

REVISTA CHILENA DE PEDIATRÍA



www.revistachilenadepediatria.cl www.scielo.cl

Rev Chil Pediatr. 2018;89(4):491-498 DOI: 10.4067/S0370-41062018005000703

CLINICAL EXPERIENCE

Clinical profile of children with diabetic ketoacidosis in fifteen years of management in a Critical Care Unit

Perfil clínico de niños con cetoacidosis diabética en quince años de manejo en una Unidad de Paciente Crítico

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Received: 13-12-2017; Approved: 17-5-2018

Abstract

Introduction: Diabetic ketoacidosis (DKA) is the main cause of morbidity and mortality in children with type 1 diabetes mellitus (T1DM) due to clinical and biochemical alterations associated, cerebral edema as one of the most critical because of the high mortality rates and long-term neurological sequelae. Objective: To analyze the clinical characteristics and complications of patients with DKA admitted to a pediatric intensive care unit. Patients and Methods: Retrospective study of DKA patients treated at the Hospital Clínico, Pontificia Universidad Católica de Chile (UPCPUC) between 2000 and 2015. Demographic characteristics, clinical manifestations, biochemical alterations, treatment, complications, and prognosis were assessed. Patients with T1DM onset were compared with those patients already diagnosed with diabetes, analyzing variables according to distribution. Results: 46 DKA events were identified, 67% of them were the first episode of DKA. 66% of patients already diagnosed with diabetes were admitted due to poor adherence to treatment. The main symptoms described were: 63% polydipsia, 56% polyuria, 48% vomiting, 39% weight loss and 35% abdominal pain, and mean blood sugar levels of 522 mg/dL, pH 7.17, and plasma osmolality of 305 mOsm/L. 89% of patients received insulin infusion, and 37% presented hypokalemia. No episodes of cerebral edema or deaths were registered. Conclusions: Most of the DKA admissions were due to T1DM onset. In the group of patients already diagnosed with diabetes, the poor adherence to treatment was the main cause of decompensation. There were no serious complications or deaths associated with DKA management during the studied period. Early diagnosis and proper and standardized treatment contributed to reducing morbidity and mortality in children with DKA.

Keywords:

Diabetes; Diabetic ketoacidosis; insulin; cerebral edema

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Introduction

Type 1 diabetes mellitus (T1DM) is an immunemediated disease that triggers, as a final consequence, the complete or partial loss of the pancreatic cells, decreasing the production of endogenous insulin, and thus generating a dependence of the affected patient on the exogenous insulin administration to maintain adequate energy production(1). Currently, this pathology is one of the most common chronic diseases in children, with a progressive increase in its global incidence in recent years (annual increase of 3% in children and adolescents, 5% in preschoolers)(2). A recent study conducted by our group reveals a significant increase in the incidence of T1DM in children under 20 years of age treated in the public health system in Chile between 2006 and 2014. In this period, 4,513 new cases of T1DM were registered, most of them were under 15 years of age, and the incidence increased from 10.3/100,000 in 2006 to 16.3/100,000 in 2014⁽³⁾. Diabetic ketoacidosis (DKA) is, along with severe hypoglycemia, the main acute complication that can occur in patients with T1DM. This can occur under two circumstances: (a) at the time of T1DM diagnosis (disease debut) or (b) in patients with a previous T1DM diagnosis who do not receive the proper insulin dose, either accidentally or deliberately, or who are suffering from an intercurrent disease that has not been adequately controlled(2). In both cases, when an endogenous insulin deficit associated with stress occurs (with the consequent increase in counter-regulatory hormones such as catecholamines, glucagon, cortisol, and growth hormone), an accelerated catabolic state is triggered, with increased hepatic and renal glucose production (through glycogenolysis and gluconeogenesis), and impairment of peripheral glucose utilization, resulting in hyperglycemia, hyperosmolarity, and an increase in the lipolysis and ketogenesis as an alternative mechanism for energy production. This finally causes the accumulation of acid metabolites (ketones and ketoacids)(4). In this way, the characteristic biochemical alterations of DKA appear, and some of them correspond to the current diagnostic criteria of ketoacidosis: hyperglycemia (blood glucose > 200 mg/ dL), acidosis (venous pH < 7.3 and/or plasma bicarbonate < 15 mmol/L) and presence of ketonemia and ketonuria(5).

The main clinical presentation of the DKA cases reported in the literature corresponds to the T1DM debut with a wide variation in its incidence among countries, which ranges from 15% to $67\%^{(6,7)}$. This is much more common in developing countries and in areas where there is a decreased T1DM prevalence because the suspicion of this disease is lower due to the low exposure of the physician to this pathology⁽⁸⁾. It

has been estimated that the risk of DKA in a patient already diagnosed with T1DM varies between 1-10% per patient/year⁽¹⁾. Most cases of DKA could be prevented, as symptoms are usually present for several days or weeks before, where the main problem is the late consultation or the low index of suspicion⁽²⁾. In this regard, systematic reviews show that the risk factors for developing DKA are younger age (< 2 years), low body mass index, ethnic minority background, no health insurance, misdiagnosis at first visit, delay in starting treatment, and history of recent infection. In addition, having immediate relatives with T1DM, parents with a higher education level or living in a region with a higher incidence of T1DM are factors that protect from presenting a DKA episode⁽⁹⁾.

DKA is the main cause of morbidity and mortality in children with T1DM1 due to secondary dehydration and the multiple associated biochemical alterations, mainly hydroelectrolytic (sodium, potassium, chlorine, and phosphorus) and acid-base^(6,10). The most feared consequence of this entity is the development of cerebral edema, with described incidences of 0.5 to 0.9%, but with an associated high mortality rate (21-24%) and the development of important neurological sequelae in the long term (impact on cognitive functions, fall in intellectual coefficient, loss of shortterm memory, among others) of 15 to 35%⁽²⁾. It is suspected that this complication is caused by a factors combination that occurs before the start of treatment and is exacerbated by the administered therapy. The main factors associated with the development of cerebral edema are the diabetes debut, younger age of presentation, longer duration of DKA symptoms, degree of acidosis at presentation (pH < 7.1), severe hypocapnia (PCO2 < 20 mmHg), the use of high volumes of fluids at resuscitation during the initial four hours of treatment, early insulin administration (first hour of resuscitation), high plasma urea nitrogen levels, delay or slowness in increasing plasma sodium concentration during DKA treatment, and the use of sodium bicarbonate(10). Thus, the management of these patients requires a fast, aggressive but controlled action in more complex units. Currently, in our country, there is a guideline from the Chilean Public Health System(11) which suggests part of the management of the main alterations observed in this pathology, and because it is a guide, each health center probably will adapt it with small modifications according to its own practices, maintaining the general principles of treatment⁽¹²⁾.

The objective of this study was to characterize the clinical profile of the children population with a DKA diagnosis who were admitted to the pediatric critical patient unit of the Clinical Hospital of the Pontifical Catholic University of Chile (UPCPUC), paying spe-

cial attention to evaluate the complications associated with the disease after the use of a standardized management protocol.

Patients and Method

A retrospective search of patients with DKA was performed in the database of hospitalized patients in the pediatric critical patient unit of the Pontifical Catholic University of Chile Clinical Hospital (UP-CPUC) between January 2000 and April 2015. After identifying the cases, the respective medical records were reviewed and data were collected for each episode diagnosed as DKA.

The data extracted from the medical record included demographic data such as age, gender, weight and height; clinical data of each episode, including whether it was a diabetes debut or a decompensation, days of symptoms before the visit, symptoms associated with the episode and laboratory tests at the time of diagnosis. In the case of a decompensation in a patient receiving insulin treatment, the adherence to the treatment and if any recent changes were made in the administered dose was recorded. In addition, the treatment used for the management of the episode and the complications associated with it were recorded. Finally, the length of stay in the pediatric intensive care unit and the survival were recorded.

For the management of these patients, the treating physicians relied primarily on a pre-established protocol for the standardized management of patients with this diagnosis, consisting of hydration management, insulin infusion, and electrolyte and acid-base management (Figure 1).

The results obtained from the medical record are shown as percentages and averages with their respective ranges or standard deviations respectively. An analysis was performed among subgroups of debutant patients versus previously diagnosed ones. For this purpose, the Student t-test, the Mann-Whitney test, and the Fisher's exact test were used for the different analyzed categories.

This study was approved by the ethics committee of the Faculty of Medicine of the Pontifical Catholic University of Chile..

Results

After completing the search of the database of the unit, 46 patients with DKA diagnosis at discharge were found. The average age of the patients was 8.9 ± 4.0 years with a range from 11 months to 17.6 years of age. 63% were female (29 patients).

The presentation symptoms of the evaluated group of patients were 63% polydipsia (29 patients), 56.5% polyuria (26 patients), 47.8% vomiting (22 patients), 43.4% fatigue and weakness (20 patients), 39.1% weight loss (18 patients), 34.7% abdominal pain (16 patients), 13% polyphagia (6 episodes), 10.8% headache (5 episodes), and 2.1% diarrhea (1 episode).

I. DKA of patients at the diabetes mellitus onset

67.4% (31 patients) had not been previously diagnosed with diabetes mellitus and were classified as having the disease for the first time.

The mean age of this group of patients was 7.2 ± 3.4 years (11 months and 14.75 years). In relation to the clinical data of this group of patients, the median length of symptoms at the time of consultation was 15 days (3 and 120 days) and the main symptoms of presentation were 87.1% polydipsia (27 patients), 80.6% polyuria (25 patients), 54.8% weight loss (17 patients), 84.2% fatigue and weakness (16 patients). Other described symptoms were 32.3% vomiting (10 patients), 22.6% abdominal pain (7 patients), 19.4% polyphagia (6 patients), and 6.5% headache (2 patients).

The laboratory data analysis showed that the mean blood glucose at diagnosis and admission was 567.7 \pm 166.2 mg/dL (269 and 859 mg/dL), and the median pH at diagnosis and admission was 7,24 (6.8 and 7.3), bicarbonate was 10.9 ± 4.6 mmol/L (2.9 and 17.9 mmol/L), the base excess was -14.7 ± 6.3 (-30 and -6.9), and the average osmolarity was 308.4 ± 15.6 mOsm/Kg (284 and 350 mOsm/Kg). Table 1 shows the general characteristics of the studied population.

II. DKA in patients with established T1DM

32.6% (15 patients) of the recorded episodes were patients already diagnosed with type 1 diabetes mellitus. Out of them, 66.6% (10 patients) were admitted due to poor adherence to the treatment. 20% (3 patients) had their insulin doses modified recently

The mean age of this group was 12.4 ± 2.5 years (9 and 17.6 years).

In relation to the clinical characterization of this group, the median length of symptoms at the time of consultation was one day (0 and 14 days). The presentation symptoms in the recorded events of these patients were mainly: 80% vomiting (12 patients), 60% abdominal pain (9 patients), and 50% fatigue and weakness (4 patients). Other symptoms reported were a headache 20% (3 patients), polydipsia 13.3% (2 patients), and polyuria, diarrhea and weight loss, all with 6.7% (1 patient each).

Out of the results obtained from the laboratory, the average glycemia at diagnosis and admission was 430.2 \pm 142.4 mg/dL (266 and 760 mg/dL), the median plasma pH at diagnosis and admission was 7.13 \pm

I. Fluid management

1. Shock

Use normal saline in bolus (10 ml/kg). Repeat if necessary until shock is compensated.

(*) All this volume must not be included in the daily fluid correction.

2. Daily maintenance and deficit replacement fluids establishment

 $\label{eq:maintenance} Maintenance volume: 1500 \ ml/m^2/day (> 10 \ Kg) \ or 100 \ ml/Kg/day (< 10 \ Kg) \\ Replacement volume according to water deficit: Weight loss 5%: 50 \ ml/Kg$

Weight loss 10%: 100 ml/Kg

Total daily fluid correction for the first 48 hours:

Maintenance volume + 50% Replacement volume

Use isotonic solutions (crystalloids) at least for the first 4 hours, then glucose and electrolytes can be added.

II. Glycemic control

1. Insulin therapy

Start insulin after 2 hours of normal saline hydration (maintenance + replacement).

Use continuous infusion insulin using a separate IV infusion pump. Starts at 0,1 UI/Kg/hour.

Insulin bolus is not indicated for DKA treatment.

Target: Decrease glycemia 50-100 mg/dL/hour.

If glycemia comes down lower than 50 mg/dL/h or there is not pH correction in 2-4 hours, increase insulin infusion in 20%.

2. Glucose administration

Start continuous glucose infusion after reach a blood glucose < 300 mg/dL or if it decreases faster than > 300 mg/dL/2 hours.

Initiate with 5% glucose and raise glucose infusion rate/concentration if needed or use the Two-bag system.

In case of progressive blood glucose decrease, you must increase the glucose infusion; do not decrease insulin infusion until acidosis is corrected.

III. Electrolytes management

1. Sodium

Give a sodium concentration of 150 mEq/L on fluids during the first 4 hours of treatment and then keep this concentration between 70-150 mEq/L.

Target: Maintain natremias between 135-150 mEq/L.

2. Potassium and phosphate replacement

Give a potassium concentration of 40 mEq/L on fluids (50% potassium chloride and 50% monopotassium phosphate) except in patients with anuria or serum K+ > 5.5 mEq/L.

Target: Maintain kalemias between 3.5-5.0 mEq/L and PO4 > 3 mEq/dL.

IV. Acidosis management

1. Bicarbonate replacement

Bicarbonate (bolus or added) is contraindicated in DKA patients.

In case of pH < 6.9, dismiss other metabolic etiologies of acidosis and discuss every particular case.

V. Laboratory

1. Immediate assessment (Emergency room)

Blood glucose (glycemia) – blood and urine ketones – blood gases – serum electrolytes (sodium, potassium, chloride, calcium, phosphate, magnesium) – blood ureic nitrogen and creatinine.

2. Patient with pH < 7.0

Hourly: Blood glucose (glycemia) or capillary glucose – blood gases.

Every 2 hours: serum electrolytes (sodium, potassium, chloride) – blood ketones.

Every 4-6 hours: calcium, phosphate, magnesium – ketones and glucose in urine – blood ureic nitrogen and creatinine.

3. Patient with pH > 7.0

Hourly: Blood glucose (glycemia) or capillary glucose.

Every 2 hours: Blood gases - serum electrolytes (sodium, potassium, chloride) - blood ketones.

Every 6 hours: calcium, phosphate, magnesium - ketones and glucose in urine - blood ureic nitrogen and creatinine.

(*) If pH ≥ 7.3 in two controls: Discontinue blood gases.

(**) If blood ketones are negative in two controls: Discontinue ketonemia.

Figure 1. General characteristics of DKA management protocol at UPCPUC.

 307 ± 13

0.1 (7.0 and 7.3), bicarbonate was 10.5 \pm 4.2 mmol/L (4.9 and 19 mmol/L), the base excess was -16.4 \pm 5.8 (-24 and -4.0), and the average osmolarity at diagnosis and admission was 303.8 \pm 9.1 mOsm/Kg (286 and 320 mOsm/Kg). All patients had positive ketonemia.

When comparing the two analyzed group of patients (onset patients versus patients with established diabetes mellitus) it was possible to observe significant differences in the presentation of their clinical picture, not only in the symptoms at the time of the visit but also in the duration of the symptoms and in the laboratory tests results at the time of the emergency service visit (Table 2).

Regarding the management, 100% of the studied patients received intravenous hydration before starting the insulin administration, most of which occurred in the emergency service or in the service from which the patient was referred. Continuous insulin infusion was indicated in 89% of the episodes of ketoacidosis admitted (41 patients), regardless of whether or not it was a debut of T1DM.

In relation to the complications associated with the management of these episodes, in 36.9% (17 patients) hypokalemia, defined as the presence of plasma potassium levels less than or equal to 3.5 mEq/dL, was observed and in 21.7% hyperkalemia (10 patients)

Table 1. General characteristics of patients with diabetic ketoacidosis (n = 46) General characteristics of patients at the time of first consultation Age Months - Mean ± SD 107 ± 48 Female gender - % (n) 63 (29) Days of symptoms - Median (range) 14 (0-120) DM 1 Debut - % (n) 67.4 (31) Symptoms at first visit - % (n) - Polydipsia 63 (29) - Polyuria 56.5 (26) - Polyphagia 13 (6) - Weight loss 39.1 (18) - Abdominal pain 34.7 (16) - Vomit 47.8 (22) - Diarrhea 2.1 (1) - Malaise 43.4 (20) - Headache 10.8 (5) Laboratory at first visit - Mean ± SD - Glycemia (mg/dL) 522 ± 170 7.17 ± 0.13 - Venous Blood pH - Bicarbonate (mmol/L) 10.7 ± 4.4 - Base excess -15.3 ± 6.1

| Characteristic | DM1 Debut Group (31) | Diabetic Group (15) | p value |
|---|--|---|--|
| Age months – Mean ± SD | 87 ± 41 | 148.9 ± 30.8 | < 0.001(1) |
| Days of symptoms - Median (range) | 15 (3-120) | 1 (0-14) | < 0.001(2) |
| Symptoms at first visit - % (n) - Polydipsia - Polyuria - Polyphagia - Weight loss - Abdominal pain - Vomit - Diarrhea - Malaise - Headache | 87.1 (27) 80.6 (25) 19.4 (6) 54.8 (17) 22.6 (7) 32.3 (10) 0 (0) 84.2 (16) 6.5 (2) | 13.3 (2) 6.7 (1) 0 (0) 6.7 (1) 60 (9) 80 (12) 6.7 (1) 50 (4) 20 (3) | < 0.001 ⁽³⁾ < 0.001 ⁽³⁾ - 0.003 ⁽³⁾ 0.021 ⁽³⁾ 0.004 ⁽³⁾ - 0.145 ⁽³⁾ 0.311 ⁽³⁾ |
| Glycemia (mg/dL) - Mean ± SD Venous Blood pH - Median (range) Bicarbonate (mmol/L) - Mean ± SD Base Excess - Mean ± SD Osmolarity (mOsm/L) - Mean ± SD Hypokalemia Hyperkalemia Arrythmia Cerebral edema Death | 567.7 ± 166.2 7.24 (6.8-7.4) 10.9 ± 4.6 -14.7 ± 6.3 308.4 ± 15.6 41.3 (13) 18.2 (4) 0 (0) 0 (0) 0 (0) | 430.2 ± 142.4 $7.13 (7.0-7.3)$ 10.5 ± 4.2 -16.4 ± 5.8 303.8 ± 9.1 $26.7 (4)$ $46.2 (6)$ $0 (0)$ $0 (0)$ $0 (0)$ | 0.009 ⁽¹⁾ 0.024 ⁽²⁾ 0.761 ⁽¹⁾ 0.387 ⁽¹⁾ 0.294 ⁽¹⁾ 0.352 ⁽³⁾ 0.123 ⁽³⁾ - |

- Osmolarity (mOsm/L)

defined as the presence of plasma potassium levels higher than or equal to 5.5 mEq/dL during the patient management. There were no significant differences in relation to these complications between the debutant group and the group of patients already diagnosed. The median length of stay in the unit was two days (one and six days). No episodes of arrhythmia, cerebral edema or death were recorded in the analyzed period (Table 2).

Discussion

67.4% of the patients discharged from the UPC-PUC due to DKA corresponded to patients who did not have a history of T1DM, thus making it the debut of their disease. This percentage is in line with what is described in the literature of developing countries^(4,8). It also coincides with the increase of the prevalence of T1DM in our country in recent years, which is why the index of suspicion of doctors who deal with patients who have not been previously diagnosed is higher, as has been reflected in previous publications⁽³⁾.

The clinical presentation of this group of patients shows clear differences between those who are making their debut with the disease and those who were already diagnosed with T1DM. Among them, the median period of symptoms which was considerably shorter in the group already diagnosed (1 day versus 15 days p < 0.001) suggesting several hypotheses such as the awareness of the disease and its consequences with an earlier consultation, more severe hyperglycemia, serial glycemic control at home, and less endogenous insulin reserve, among others. Another difference between the two groups was the clinical features of the recorded events, which corresponded mainly to symptoms associated with the biochemical consequences of hyperosmolarity in those patients who had no previous diagnosis and who, as a consequence, present the classic manifestations of diabetes that persist over time, as described in other international and national series(13). With respect to the biochemical analysis at the time of consultation of these patients, a lower average glycemia was observed in the group of patients already diagnosed, probably associated with fewer days of symptoms and the use of exogenous insulin. Despite this, the degree of metabolic acidosis in the venous blood gases was higher than in the debut group (pH 7.13 vs 7.24 p = 0.024; bicarbonate 10.5 vs 10.9 mmol/L p = 0.761).

In relation to the management of these patients, the protocol of the unit was followed, which considers the management of shock and dehydration, initially with normal saline solution in the emergency service and at admission to the critical patient unit, followed by the supply of glucose when more adequate blood glucose levels have been reached, the use of intravenous insulin in continuous infusion avoiding boluses administration in order to reduce some of the complications such as hypoglycemia, and hydroelectrolytic correction that involves an adequate supply of sodium, potassium, and phosphorus, contraindicating the use of sodium bicarbonate as part of the standard management in these patients. Therefore, 100% of the recruited patients received intravenous hydration with normal saline solution before starting the insulin supply, which was administered in continuous infusion in 89% of the patients. Out of the seven patients who did not receive continuous insulin infusion, five patients were diagnosed with T1DM before the ER admission, and it was decided to manage with the adjustment of their treatment scheme by their treating endocrinologist; and two patients who debuted with T1DM and did not receive continuous infusion, were patients transferred from the emergency service of other hospitals where they received insulin in boluses, followed by the continuous infusion for a short period of time in our unit. There are currently several studies that have demonstrated the beneficial effect of the use of insulin in continuous infusion, recommending its initial use in low doses (0.05-0.1U/K/h), although it has not shown better effectiveness, it has been associated with lower incidence of hypoglycemia^(5,14). Due to the need to control acidosis and ketosis as soon as possible, we use the infusion at 0.1U/K/h, managing glycemia with increasing or decreasing glucose load. Unfortunately, there are not comparative studies on the use of insulin in other forms of administration in children with DKA, which is why international guidelines continue to recommend this form of administration(5).

In the studied group patients, no severe complications associated with the ketoacidosis management were observed during the analyzed period, being hypokalemia the main alteration present in 37% of the recorded episodes, all of them in a mild to moderate range, where their management was an increase in the supply of potassium using the enteral route. In our group of patients, there were no episodes of arrhythmias, cerebral edema, or death. One of the reasons that, in our opinion, explains the low morbidity and absence of mortality in the studied group, was the standardized management protocol with specific goals on the times of hydration, glycemia and osmolarity decrease, the start of insulin and glucose administration, and electrolyte management, mainly focused on maintaining adequate plasma sodium concentrations and avoiding the use of sodium bicarbonate in these patients. The entire medical team knows this protocol, both staff and residents, which allows for a homogeneous management on arrival at the emergency service and in the Critical Patient Unit. The content of this protocol is based on the recommendations proposed by international guidelines⁽⁵⁾ and also on the available national guidelines for the management of the diabetes mellitus⁽¹¹⁾. On the other hand, most of these patients do not present severe hemodynamic compromise or significant tissue perfusion, which allows for the correction of hyperglycemia, acidosis and dehydration gradually, usually within 48 hours, due to the role that the rate of change of effective osmolality would play in the risk of developing cerebral edema⁽¹⁵⁾.

The main strengths of our study are that we have analyzed the total number of hospitalized patients over a period of time, without exclusions that would constitute a bias in the analysis of the data; and that we have treated all cases under the same protocol, which makes them fully comparable. We also collected a significant number of cases to analyze a relatively common cause of hospitalization in all pediatric ages and we could not find other recent Chilean studies describing these findings. One of the weaknesses of our study may be that it was a retrospective study with a review of the medical record, although it is a standardized medical record that has all these data available in all our patients.

Conclusion

DKA is one of the most serious complications of T1DM and can present high morbidity if it is not diagnosed early and managed promptly. Early diagnosis should be based on a high rate of suspicion, which is given by knowing the characteristic symptoms. DKA occurs with severe hydroelectrolytic and acid-base alterations; therefore, a timely and especially protocolized management reduces its morbidity and mortality.

In our group of patients, the protocolized management by a specialized team in relation to the contribution of volume, insulin initiation and hydroelectrolytic and acid-base alterations correction, allowed an adequate correction of the alterations, without severe complications

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.

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.

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