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Endocrine Abnormalities and Growth Characterization in Colombian Pediatric Patients with 22q11 Deletion Syndrome

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What is already known on this topic?

It is known that different endocrinopathies occur in 22q11 deletion syndrome, the most common of which are hypoparathyroidism and hypothyroidism. The intervention of a multidisciplinary team is also highlighted within the follow-up of the patients, including the follow-up of their growth pattern, which can be altered in a multifactorial way.

What this study adds?

This study reinforce the importance of follow-up according to the guidelines and trying to detect endocrinopathies early, such as hypoparathyroidism, which can be detected late and with serious presentations such as convulsive episodes.

Abstract

Objective: Several endocrine manifestations have been described in patients with 22q11 deletion syndrome, including growth retardation, hypoparathyroidism, and thyroid disorders. This study aimed to characterize these abnormalities in a Colombian retrospective cohort of children with this condition.

Methods: A retrospective study comprising a cohort of children with 22q11 deletion syndrome in Medellín, Colombia followed up between 2011 and 2017 was conducted.

Results: Thirty-seven patients with a confirmed diagnosis of 22q11 deletion syndrome were included. 37.8% had some endocrinopathy, the most frequent being hypoparathyroidism (21.6%), followed by hypothyroidism (13.5%), hyperthyroidism (2.7%) and growth hormone deficiency (2.7%). There was wide heterogeneity in the clinical presentation, with late onset of severe hypocalcemia associated with seizure or precipitated in postoperative cardiac surgery, which highlights the importance of continuous follow-up as indicated by the guidelines. Short stature was mainly related to nutritional factors. Growth monitoring is required with the use of syndrome-specific charts and careful monitoring of the growth rate.

Conclusion: As previously reported, a significant proportion of patients with endocrine abnormalities were found in this cohort. This highlights that it is essential to carry out an adequate multidisciplinary follow-up, based on the specific clinical guidelines, in order to avoid serious complications such as convulsions due to hypocalcemia. It is important to track size with curves specific to the syndrome and analyze the growth rate.

Keywords: 22q11 deletion syndrome, DiGeorge syndrome, hypoparathyroidism, hypothyroidism, growth disorders, endocrine system diseases

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Introduction

The 22q11 deletion syndrome, also known as DiGeorge syndrome (DGS), corresponds to the classic triad of thymus aplasia, hypoparathyroidism, and congenital heart disease (1). It has its origin in an alteration of the embryological development of the third and fourth pharyngeal arcs, which is due to a deletion in the chromosome region 22q11, with a size between 0.7 and 3 million base pairs. The variable phenotypic expression of 22q11 deletion syndrome includes, in addition to DGS, other previously known syndromes such as velocardiofacial (VCFS), Cayler, Opitz G/BBB, and facial conotruncal anomaly (CTAFS) (1,2,3). With an estimated prevalence of 1 per 4,000 live newborns and is considered the most common microdeletion syndrome. In addition, it is the main cause of palatal abnormalities of syndromic origin and the second most common cause of congenital heart disease and neurodevelopmental delay. There is no predominance by gender, but it is more prevalent in Hispanics, and in 90-95% of cases, it is due to *de novo* deletions (1,2,3).

The clinical spectrum of this condition is highly variable and includes congenital heart disease, recurrent infections, nasal regurgitation, nasal voice, hypocalcemia, feeding problems, developmental delay mainly on language, laryngotrachoesophageal abnormalities, renal abnormalities, hypothyroidism, low stature, vertebral abnormalities, polydactyly, scoliosis, thrombocytopenia, microcephaly, seizures and hypotonia, and additionally, a history of intrauterine growth restriction is common (1,2,3,4).

Taking into account the diversity of conditions and diseases presented by these patients, in 2011, Bassett and collaborators developed the "practical guidelines for the management of patients with 22q11 deletion syndrome", which stress a required multidisciplinary follow-up and highlight an active search for various conditions, including endocrinopathies (3). Within this last group, hypoparathyroidism, followed by hypothyroidism, short stature, and less frequently hyperthyroidism and growth hormone (GH) deficiency stand out in decreasing order of frequency (1,5).

Hypoparathyroidism occurs frequently with hypocalcemia, usually in the neonatal period; however, cases have been reported of patients with no evidence of hypoparathyroidism in the first years of life, who later may develop hypocalcemia in times of stress in the context of acute diseases, surgeries, or the physiologically difficult periods of adolescence and pregnancy. Additionally, descriptions of *de novo* diagnoses of hypoparathyroidism have been made in adolescent or adult patients who have consulted for episodes of severe hypocalcemia (2,5,6). The frequency of hypocalcemia varies widely depending on the selection criteria applied; an even lower prevalence of hypocalcemia has been reported in patients for whom calcium is not routinely measured, which shows that the wide discrepancy of prevalence between the different reports may be influenced by these selection and follow-up differences. For DGS, the hypocalcemia prevalence is 69-72% (7,8), for VCFS, it is 13-22% (9,10,11), for CTAFS, it is 10% (12), and for 22q11 deletion syndrome, the reported prevalence is 49-60% (13,14).

In 22q11 deletion syndrome, primary hypothyroidism is also present due to a defect in the development of the pharyngeal arches and to the greater frequency of autoimmune alterations. The reported prevalence varies according to the name given to the syndrome: for 22q11 deletion syndrome, it is 0.7-9.5% (14,15), and the presence of Graves' disease has also less frequently been reported, with a prevalence of 1.8% (1,5,15).

Patients with 22q11 deletion syndrome may have short stature and constitutional growth retardation; this is closely related to low weight due to nutritional problems and heart disease (1). However, the probability of GH deficiency, which has also been associated with short stature in these patients, should not be underestimated (2,5,16,17). In VCFS, a prevalence of short stature of 39-41% and constitutional growth and development delay of 30% have been reported (11,18,19). For 22q11 deletion syndrome, the prevalence of short stature is 36-41% and GH deficit is 4% (14,20,21). These differences in the growth of these patients have led to the development of growth curves specific for this condition, which allow early and timely detection of patients who are growing more slowly than is expected for their condition and thus prioritize the search for other causes which may explain this alteration (22,23,24). In addition, follow-up on these specific curves could avoid a possible over-diagnosis of growth retardation in these patients, which could occur if this follow-up is performed with growth patterns for the general population. Unfortunately, there is a lack of broad knowledge of such growth curves in pediatric clinical practice, and we do not have a growth curve of this type developed for the local population, nor validation of those previously stated in our environment, which can lead to diagnostic errors at the time of the interpretation of the growth of these patients.

Endocrinopathies associated with 22q11 deletion syndrome show wide variability in their prevalence, depending on the populations studied. Levy-Shraga et al. (25) described a cohort of 48 patients in Israel with 22q11 deletion syndrome, in whom only 27% had hypoparathyroidism and

10.4% were suffering from hypothyroidism, and in terms of the auxological evaluation, these patients showed a delayed growth pattern, which placed them in the low normal range for height, according to world growth standards. On the regional level, in Latin America, studies by Fomin et al. (26) and Del Carmen Montes et al. (27), which correspond to clinical characterization, stand out. Specifically, in Brazil, 14 patients were described, among whom 35.8% had hypoparathyroidism and 7.1% hypothyroidism. Del Carmen Montes et al. (27) in Argentina found that out of 32 patients with 22q11 deletion, only 3.1% had hypoparathyroidism, without any other endocrinopathies.

On the local level, we do not have clinical characterization studies of endocrinopathies and other comorbidities in patients with 22q11 deletion syndrome. In addition, since the frequency of endocrinopathies reported differ according to the population studied, we cannot extrapolate these data to our population. Therefore, this study aimed to characterize the different endocrinopathies related to 22q11 deletion syndrome, including auxological evaluation in a group of patients who attended the Hospital Universitario de San Vicente Fundación in the city of Medellín during the period from January, 2011 to December, 2017.

Methods

Study Setting and Participants

This study was conducted at the Hospital Universitario de San Vicente Fundación, in the city of Medellín, Colombia. For this study, a retrospective review of the medical records of patients treated in the pediatric endocrinology division was performed during the period from January, 2011 to December, 2017. The sample size was determined by convenience sampling. Patients younger than 18 years who had the International Classification of Diseases-10 (ICD-10) code "D821" (DGS) in their medical charts were included. Those patients who had a fluorescent in situ hybridization (FISH) test negative for 22q11 deletion or whose results were not available in the medical charts were excluded. Each of the medical records was reviewed by two of the study researchers in order to decide on the case's entry into this study. For those cases included, the largest amount of information available was collected, taking the first clinical record as the first assessment and the subsequent information as follow-up measurements.

This study was approved by the Ethics Committee of the Hospital Universitario de San Vicente Fundación (no: 11-2018, date: 13.04.2018) and was carried out in compliance with the standards of resolution 8430 of 1993 of the Ministry of Health of the Republic of Colombia, which regulates research with human subjects in the country, and in adherence to the ethical principles set out in the Helsinki Declaration. Confidentiality regarding the identity of patients was maintained throughout this investigation.

Definitions

The diagnosis of each endocrinopathy was based on the data reported in the medical records, the pathological history or upon the evaluation of the relevant laboratory tests. The auxological evaluation was carried out with weight and height data taken from the clinical history, the body mass index (BMI) was calculated, and the standard deviation was determined for each of these values according to World Health Organization (WHO) growth curves (28).

The diagnosis of hypoparathyroidism was established with decreased serum calcium levels for age, associated with decreased or inappropriately normal parathyroid hormone (PTH) levels accompanied or unaccompanied by hyperphosphatemia or based on physician-based diagnosis written in the medical record. Hypothyroidism was diagnosed by elevated thyroid stimulating hormone (TSH) levels with or without decreased free T4 levels, and hyperthyroidism was defined as the presence of decreased TSH levels with elevated T3 and/or T4 levels. The diagnosis of GH deficit considered the presence of short stature accompanied by low growth rate, decreased serum levels of insulin-like growth factor-1 (IGF-1), and two suboptimal GH challenges (29,30,31). Short stature was defined as a z-score below -2 standard deviations; low weight was catalogued in children under 5 years at a z-score for the weight-to-size ratio of -2 standard deviations and for those over 5 years, a z-score for BMI lower than -2 standard deviations.

Statistical Analysis

A descriptive analysis was performed using the software Statistical Package for the Social Sciences (version 20 for Mac) and Epidat 4.1. The quantitative variables and their results are presented as mean and standard deviation in cases of normal distribution; otherwise, they are summarized as medians and interquartile intervals. Qualitative variables are shown as frequency and proportions. In addition, an analysis was performed among the subgroups of the patients with short height and normal height, comparing clinical characteristics, and a chi-squared test was applied with a level of statistical significance of $p < 0.05$.

Results

Demographics and Clinical Characteristics of the Patients

A total of 125 records of patients diagnosed with DGS were obtained using the ICD-10 code D821, of which 47 patients

were excluded because they had a negative FISH for 22q11 deletion and 41 patients who had not yet been molecularly evaluated during follow-up. Finally, after review, 37 patients met the selection criteria, of which 20 were female (54%) and 17 were male (46%) (Figure 1).

Table 1 summarizes the demographic and clinical characteristics of the patients included; of these, 14 patients (37.8%) had some endocrine abnormality. The most frequent endocrinopathy was hypoparathyroidism, followed by hypothyroidism and, at a lower frequency, hyperthyroidism, GH deficiency, and precocious puberty. Additionally, other characteristics of these patients were reported, such as the presence of heart disease, immunodeficiency, feeding problems, and/or perinatal history.

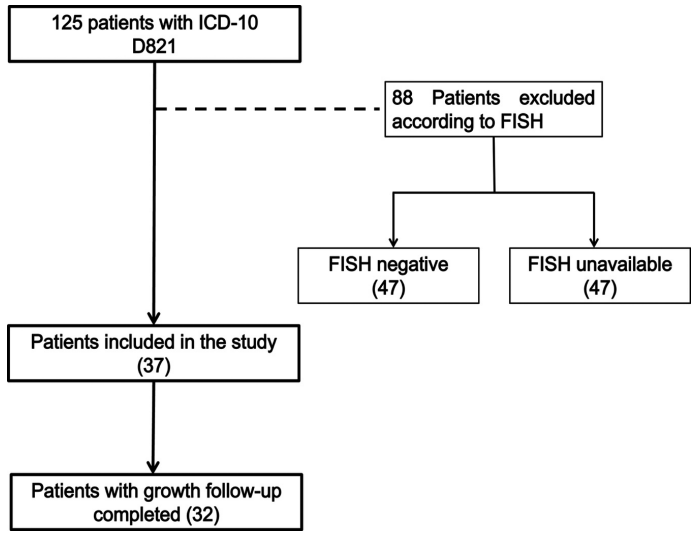

Figure 1. Flow diagram for inclusion of patients. There were 125 registries of patients with International Classification of Diseases-10 D821 diagnosis, of which 47 patients were excluded because they had a negative fluorescent in situ hybridization study for 22q11 deletion and 41 patients who did not have a molecular diagnostic study during follow-up. Thirty-seven patients met the selection criteria and of these, in 32 cases, the information was available for auxological follow-up

ICD-10: International Classification of Diseases-10, FISH: fluorescent in situ hybridization

Endocrine Abnormalities

Hypoparathyroidism was the most common endocrine disorder, which was diagnosed in 21.6% of the study subjects. Among the patients with reported data from phosphocalcic metabolism tests at diagnosis, initial PTH levels were found ranging between 6.1 and 53.1 pg/mL (local reference level 10-65 pg/mL), and all of them had low calcium levels, between 7.6 and 8.2 mg/dL (local reference level 8.7-10.1 ng/dL). Some of these PTH values were inappropriately normal in the setting of hypocalcemia. Specifically, in three

Table 1. General characteristics of the 22q11 deletion syndrome patients included in this study

Characteristics	All patients (37) n (%)
Male	17 (46)
Female	20 (54)
Age (years) at diagnosis (median, IQR)	5.33 (0.66-10)
Age (years) at first assessment (median, IQR)	3.25 (1.08-8.2)
Age (years) at last assessment (median, IQR)	6.54 (4.47-9.81)
Clinical data	
Total of patients with endocrine abnormalities	14 (37.8)
Hypoparathyroidism	8 (21.6)
Hypothyroidism	5 (13.5)
Hyperthyroidism	1 (2.7)
GH deficiency	1 (2.7)
Precocious puberty	1 (2.7)
Congenital cardiopathy	28 (75.6)
Immunodeficiency	4 (10.8)
Feeding difficulties	12 (32.4)
Perinatal history	
Prematurity	8 (22.2)
Low birthweight	9 (25)
Birthweight, g (median, IQR)	2,700 (2,300-3,000)
Length at birth, cm (median, IQR)	47 (44.75-49)

IQR: interquartile range, GH: growth hormone
Data are shown as absolute frequencies plus percentages for categorical variables and as median plus interquartile ranges for quantitative traits

of the patients, the diagnosis was reached early, during the first year of life, and one of them during hospitalization for the correction of heart disease at 3 months of age. Two of the patients were diagnosed during adolescence; one of them presented with a seizure secondary to hypocalcemia.

In this cohort, hypothyroidism was the second most frequent endocrine defect, affecting 13.5% of the population studied. All the cases were determined to be acquired hypothyroidism, and of these, it was only possible to demonstrate autoimmunity with positive antibodies in one of the cases. Baseline TSH levels ranging from 6.23 to 14.1 mIU/L were found among patients with reported thyroid test data, but complete free T4 (fT4) data was not found at diagnosis. During follow-up, compensation of thyroid function was achieved.

Within the data of the hormonal studies carried out, it was found that one patient presented with a diagnosis of GH deficiency, having two subnormal challenges with peaks of 2.82 ng/mL and 6.3 ng/mL, through a stimulus test with clonidine and L-DOPA, respectively. The somatomedin C (IGF-1) value was 90.2 ng/mL [-1.1 standard deviation (SD)]. This patient had a growth rate below the 3rd percentile (3.9 cm/year), in the context of poor weight gain associated with loss of appetite and congenital heart disease (atrial and interventricular septal defect plus aortic coarctation). Additionally, this diagnosis was reached during the last visit of this patient and, at this point, GH treatment was not considered.

Growth Characterization

Regarding the auxological evaluation, according to WHO curves in the first assessment, the average z-score for height was -2.36 SD, for weight, it was -1.89 SD, and for BMI, it was -0.46 SD. In this first assessment, 24 patients (64.8%) were classified as short stature. In those under 5 years of age, 8 patients (38%) had low weight, while in those over 5 years of age, no patient had a BMI less than -2 SD. We had follow-up information from 32 patients, with an average time of 29 months. In the last assessment, the average z-score for height was -1.81 SD, for weight, it was -1.59 SD, and for BMI, it was -0.67. At this last assessment, 19 patients (59.3%) had short stature. In those under 5 years of age, 3 patients (33.3%) were underweight, and in those over 5 years of age, 4 patients (16.6%) had BMI less than -2 SD. The differences between the measurements of the first and the last assessment are also shown (Table 2). In the 24 patients with short stature, a z-score of -3.2 SD was found at the first visit, and it was -2.42 SD for the last evaluation, indicating an improvement of 0.78 SD. The subgroup of 8 underweight patients who had a z-score of -2.73 SD at the first visit was subsequently scored at -3.28 SD at the last evaluation, and so worsening by 0.55 SD.

Additionally, those patients with short stature in the first assessment were compared with those with normal height, and it was found that there was a higher proportion of underweight in those with short stature (33% vs. 0%; $p = 0.01$). It was also observed that there was a higher frequency of endocrinopathies in the group of patients with normal height, as well as a higher frequency of heart disease and feeding problems in those patients with short stature, but these differences were not statistically significant (Table 3).

Discussion

To the best of our knowledge, this study is the most extensive clinical characterization of patients with 22q11 deletion syndrome reported in Colombia. Although the focus was on endocrinological findings and growth characterization, the frequencies of other conditions typical of the syndrome are also described, such as heart disease which was present in 75.6% of patients, feeding disorders in 32.4% of patients and immunodeficiency in 10.8% of cases, all with prevalences similar to those previously reported in different cohorts (32,33,34). Regarding the endocrinological findings, 37.4% of the patients had some type of endocrine

Table 2. Growth characterization of the 22q11 deletion syndrome patients included in this study

	First visit (n = 37)		Last visit (n = 32)	
Height z-score (SD)	-2.36 (1.46)		-1.81 (1.25)	
Weight z-score (SD)	-1.89 (2.06)		-1.59 (1.76)	
BMI z-score (SD)	-0.46 (1.76)		-0.67 (1.94)	
Short stature (%)	24 (64.8)		18 (56.2)	
Underweight	< 5 years old (n = 21)	> 5 years old (n = 16)	< 5 years old (n = 9)	> 5 years old (n = 23)
Low weight/height n (%)	8 (38.09)		3 (33.3)	
Low BMI n (%)		0 (0)		4 (16.6)

SD: standard deviation, BMI: body mass index, WHO: World Health Organization
Data are shown as absolute z-score with its respective standard deviation for anthropometric measurements and as frequencies plus percentages for weight classifications. In order to carry out a more objective progression evaluation, the follow-up was carried out using the WHO growth curves

Table 3. Comparison of clinical characteristics between subgroups with short height and normal height

	Short stature (n = 24)	Normal height (n = 13)	p
M:F	12:12	5:8	0.37
Endocrinopathy, n (%)	7 (29.1)	7 (53.8)	0.13
Hypoparathyroidism, n (%)	5 (20.8)	3 (23)	0.59
Hypothyroidism, n (%)	1 (4.1)	4 (30.7)	**0.04**
Hyperthyroidism, n (%)	0	1 (7.6)	0.35
GH deficit, n (%)	1 (4.1)	0	0.64
Precocious puberty, n (%)	0	1 (7.6)	0.35
Underweight n (%)	8 (33.3)	0	**0.01**
Cardiopathy, n (%)	20 (83.3)	8 (61.5)	0.14
Immunodeficiency, n (%)	3 (12.5)	1 (7.6)	0.55
Feeding disorders, n (%)	8 (33.3)	4 (30.7)	0.58

Data are shown as frequencies plus percentages. The comparisons were carried out using the chi-squared statistic.
M:F male female ratio, GH: growth hormone

alteration; of these, hypoparathyroidism was the most frequent condition, followed by thyroid disorders, GH deficit, and precocious puberty.

Hypoparathyroidism was identified in 8/37 (21.6%) patients with 22q11 deletion syndrome. It should be noted that one of the patients was diagnosed with hypoparathyroidism when debuting with a seizure secondary to hypocalcemia in adolescence, and another presented with hypocalcemia during hospitalization to correct his congenital heart disease. These two cases exemplify the heterogeneity in age and clinical presentation of hypoparathyroidism, so routine follow-up of phosphocalcic metabolism is essential in these patients (2,6,25), especially considering the high risk of presentation with severe forms of hypocalcemia, such as seizures (35). In general terms, the detected prevalence of hypoparathyroidism is in an intermediate range of those previously reported in Latin America, with 3.1% in Argentina (27) and 35.8% in Brazil (26), and very similar to a previous report made in Israel (25).

Different thyroid disorders have been described in patients with 22q11 deletion syndrome. They can be explained by developmental defects of the pharyngeal arches, morphological alterations of the gland (36), and the greater frequency of autoimmune alterations which these patients develop (37). In line with this, our study identified a prevalence of hypothyroidism of 13.5% (5/37), while one patient (2.7%) presented hyperthyroidism, findings similar to those reported by Shugar et al. (15), who documented a 9.5% prevalence of thyroid disorders in 169 patients with 22q11 deletion syndrome, with 7.7% hypothyroidism and 1.8% hyperthyroidism, while they are higher than the rate of thyroid disorders noted by Choi et al. (38) at 3.2% in 61 patients. GH deficit and precocious puberty were each documented in one patient. These findings are consistent with previous anecdotal reports of these conditions in patients with 22q11 deletion syndrome (21,39), and so reaffirms their low prevalence.

We examined the growth of the patients by comparing the auxological parameters recorded during the follow-up visits of approximately 29 months, which were available in 32 out of 37 patients. For this evaluation, WHO growth curves were preferred over those previously published, as they allow for an arithmetic monitoring of growth progression with exact values which facilitate the calculations of deltas. With this approach, it was documented that 89.1% of the patients had negative z-scores for height at their first assessment, compared with 100% described in other cohorts (25). Although follow-up was not possible for the entire sample, at the last evaluation, it was estimated that 87% of the patients had negative z-scores for height. Although there is no significant difference between these two data, it is known that the growth of these patients has a delayed pattern with height, which initially results in negative z-scores, but that in the end, they can approach normal height (5,22,25,26).

When we analyzed the auxological evaluation in detail, 64.8% of the patients had short stature at the initial assessment, which improved over time with an average change of 0.55 standard deviations, and at the last visit, only 56.2% of the patients were of short stature. It is plausible that on continuing with an adequate follow-up of this cohort, their height would continue to improve, and that possibly a good percentage of these patients would not present with a final short stature (5,22,24,25). It is to be noted that of 24 patients with initial short stature, 16 continued with short stature at their last assessment, and 4 presented with improvements in their z-score, so that they were no longer classified as being of short stature. These 4 patients had in common that they did not have any eating disorder, which

further supports the explanation that the affectation of height can be secondary to other factors, such as nutritional factors. It was also seen that 3 patients who previously were classified as normal height with decreased z-scores at their last assessment were classified as short stature, without it being possible to identify any factors related to this finding.

In the subgroup of patients with short stature, when charted on growth curves specific to the syndrome, the prevalence of short height decreased to 16.2% (only 6 patients). This highlights the importance of auxological follow-up of these patients and shows how the frequency of height alterations can vary widely according to the standard used. This proper evaluation, accompanied by a good clinical follow-up of the rest of the auxological parameters, can reduce unnecessary evaluations of these patients (22,24). When comparing subgroups between those patients with short stature and those with normal height according to the WHO curves, at the first assessment, those with short stature were found to have a greater frequency of heart disease and/or feeding problems; in 7 patients, these two conditions occurred simultaneously. In addition, all patients with low weight had associated short stature. Interestingly, the frequency of endocrinopathies was lower in the group of patients with short stature. This is consistent with the fact that the compromise of height of these patients was not exclusively related to endocrine alterations as with feeding problems, low weight, or the presence of heart disease (5,22).

Study Limitations

As a weakness of this study, it should be considered that this was retrospective and it was based on a review of medical records, so our analysis of these patients depended on the adequate recording of data by the physician who performed the clinical evaluation, as well as the complete recording of some perinatal or personal history data. In addition, the population was not captive, so the multidisciplinary follow-up required by these patients was not performed exclusively in our institution. This may partly explain why the laboratory follow-up reports were not consistent.

Conclusion

In summary, our results confirm that 22q11 deletion syndrome shows a varied clinical presentation with frequencies of endocrinopathies different from those previously reported in the literature, which is consistent with the known heterogeneity of this syndrome among different populations. The compromise of height of these patients seems to be transitory. In general, improvement during the follow-up was seen in a good percentage of the patients and this was mainly related to nutritional factors. The number of patients who are actually short for age decreases almost by a factor of 3 when using syndrome specific curves for this diagnosis, which shows the importance of follow-up on the growth curves. In addition, it is evident that the auxological follow-up of these patients with the analysis of growth rate is of great importance.

Our results emphasize the importance of adequate multidisciplinary follow-up, based on specific clinical guidelines, in order to avoid complications related to the late diagnosis of any endocrinopathies, as in the case of hypocalcemia due to hypoparathyroidism. Specific studies related to this topic are required with larger sample sizes and preferably prospective evaluation, which will lead to a more accurate knowledge of the clinical conditions of those patients with 22q11 deletion syndrome at a local level.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Hospital Universitario de San Vicente Fundación (no: 11-2018, date: 13.04.2018).

Informed Consent: Patient consent was waived due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Juan Lasprilla-Tovar, Nora Alejandra Zuluaga, Carolina Forero, Design: Juan Lasprilla-Tovar, Javier Mauricio Sierra, Data Collection or Processing: Juan Lasprilla-Tovar, Analysis or Interpretation: Juan Lasprilla-Tovar, Oscar Correa-Jiménez, Javier Mauricio Sierra, Literature Search: Juan Lasprilla-Tovar, Nora Alejandra Zuluaga, Carolina Forero, Oscar Correa-Jiménez, Javier Mauricio Sierra, Writing: Juan Lasprilla-Tovar, Oscar Correa-Jiménez.

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