intake can lead to both risk assessment and intervention by creating complex health education programs.