REVISTA CHILENA DE PEDIATRÍA
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Rev Chil Pediatr. 2018;89(6):709-717
DOI: 10.4067/S0370-41062018005001001

ORIGINAL ARTICLE

Characterization of celiac disease in chilean public hospitals

Caracterización de la enfermedad celiaca en niños atendidos en hospitales públicos chilenos

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Received: 29-1-2018; Approved: 13-7-2018

Abstract

Introduction: The worldwide prevalence of celiac disease (CD) is ~1% of the population. In Chile, the National Health Survey 2009-2010 showed a serological prevalence in individuals older than 15 years of 0.76% (IgA-tTG2), which corresponded in Concepción to 0.6%. **Objective:** Determine clinical characteristics, search, diagnosis, treatment and follow-up of CD in the two public hospitals in Concepción that have a Gastroenterology Department. **Patients and Method:** Descriptive study. Data were collected from electronic medical records (CIE10 code) and medical records of patients younger than 18 years of age, assessed for CD during 2010 - 2016 from two public hospitals in the city of Concepción, Chile. Cases whose diagnostic protocol met the ESPGHAN 2012 criteria (confirmation with intestinal biopsy), 207 out of 216 identified patients met the inclusion criteria. The nutritional status was classified according to age group (in children under five years old by WHO 2006 and in children between five and 18 years old by WHO 2007). The Z-score (Z) was calculated using the WHO Anthro software (in children under five years old) and WHO Anthro Plus software (in those between five and 18 years old). Antiendomysial antibodies were assessed by immunofluorescence test in cuts of the esophagus of mono, IgA and IgG anti-transglutaminase antibodies via ELISA, as well as serum IgA. **Results:** CD was confirmed by duodenal biopsies in 33.8% of the patients. IgA-tTG was identified in 70% and IgG-tTG in 52.9%, although only two patients had IgA deficiency. The main reasons for consultation were gastrointestinal (80%) and/or referral by an endocrinologist (45.7%). The main clinical presentation was gastrointestinal, with diarrhea (71.4%). 17.1% of the patients had Down syndrome (DS), 11.4% short stature, and 5.7% had type 1 diabetes mellitus. At diagnosis, the obesity:malnutrition ratio (Z-score BMI) was 2:1 and 6.8% of the patients were obese. One year after diagnosis, in 26 patients without DS, the frequency of eutrophic patients decreased from 65.4% to 42.3%, increasing overweight from 23.1% to 34.6% and obesity from 0 to 7.7%. **Conclusions:** In Concepción, endocrinologists conduct a significant and successful active search of CD, being responsible for 47.3% of the diagnoses. The high proportion of overweight/obese patients is consistent with the phenomenon currently described in Chile and other countries.

Keywords:
Celiac disease;
children;
nutritional status;
clinical presentation

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Introduction

Celiac disease (CD) is a chronic, immune-mediated enteropathy triggered by gluten intake in genetically susceptible people[1]. It is characterized by a highly variable combination of clinical manifestations, antibodies typically present in blood (anti-endomysium, anti-transglutaminase 2, anti-deamidated gliadin peptide), and small intestine mucosal alterations of variable intensity[2]. Globally, the estimated prevalence is around 1% of the population, with an increasing frequency of diagnosis in recent decades[3]. Several factors would influence this phenomenon, such serological markers with more sensitivity and specificity, greater knowledge of the disease in the general population and in professional teams, which allow earlier diagnosis, and a real pathology increase[4]. A relevant factor in the increase in the number of people diagnosed is the "active search" strategy[5], which proposes looking for the disease in people who do not necessarily consult for their symptoms but belong to the so-called risk groups. These are groups of patients with certain pathologies that show a CD frequency ten times higher or more than that observed in the general population. Typical examples of this situation are type 1 diabetes mellitus (T1DM), Hashimoto's thyroiditis, Down Syndrome (DS), Turner syndrome, among others[6]. First-degree relatives of patients already diagnosed with CD are also included in the active search since frequencies up to 20% higher than in the general population have been described in them[7,8].

In Chile, the National Health Survey 2009-2010, by measuring anti-transglutaminase 2, showed a serological 0.76% prevalence in people over 15 years of age[9]. When stratified by gender, as the global trend, prevalence was higher in women (1.1%) than in men (0.4%). In this survey, the prevalence of the city of Concepción was 0.6%, which allows estimating 12,112 celiac patients in the region, according to data from the last census[10].

Due to the increase in the diagnosis frequency, in several countries, national programs have been incorporated in order to improve their management, for which national information is essential. In our country, the evaluations currently available show that the existing data are scarce and almost entirely obtained in the Metropolitan Region[8,11]. The Concepción District belongs to the Biobío Region and is made up of 12 communes (Concepción, Coronel, Chiguayante, Florida, Hualqui, Lota, Penco, San Pedro de la Paz, Santa Juana, Talcahuano, Tomé). The public health system is covered by two healthcare networks, the Concepción Health Service[12] and the Talcahuano Health Service[13]. Only the Regional Clinical Hospital Dr. Guillermo Grant Benavente and Las Higueras Hospital have Pediatric GastroenterologyDepartments, therefore, children with suspected CD should be referred to these centers to confirm their diagnosis. The objective of this study was to determine the clinical and search characteristics, diagnosis, treatment, and follow-up of CD in pediatric patients treated between 2010-2016, in the two public hospitals in the Concepción province that receive referrals to gastroenterology.

Patients and Method

Design

Descriptive study of electronic records (CIE10 code) and clinical records of children under 18, with consultations for suspected CD (K90.0), in the Las Higueras Hospital (2011-2016) and Regional Hospital Dr. Guillermo Grant Benavente (2010-2016), Concepción province. The start date of using an electronic recording system defined the year in which data collection started, and the sample consisted of 100% of the observations from that period. 216 results were obtained, of which nine were excluded; one because the record was not found, one because the diagnosis was made and the information was obtained in another health center not available; two cases because the diagnosis confirmation was still pending, four because of lack of information, and one because the diagnosis was made based on clinical improvement and with normal biopsy. Thus, the selected group consisted of 207 records. The general and demographic characteristics of the excluded patients were not different from those included in the analysis. The cases whose diagnostic protocol met the criteria of ESPGHAN 2012 (confirmation with intestinal biopsy)[2] were identified and the group of "confirmed celiac patients", made up of 70 patients, was defined. The study was approved by the Ethics Committee of the Institute of Nutrition and Food Technology (INTA) and the Scientific Ethics Committee of the Concepción Health Service. It also had the Research Authorization of the Scientific Ethics Committee of the Talcahuano Health Service.

Clinical characteristics

The following were recorded: birth date, gender, reason for first visit, age of onset of symptoms and at diagnosis, main symptoms and signs leading to diagnosis, family history, previous pathologies, antibodies values measured at diagnosis and follow-up, duodenal biopsy report, anthropometric measurements and nutritional status at diagnosis and follow-up. In addition, in order to meet one of the objectives, the record made by the treating physician about adherence to the gluten-free diet (GFD) and attendance at medical and nutritional checks was sought. Unfortunately, these data were found in few records and could not be analyzed.

According to the symptomatology at the moment of diagnosis, the clinical presentation was classified into gastrointestinal and extra-gastrointestinal, according to the predominant symptoms that led to diagnosis.

Nutritional status

It was classified according to age group; in children under five years through the 2006 WHO standards[14], which were interpreted according to the norm of the Ministry of Health of Chile[15]; in children between five and 18 years of age, 2007 WHO standards were applied[16], and they were also interpreted according to the corresponding norm of the same ministry[17]. In both cases, the Z-score (Z) was calculated with the WHO Anthro software in children under five years, and with the WHO Anthro Plus software in children between five and 18 years. In patients with Down Syndrome (DS), the BMI was calculated and interpreted according to American standards[18], categorizing as normal the values between the 10th and 90th percentiles, both for BMI and Height/Age.

Antibodies in blood

According to the information obtained from the clinical and electronic records, determinations were carried out in the immunology laboratories of both hospitals, through commercial kits. Antiendomysial antibodies (EMA) were evaluated by immunofluorescence in monkey esophagus sections following the manufacturer's instructions (Immco ®), and the anti-transglutaminase 2 antibodies (TTG) measurement in their IgA and IgG versions through ELISA technique, according to the manufacturer's instructions (Diesse®). In addition, routine blood IgA measurement was recorded at the respective hospital, also performed according to ELISA techniques (ALPCO®, USA).

Clinical Symptomatology

Due to a trend towards gastrointestinal presentations has been observed in pre-pubertal ages[19], an analysis dividing patients into < 10 years and > 10 years was included.

Statistical analysis

The analysis of qualitative variables was carried out using frequency tables and associations through Chi-square test. For the analysis of the nutritional status follow-up, the mean BMI Z of all the controls with available information were estimated and stratified by gender and by periods of six months for a total period of up to two years after diagnosis. These data were analyzed through ANOVA test of two factors. The values of $P \leq 0.05$ were considered significant. The data was processed in Excel and analyzed with Stata software version 13.

Results

CD was confirmed in 70 (33.8%) out of the 207 evaluated patients (table 1). 31.4% of them were six to nine years old and their main reason for consultation was the presence of gastrointestinal symptoms (80%). 45.7% were referred for study by an endocrinologist, who either detected a condition considered of risk or in a routine control (annual) with IgA-TTG measure-

Table 1. General characteristics of the 207 patients < 18 years that consulted for evaluation of celiac disease

Variables		Celiacs		Non-celiacs		Totales	
		n	%	n	%	n	%
Patients assessed		70	33.8	137	66.2	207	100
Sex	Boys	25	35.7	66	48.2	91	44
	Girls	45	64.3	71	51.8	116	56
Age 1st consultation	< 2 y	12	17.1	28	20.4	40	19.3
	2-5 y	11	15.7	37	27.0	48	23.2
	6-9 y	22	31.4	37	27.0	59	28.5
	10-18 y	18	25.7	32	23.4	50	24.2
	No data	7	10	3	2.2	10	4.8
Main symptoms leading to consultation*	GIT	56	80	94	68.6	57	72.5
	Endocrinologist referral	32**	45.7	66***	48.2	98	47.3
	First degree relative	4	5.7	6	4.4	10	4.8
	Dg. Previously made elsewhere	3	4.3	3	2.2	6	2.9

*Symptoms leading to consultation may be more than 1. **12 Down syndrome, 6 short stature, 4 DMT1, 4 anemia, 1 cystic fibrosis, 1 Williams syndrome, 1 Hypoalbuminemia, 1 S. Kabuki, 1 weight loss, 1 Hashimoto thyroiditis. ***24 Down syndrome, 21 short stature, 6 DMT1, 4 anemia, 1 cystic fibrosis, 1 mucopolysaccharidosis, 1 S. de Raymond, 1 Hashimoto thyroiditis, 1 Guillén Barré, 4 weight loss, 1 failure to thrive, 1 IgA deficit.

Table 2. Clinical characteristics of the 70 patients diagnosed celiac disease, by age

Characteristics	<10 years (n)	≥ 10 years (n)	p
Boys: Girls	1: 35 (20B:27G)	1: 5 (5B:15G)	
Diarrhea	28	7	0.065
Abdominal distention	16	4	0.250
Abdominal pain	10	5	0.738
Vomiting	7	3	0.991
Failure to thrive	6	0	N.A
Constipation	4	3	0.427
Anemia	4	1	0.617
Short stature	8	5	0.450
Weight loss	6	2	0.749
Overweight/obesity	12	4	0.249
Eutrophic & Undernourished	21	15	0.199

Table 3. Nutritional status (IMC Z-score) at time of diagnosis in 70 patients diagnosed celiac disease

Nutritional status	n	(%)
Undernutrition	7	(10.0)
Eutrophic	32	(45.7)
Overweight/obesity	14	(20.0)
No data	17	(24.3)

Table 4. Nutritional status (IMC Z-score) in 26 celiac patients without Down's syndrome, at diagnosis and after one year on gluten-free diet

	At diagnosis		After 1 year on GFD	
	Fr	%	Fr	%
Underweight	3	11.54	4	15.38
Eutrophic	17	65.38	11	42.31
Overweight	6	23.07	9	34.61
Obesity	0	0	2	7.69

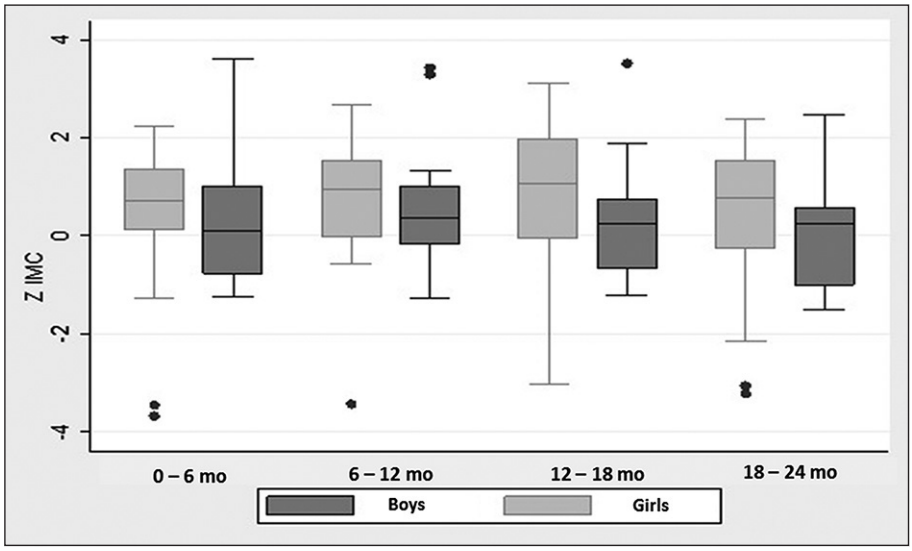
χ^2 P = 0.06.

ment, this was positive or increased in relation to the previous one (see table 1). Annual diagnostic frequencies ranged from 7.3% (2010) to 17.7% (2012). At the beginning of the data collection period, only 12 patients were identified who were previously diagnosed and continued in follow up; they do not represent the total number of cases diagnosed before 2010. The predominant clinical presentation was the classic gastrointestinal type (71.4%); the extra-intestinal and asymptomatic types reached 17.1% and 10% respectively; no cases of first-degree relatives identified by active search from a pediatric case were described. Only four family members reported a history of having been previously diagnosed with celiac disease. Only in one patient (1.5%), who presented a previous diagnosis made elsewhere, no record was found on the symptomatology of CD that would allow the classification of its clinical presentation. Diarrhea (52.2%), abdominal distension (30.4%), and abdominal pain (24.6%) were the most frequent symptoms in the 70 celiac patients, while constipation was present only in 11.6%. Diarrhea was more frequent in children under 10 years but did not reach statistical significance (p = 0.065) (table 2).

Out of the 70 patients with confirmed diagnosis, none had genetic study records; EMA measurement was available in 58.6% of cases, of which 61.9% were positive. IgA-TTG was recorded in 70% and was positive in 65.3%, while IgG-TTG was performed in 52.9% of the patients and was positive in 78.4%; of them. Only two patients had IgA deficiency. According to the categories defined by Marsh (20), the histological lesion was classified as 2, 3a, 3b and 3c in 11.4%, 24.3%, 30%, and 5.7% respectively. In 25.7% of the reports, the lesion found was only mentioned as "compatible" with CD and in 2.9% the data was not recorded. In 44.3% of patients, the diagnosis was made within three months of the first consultation. It took a year or more to make the diagnosis in six patients (8.6%). Out of the confirmed celiac patients, 44.3% presented another pathology previously diagnosed, 17.1% (n=12) DS, 11.4% (n=8) short stature, 5.7% (n=4) anemia, 4.3% (n=4) type 1 diabetes mellitus, and in 5.7% (n=4) there was another diagnosis (Williams syndrome, Hashimoto's thyroiditis, cystic fibrosis, Kabuki syndrome).

Table 3 shows the analysis of the nutritional status classification by Z-score of BMI in the total number of evaluated celiac patients (including DS). Out of the patients with DS, 75% were eutrophic and only one patient (8.3%) had a BMI deficit. There was short stature in 11.4% in the total number of evaluated celiac patients (10.3% in patients without DS and only one celiac patient with DS). The ratio between obesity and malnutrition was 2:1 and 6.8% of the patients were obese. Nutritional status categorized as low/normal weight and overweight/obesity showed no relationship with the presence of diarrhea (p = 0.328) or with the intensity of the histological lesion at diagnosis (p = 0.112).

In 26 patients without DS, anthropometric records were found at diagnosis and one year after starting treatment, which allowed the analysis of the nutritional evolution. The number of eutrophic patients tended to decrease while those with overweight and obesity in-



Graphic 1. Z IMC Changes in 46 celiac patients < 18 years, at diagnosis and after 2 years on gluten-free diet, by sex.

creased (table 4, χ^2 p = 0.06).

In the 46 patients who had anthropometric data during the first two years of follow-up, no significant variations were found in mean BMI Z (Graph 1, p = 0.668), nor by gender, although there was a tendency for the BMI Z to be higher in girls (p = 0.055). Height/age in the first two years after diagnosis showed no significant changes over time in the whole group (p = 0.733) or in patients with short stature (p = 0.592). There was a difference by gender, where the average height of girls was higher than of boys (p= 0.000). There was no age adjustment for puberty because that information was not available in the analyzed records.

All patients received GFD indication and this was controlled in the follow-up consultations, mainly by IgA-TTG measurements, which were available in 52/70 patients. Unfortunately, the time from diagnosis to the first evaluation of IgA-TTG ranged from two months to more than three years. There were no recorded data on adherence to the diet. The variability of these data did not allow the analysis of this aspect.

Discussion

This study is the first formal effort to characterize CE outside the Metropolitan Region. Although the group of patients is smaller than expected, it represents the experience of the two hospitals in the Concepción province where there is a Pediatric Gastroenterology department and patients are received for diagnosis. The high percentage of clinical records that could be analyzed (95.8%) is relevant, they allowed confirming the diagnosis in 33.8% of the patients. The data reported in this study do not allow prevalence calculations to be compared with those of the 2009-2010 National Health Survey. This described a 0.76% serological prevalence[9] and was carried out on a representative sample of Chileans over 15 years of age, therefore national information is still lacking on those under 18 years of age. A study of the 90s reported in Santiago a CD incidence of 1:1800 live births, but only included children consulting for gastrointestinal conditions, diagnosed by duodenal biopsy[21]. Another national study, conducted in 2011 through telephone surveys, included children and adults and does not provide information on prevalence[22]. The fact that almost half of the patients were diagnosed in the first three months after the first consultation suggests a significant improvement in relation to previously reported figures in the country[23]. The ratio of 1.8:1 in girls and boys obtained in this study is consistent with the international literature, which reports figures between 1.4:1[24], 1.5:1[25], and 1.63:1[26]. It is interesting that the main cause of consultation was gastrointestinal presentations with a predominance of diarrhea, bloating and abdominal pain (71.4%), given that globally there is a clear increase in the frequency of diagnosis of extra-intestinal presentations. This finding reinforces the need to implement an active research by the healthcare teams in order not to leave asymptomatic patients or with extra-intestinal manifestation without diagnosis or with a late one[27,28]. On the other hand, within the intestinal symptoms, constipation is currently presented with higher frequencies[25,28] (unpublished data), and in this study, only 11.6% presented this characteristic. The fact that almost half of the patients (45.7%) were referred from the Endocrinology Department suggests that in some subspecialties the concept of active search is successfully applied and achieves the diagnosis of the CD in risk pathologies

in percentages comparable to those described in other countries[29]. It is now common for CD patients to present other pathologies, mainly autoimmune, but the published national evidence in this area is scarce. The association with DS is interesting. In the United States, it has been estimated that 10% of patients with this condition have the CD[5], while in Spain this condition has been described in 2.9% of celiac patients[24]. It is possible that the high percentage of patients with DS in our series (17.1%) does not reflect the actual frequency of association but rather that a subspecialty has incorporated active search and others have not yet done so. In relation to T1DM, our data are within the frequencies reported by other authors[3]. For instance, in Madrid, in a population of celiac children at the time of diagnosis, 3.9% had T1DM[30].

The high number of IgG-TTG measurements found deserves special comment. IgG-TTG measurement has high sensitivity and specificity for CD diagnosis in individuals with IgA deficiency, but these are lower in patients with sufficient IgA. In addition, IgG- and other TTG subtypes are present in other autoimmune conditions. All this has led to the current recommendation that its measurement should not be recommended as a routine test for the diagnostic study of CD in IgA-sufficient individuals[2,21]. Which transglutaminase isoform measure in each autoimmune picture is a controversial issue since autoimmune conditions present variable results according to the transglutaminase isoform that is measured[31]. This aspect is important in our study given that 45.7% of the evaluated patients were referred from the Endocrinology department, many of them with autoimmune conditions. Currently, the consensus of specialists is that when there are doubts about the diagnosis, the intestinal biopsy and the response to treatment are indicated to clarify it. It is also important to mention the need for histopathological reports to follow internationally accepted criteria and to allow for guidance on the quality of intestinal mucosal damage.

The fact that 20% of patients were overweight/obese and only 10% were malnourished or at risk of malnourishment at diagnosis represents a good example of the change in clinical CD presentations and warns us not to underestimate a possible diagnosis of CD in this group of patients. Historically, the CD was characterized by malnutrition and nutritional deficiencies derived from nutrient malabsorption syndrome[32]. Our results coincide with other recent research[28] showing that there is no correlation between nutritional status and clinical presentation and/or histological findings. This means that the presence of gastrointestinal symptomatology and more intense villi atrophy is not necessarily associated with malnutrition. In recent years, the research on overweight/obese celiac children has been published repeatedly[33-35]. The change is associated with the increase in the frequency of malnutrition by excess observed worldwide, which also affects our country and our celiac patients. In Chile, the prevalence of overweight/obesity in first-grade children reaches 50.3%, and in ninth grade adolescents 46.1%, according to data from 2017[36]. In the Biobío Region, according to 2016 data, 53.6% of overweight/obesity was observed in first-grade students and 44% in ninth grade ones[37]. Therefore, our findings are consistent with the epidemiological-nutritional reality of our country.

In order to evaluate nutritional status and its evolution while on GFD, the ability to measure adherence needs to be improved. The data found on compliance during follow-up were so scarce that they did not allow for analysis of adherence to GFD, and this was an important objective considering that almost half of the evaluated patients had other associated pathologies. We did not observe significant differences in the mean BMI Z over the first two years of GFD (Graph 1). However, comparing the time of diagnosis and after one year of treatment, the BMI did show an increase (table 4), which correlates with other researches that evaluate the follow-up in these patients and suggest as possible causes the nutritional composition of gluten-free foods, current lifestyles and quality of the diet in general. The evaluation of the nutritional treatment, which is gluten-free and nutritionally adequate, is not only relevant at the beginning of the GFD but also during the follow-up, in order to control excessive weight gain and the nutritional quality of the diet[33]. This is interesting, but the low number of patients with data recorded in the evaluated period (26/70) represents a clear limitation of the study. Attempts were made to locate patients, but the idea was abandoned because it was evident that there would be a very significant reduction in the study group. The results analysis was also limited by the inability to adjust age according to pubertal development. We can only mention that no differences have been reported between the ages of puberty among children with CD, DS[38] and/or T1DM with insulin treatment[39].

In summary, in this first formal effort to characterize CD outside the Metropolitan Region, we found that in Concepción CD is diagnosed mainly in gastrointestinal presentations with diarrhea, with little presence of constipation and extra-gastrointestinal presentations. The diagnostic process generally follows international criteria (measurement of antibodies (IgA -TTG and/or -EMA) and duodenal biopsies, although only 71.4% of patients were found to categorize histological damage and no records of genetic studies were found. The high frequency of IgG-TTG measurement found is not justified; the current consensus is that this measurement should not be used in individuals with sufficient blood

IgA values. The low presence of cases found among first-degree relatives is striking, suggesting that active search is insufficient. The high number of cases referred by DS suggests that some subspecialties have successfully incorporated active search criteria. Finally, it is relevant that only 10% of the diagnosed patients had malnutrition or risk of malnutrition and 20% were overweight or obese. These findings show that in our country there has also been a change in the nutritional profile of celiac patients, as described in other countries.

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 state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Aknowledgments

Authors acknowledge the help received from professionals of Hospitals Guillermo Grant Benavente and Las Higueras.

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