

Celiac disease in children with Down syndrome

Enfermedad celíaca en niños con síndrome de Down

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Abstract

Celiac disease (CD) in children with Down syndrome (DS) has been published by several countries, without available data for Colombia. **Objective:** To determine the frequency and related factors of CD in children with DS, compared with a group of children without DS, analyzing the clinical, immunological, and genetic manifestations. **Patients and Method:** A total of 209 children between 1-18 years of age (8.4 ± 4.1 years, 55.5% female) were studied, 97 with DS and 112 without DS, using anti-transglutaminase antibodies as serological marker (tTG2). Variables of age, gender, race, origin, weight, height, and digestive symptoms were studied. Children with positive tTG2 underwent duodenal biopsy and genotype. The proportion of children with DS, without DS, and CD was estimated and their 95% CI; measures of central tendency, univariate and bivariate analysis, considering a $p < 0.05$ significant. **Results:** Eight children with DS (8.2%) and five children without DS (4.5%) were tTG2 positive ($p = 0.200$). None presented serum IgA deficiency. One child with DS presented CD with Marsh II (1.0%), and two children with DS (2.1%) and two without DS (1.8%), presented potential CD ($p = 0.432$). Three children were HLA-DQ2. CD was more likely in the preschool group (OR = 6.14 95%CI = 0.41-87.35 $p = 0.0462$). **Conclusions:** The CD frequency due to intestinal biopsy in children with DS is much lower than that reported in the literature, being associated with preschool, and having DQ2 as its main allele. These findings are similar to those described worldwide.

Keywords:

Genotype;
celiac disease;
potential celiac disease;
Down syndrome;
children

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Introduction

Celiac disease (CD) is an immune system-mediated systemic disorder caused by gluten and related prolamins in genetically susceptible individuals, characterized by a combination of variable clinical manifestations dependent on gluten, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy¹.

The CD prevalence worldwide is between 0.1% and 5.6%². A systematic and meta-regression review conducted in Colombia concludes that CD seems to be a rare condition in Colombians³, however, a 7.1% of prevalence is reported in a group of children with type 1 diabetes mellitus, with no symptoms that suggest a risk of developing CD⁴.

Some genetic syndromes are recognized for their association with CD, such as Down syndrome (DS)⁵. The first case of a patient with DS and CD was described in 1975⁶. A prevalence between 1.6% and 13.0%⁷⁻²¹ of CD is reported in children with DS diagnosed through biopsy, with an increased risk of up to 6 times of CD in these patients²². The American Academy of Pediatrics (AAP) Guidelines on DS and CD recommend screening for CD in children with symptomatic DS²³, and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines also recommend it in asymptomatic children and adolescents at genetic risk of developing CD, such as DS¹. The CD diagnosis is made through blood analyses of specific antibodies (IgA anti-tTG2, IgA EMA, or IgA/IgG anti-DGP), HLA-DQ2/HLA-DQ8 haplotypes, and duodenal biopsy¹. Early CD detection decreases the risk of both lymphoma^{24,25} and mortality²⁶. Although the presence of CD in children with DS has already been published by several countries, there are no data on these two conditions in Colombia. The objective of this work is to determine the frequency and related factors of CD in children with DS, compared with a group of children without DS, analyzing the clinical, immunological, and genetic manifestations.

Patients and Method

Down syndrome (DS) is a genetic disorder caused by the presence of an extra copy of chromosome 21 (or part of it), rather than the usual two (trisomy 21), characterized by a variable degree of intellectual disability and characteristic physical features that give it a recognizable appearance²⁷. The CD diagnosis is confirmed when the IgA anti-transglutaminase (anti-tTG2) is positive, haplotype HLA-DQ2 and HLA-DQ8 are compatible, duodenal histopathology shows intestinal villi abnormality with a Marsh II score or higher, and a variable combination of gluten-dependent clinical ma-

nifestations is presented; and potential CD when tTG2 is positive, HLA compatible, and without histological abnormalities in the duodenal biopsy, with or without signs and symptoms¹.

A descriptive observational comparative study was conducted between May 9, 2014 and May 23, 2018 on children diagnosed with DS who attended the Pediatric Outpatient Consultation of the *Hospital Universitario del Valle 'Evaristo García'* (HUV) in Cali, Colombia, a tertiary level facility in the southwest of the country, and the *Fundar Hu-manos Down* Foundation (Fundown) in Bucaramanga, Colombia, an institution where the children with DS from the northeast of the country are treated. The inclusion criteria were children with DS diagnosis, of both sexes, aged between 6 months who had already intake gluten in their complementary diet and up to 18 years; and the exclusion criteria were children with DS with type 1 diabetes mellitus, with autoimmune diseases such as hypothyroidism, with previous diagnosis of CD, with inflammatory bowel disease, and no gluten users. A randomly selected group of children, of both sexes, aged between 6 months and 18 years, gluten users, asymptomatic, with no DS or pathologies, and no family history of CD who attended the Pediatric Outpatient Consultation of the HUV in Cali, Colombia and two Public Educational Institutions in Cali and Floridablanca, Colombia were considered as controls. Sociodemographic variables such as age, sex, race, and origin were considered as well as anthropometric variables such as weight and height. The clinical digestive variables considered were constipation, vomiting, abdominal distension, steatorrhea, diarrhea, abdominal pain, flatulence, and weight loss.

All children were screened with an IgA anti-transglutaminase (anti-tTG2) Biocard™ Celiac Test (Ani Biotech Oy, Vantaa, Finland) which has 97.4% of sensitivity and 96.9% specificity^{28,29}. Children with total IgA absence in the Celiac Test Biocard™, a blood sample was taken to analyze serum IgG anti-transglutaminase for CD. The tTG2-positive children underwent upper endoscopy with biopsy collections and HLA-DQ2/HLA-DQ8 haplotypes analysis. A minimum of 4 biopsies of the bulb and the second portion of the duodenum were collected. The biopsy material evaluation was carried out by the same pathologist after hematoxylin and eosin staining. The immunohistochemistry of the leukocyte common antigen was used for the evaluation of the intraepithelial leukocyte count, and the presence of more than 30 intraepithelial lymphocytes versus 100 epithelial cells detected by the leukocyte common antigen was considered as intraepithelial lymphocytosis^{30,31}. According to the Marsh-Oberhuber classification, the histopathology was classified as Marsh I when observing 'infiltrative lesion', as Marsh II

when observing 'infiltrative-hyperplastic lesion', and as Marsh III when observing 'villous atrophy' (partial IIIa, subtotal IIIb, and total IIIc)³². The HLA-DQ2 and HLA-DQ8 genotyping were performed through polymerase chain reaction³³.

According to age groups, they were classified as infants (< 2 years of age), preschoolers (> 2 and up to 5 years of age), schoolchildren (> 5 and up to 12 years of age), and adolescents (> 12 and up to 18 years of age). The race was classified as mixed-race, of African descent, white, and indigenous. For children without DS, according to WHO, they were classified as malnourished when the BMI-for-age and sex were affected (obesity $\geq +2$ SD, overweight between $+1$ and $+2$ SD, moderate malnutrition between -2 and -3 SD, and severe malnutrition $\geq$ or $= -3$ SD), and altered height when height-for-age (H/A) was affected (high height $\geq +3$ SD, low height between -2 and -3 SD, and severe low height ≥ -3 SD)³⁴. For children with DS, the growth charts of The Down Syndrome Growing Up Study by the U.S. Centers for Disease Control and Prevention³⁵ were considered.

In order to elaborate table 3 of the results, a search was made in the ProQuest, OvidSP, and EBS-COHOST platforms of the Electronic Library of the HUV in Cali, Colombia. Original articles between 2000 and 2017 were included whose research designs were meta-analyses, controlled clinical trials, analytical (cases and controls, and cohorts), and non-analytical (prevalence) with diagnosis of CD and DS with keywords in English (celiac disease and Down syndrome) and in Spanish (*enfermedad celiaca* and *síndrome de Down*).

By signing the informed consent and assent, parents or guardians and children over the age of 7, respectively, accepted to participate in this study, which was approved by the Ethics Committee of the HUV.

Convenience sampling was used where all children with and without DS participated, who met the study inclusion criteria, agreed to participate in the study and attended the Pediatric Outpatient Consultation at the HUV in Cali, Colombia, the Fundown in Bucaramanga, Colombia, and the Public Educational Institutions in Cali and Floridablanca, Colombia. The proportion of children with and without DS, and CD was estimated and its corresponding 95% confidence interval (CI). Out of the total of participating children, we estimated percentiles, averages, medians, and the other descriptive measures with their corresponding standard deviations and ranges, and to evaluate the possible associations, we initially carried out a univariate analysis between each of the exposure variables of interest and the effect variable. In addition, the possible association between the exposure variables of greatest interest and other covariates, and between the result

variable of interest (CD) and the other covariates, was explored in order to assess possible confusion. To this end, graphs and 2x2 tables were made, and the ORs with their respective CI (95%) were estimated. To assess statistical significance, Fisher's exact test was used, and a 2-tailed $p < 0.05$ value was considered as statistically significant.

Results

97 children with DS from the HUV in Cali, Colombia and from the Fundown in Bucaramanga, Colombia were included as controls, and 112 children without DS from the HUV in Cali, Colombia and from two Public Educational Institutions in Cali and Floridablanca, Colombia. Table 1 shows demographic, anthropometric, and clinical data of study participants. Overall, the nutritional status of children with DS was more affected than children without DS in BMI ($p=0.000$) and H/A ($p=0.000$). Although tTG2 had more positive cases in children with DS compared with control children without DS, there were no significant differences, as well as in the frequency of diagnosing CD (Table 1).

Out of the 209 children included, none presented serum IgA deficiency, 13 had positive tTG2 (6.2%), and 11 of them underwent upper endoscopy with intestinal biopsies and haplotypes HLA DQ2 and HLA DQ8; and finally, five children (3 with DS and 2 without DS) presented findings in intestinal biopsies compatible with positive immunohistochemistry and Marsh between 0 and II (Figure 1 and Table 2). These 5 children with CD diagnosed by immunohistochemistry presented in the CD3, CD8 and CD45 antibodies a number and location concordant with CD compared with appropriate controls. The patient with the biggest lesion in the biopsy was a 3-year-old girl with Marsh II score (infiltrative hyperplastic lesion) who presented 30%-40% of the lamina propria (LP) CD3 cells, up to 45 intraepithelial cells per 100 enterocytes; 10% of the LP CD8 cells, up to 40 intraepithelial cells per 100 enterocytes, and in the CD45 total lymphocytes, up to 50 intraepithelial cells per 100 enterocytes.

Table 3 shows the prevalence of CD in children with DS in different countries worldwide⁸⁻²⁰. In the association analysis, comparing children with DS ($n = 97$) and children without DS ($n = 112$), there was a greater odds ratio in infants with DS (OR = 4.54 95%CI = 1.51-16.32 $p = 0.0022$), males (OR = 3.00 95%CI = 1.64-5.51 $p = 0.0001$), and of African descent (OR = 7.76 95%CI = 1.64-72.65 $p = 0.0023$); and comparing children with CD ($n = 5$) and children without CD ($n = 204$), there was a greater odds ratio in preschoolers with CD (OR = 6.14 95%CI = 0.41-87.35 $p = 0.0462$).

Table 1. Characteristics of children with and without Down Syndrome (N=209)

	DS (n = 97)	Without DS (n = 112)
Age (years) (X+/-SD)	8.3+/-5.1	8.5+/-3.0
Groups of age (n, %) (years)		
Infant (1-2)	17 (17.5)	5 (4.5)
Toddler (2-5)	17 (17.5)	6 (5.4)
Schoolchil.dren (5-12)	40 (41.3)	91 (81.3)
Adolescent (13-18)	23 (23.7)	10 (8.9)
Sex (n, %).		
Female	40 (41.2)	76 (67.9)
Male	57 (58.8)	36 (32.1)
Origin (n, %)		
Cali	50 (51.6)	54 (48.2)
Bucaramanga	47 (48.4)	58 (51.8)
Race (n, %)		
Mestizo	59 (60.8)	42 (37.5)
White	24 (24.4)	67 (59.8)
Afro	12 (12.4)	2 (1.8)
Native	2 (2.1)	1 (0.9)
Weight (kg) (X+/-SD)	28.5+/-16.8	32.9+/-14.7
Height (cm) (X+/-SD)	114.5+/-27.0	130.4+/-20.8
Nutritional status	(n=93)	(n=90)
Malnutrition according to BMI (n, %)		
No	56 (60.2)	34 (37.8)
Yes	37 (39.8)	56 (62.2)
Altered height according to HA (n, %)		
No	42 (45.2)	85 (94.4)
Yes	51 (54.8)	5 (5.6)
tTG2 (n, %)		
Negative	89 (91.8)	107 (95.5)
Positive	8 (8.2)	5 (4.5)
Celiac disease (including potential CD) (n, %)		
No	94 (96.9)	110 (98.2)
Yes	3 (3.1)	2 (1.8)

DS = Down syndrome; X = mean; SD = standard deviation; kg = kilograms; cm = centimeters; BMI = body mass index; HA = height/age; tTG2 = anti-transglutaminase antibodies; CD = celiac disease.

Discussion

This is the first study that shows the CD frequency in children with and without DS in Colombia. Although there is a higher CD frequency (including potential CD) diagnosed by both tTG2 (8.2% vs 4.5%, $p=0.334$) and histopathology (3.1% vs 1.8%, $p=0.432$) in children with DS compared with children without DS, this cannot be inferred nor confirmed through the results of this study.

When comparing this frequency with the prevalence in other Latin American countries, it is possible to

observe that it is very similar to the results of Rumbo et al²¹, who reported 3.6% of prevalence in Argentine children with DS, however, their histopathological description is defined as a severe enteropathy and they do not use the Marsh classification nor do they report the control group data, and it is much lower than that described by Gomes et al⁷ in Brazilian children with DS, who reported 13.0% of prevalence. Globally, the CD prevalence in children with DS diagnosed by biopsy ranges from 1.6% to 11.0% (Table 3)⁸⁻²⁰.

There were no significant differences in screening to identify CD through tTG2 (8.2% children with DS versus 4.5% children without DS; $p=0.200$). These findings are different from those reported by Nishiha et al³⁶, who in Brazilian children with DS found a 17.5% seroprevalence of tTG2 versus 0.0% in children without DS ($p<0.001$). This positive tTG2 seroprevalence in other countries ranges from 5.2% to 31.8% (Table 3) in children with DS^{8,9,12-17,37}. When analyzing the 5 children without DS and positive tTG2, we found that when asked about digestive symptoms, 3 of them presented constipation, 2 abdominal pain, and 1 diarrhea with steatorrhea which could indicate selection bias and that this population of children without DS was not completely asymptomatic. However, when studying the intestinal biopsies and haplotype of these 5 children without DS, only in 2 of them it was possible to identify CD, and were classified as potential CD, which by definition according to ESPGHAN, are children who do not present intestinal villi atrophy, who may or may not present symptoms, and who may or may not develop CD in the future¹. Regarding other serological markers, such as AGA and EMA, CD seroprevalence in children with DS ranges from 6.7% to 41.0%^{8,9,12-17,37} and 0.0% to 14.3%, respectively (Table 3)^{8,11-20,38}. Some authors recommend the use of tTG2 to identify CD in children with DS^{16,39,40}, as was done in this study, however, it should be stressed that the AAP suggests screening for CD in symptomatic children with DS²³, while ESPGHAN recommends it in asymptomatic children and adolescents at genetic risk of developing it¹.

Most of the children with DS and CD in this study present positive HLA-DQ2, similar to that reported by Book et al³⁸ in the United States, by Wouters et al¹⁵ in the Netherlands, and by Rodríguez et al¹³ in Spain, from which we are descendants (Table 3). It should be noted that in southwestern Colombia, one of the regions where this study was carried out, the allele most frequently found is HLA-DQ2 at 25.3%⁴¹ which are the most common in the Colombian population⁴²⁻⁴⁴.

The results of frequency, tTG2 seropositivity, and CD genotype variability in children with DS in this study, in Latin American and worldwide, may be due, among others, to regional differences, age and

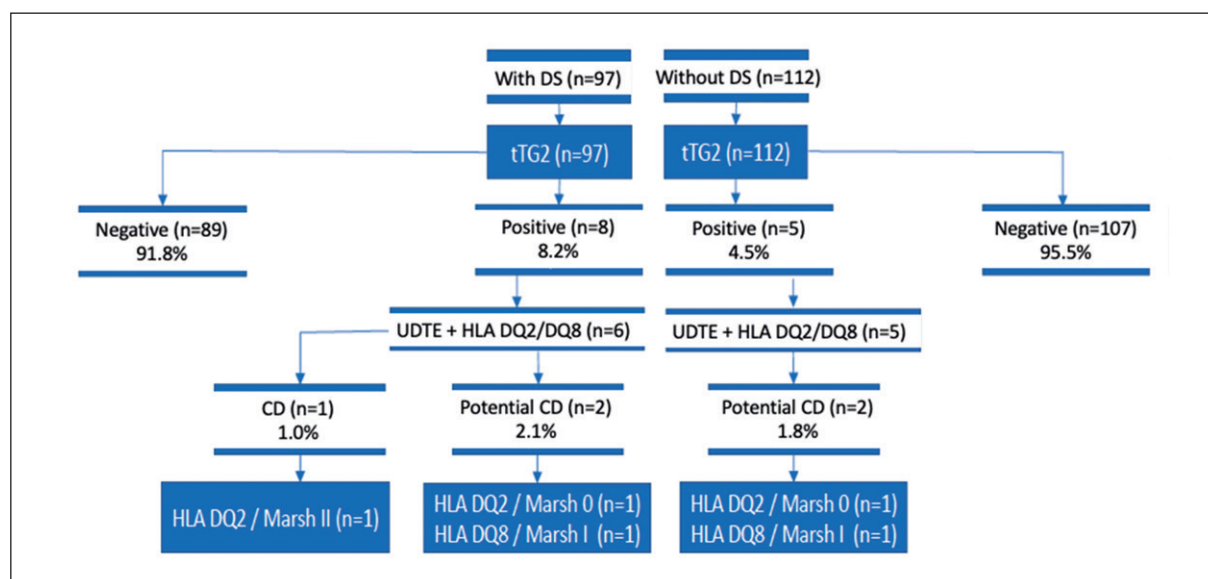


Figure 1. Enrollment flowchart and inclusion of children with and without Down syndrome. DS=Down syndrome; tTG2=anti-transglutaminase antibodies; UDTE=upper digestive tract endoscopy; HLA=antigens of histocompatibility; DQ=serotyping system; CD=disease celiac; n=number

Table 2. Characteristics of children with Celiac disease (n = 5)

Age (years)	Sex	Race	Digestive symptoms	Nutritional diagnosis	Immunohistochemistry			Marsh	HLA	Dx
					CD3	CD8	CD45			
3	F	White	Steatorrhea Constipation	Low height	++	+	+++	II	DQ2	CD with DS
1	M	White	Flat Vomiting Constipation	Normal	++	+	+++	I	DQ8	Potential CD with DS
5	F	Mestizo	Flat Abdominal distention Abdominal pain Constipation	Low height	++	+	+++	0	DQ2	Potential CD with DS
10	M	White	No	Normal	++	+	+++	I	DQ8	Potential CD with DS
7	M	Mestizo	Constipation Hyporexia	Normal	+	+	++	0	DQ2	Potential CD with DS

F = female; M = male; HLA = histocompatibility antigen; Dx = diagnosis; CD = celiac disease; DS = Down syndrome; CD = cluster of differentiation antigen; DQ = serotyping system

sex distributions, genetic characteristics, indications, symptoms, the timing and repetition of screening tests performed on these children, and the different criteria used for the CD diagnosis.

In this study, despite reporting 1.8 times more likely to have CD in children with DS than in children without DS (95%CI 0.19-21.30), it was not statistically significant ($p=0.5374$). Other authors have reported

increased risk of CD in individuals with DS compared with individuals without DS, such as Marild et al²² in Sweden (OR=6.2 95%CI=5.09-7.43 $p<0.05$), whose national study included 65,636 individuals. We do not seek associations between CD, DS, and heart diseases or diet, however, some authors have failed in finding these associations as Noori et al³⁷ in children with DS with and without congenital heart disease, and as Ro-

Table 3. Prevalence of Celiac disease in children with Down syndrome

Author, country	n	Age (years)	Prevalence
AlRuwayli ⁴ Arabia Saudita	84 DS	1-18 6.1 ± 3.1	32.1% AGA; 14.3% EMA; 15.5% tTG2 10.7% biopsy
Szaflarska-Popławska ⁵ Polonia	301 DS	1-34	9.0% AGA; 6.3% tTG2 5.4% biopsy
Noori ³² Irán	132 DS 88 DS with CHD 24 Ds without CHD 20 without DS	 7.1 ± 3.0 7.8 ± 4.4 7.3 ± 3.8	 5.7% seroprevalence children without DS 31.8% seroprevalence DS 33.3% with CHD 30.0% without CHD
Stordal ⁶ Noruega	3006 DS	0-12	1.6% biopsy
Bhat ⁷ India	100 DS	2-18	7.0% EMA 6.0% biopsy
Pavlović ⁸ Serbia	91 DS	mean 6.3	0.0% EMA; 5.5% tTG2 4.4% biopsy
Rodriguez ⁹ España	255 DS 28 with DS with CD 53 without DS with CD	Under 15 years old 4.2±2.8 4.8±3.2	9.8% AGA; 3.9% EMA; 5.5% tTG2 11.0% biopsy 58.8% DQ2 children with DS; 58.3% DQ2 children without DS
Cerqueira ¹⁰ Portugal	98 DS	1-45	9.2% EMA; 8.2% tTG2 6.1% biopsy
Wouters ¹¹ Holanda	155 DS	2-19 7.4 ± 4.6	5.2% EMA + tTG2 + biopsy 100.0% DQ2/DQ8
Shamaly ¹² Arabia Saudita	52 DS 52 without DS	promedio 11.5	23.1% AGA; 0.0% EMA; 9.6% tTG2 3.8% biopsy
Uibo ¹³ Estonia	134 SD	6 meses-45 promedio 11	41.0% AGA; 3.0% EMA; 6.0% tTG2 3.7% biopsy
Cogulu ¹⁴ Turquía	74 DS	2-18; promedio 6.1 6.5 ± 3.8	21.3% AGA; 12.8% EMA 6.4% biopsy
Book ³³ Estados Unidos	97 DS	2-18	10.3% EMA 88.0% DQ2
Bonamico ¹⁵ Italia	1110 DS 55 CD 55 AGA + EMA - 55 AGA - EMA -	1.3-18	21.3% AGA; 5.0% EMA 4.3% biopsia
Zachor ¹⁶ Estados Unidos	75 DS (73 children)	1-30	6.7% AGA; 13.3% EMA 6.7% biopsy

DS = Down syndrome; AGA = anti-gliadin antibodies; EMA = anti-endomice antibodies; tTG2 = anti-transglutaminase antibodies; CHD = congenital heart disease; CD = celiac disease; DQ = serotyping system; n = number

driguez et al¹³ in children with CD with and without DS, regarding the beginning and continuity of breast-feeding or the gluten introduction.

In Colombia, there is no national program for the CD detection in children with DS, which requires a higher awareness and screening of these two entities, and thus reduce their morbidity and mortality⁴⁵ as proposed by authors such as Csizmadia et al⁴⁶ and Sharr et al⁴⁷.

The strengths of the study are that all in-hospital children are treated by the same health care professionals (endocrinologist, gastroenterologist, and patho-

logist) for several years of follow-up and that all children belong, since some years, to the same foundation. Among the limitations of the study, despite describing the population of a tertiary hospital attended by a large number of children in southwestern Colombia, and of a foundation where most children with DS in the northeastern part of the country belong, the sample size is considered limited, therefore, the results cannot be reported as prevalence, but rather as frequency, and cannot be generalized throughout Colombia, nor to each city from which the children were included. Similarly, no questions were asked about other possible risk

factors such as quality of life, psychological, social, nutritional, and environmental, among others, that could explain the multifactorial model of this entity. Finally, our data were obtained from an in-hospital environment, from a foundation, and from Public Educational Institutions, which allows for some degree of selection bias.

In conclusion, the CD frequency diagnosed by intestinal biopsy in these children with DS is much lower than that reported in the literature. Also, it is associated with preschoolers, and its main allele is DQ2, findings similar to that described worldwide.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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