

Anisakis Allergy: Raising Awareness

Alergia ao Anisakis: Sensibilizar para o Seu Diagnóstico



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Acta Med Port 2022 Jul-Aug;35(7-8):578-583 • <https://doi.org/10.20344/amp.15908>

ABSTRACT

Introduction: Ingestion of *Anisakis* is a common cause of allergic reactions to seafood in countries in which undercooked/raw seafood is part of gastronomic traditions. Despite current trends for the ingestion of raw/marinated/undercooked fish, the prevalence rate of anisakiasis and allergy to *Anisakis* is still considered to be low in Portugal. We aimed to review the current pathogenic mechanisms, the clinical and diagnostic approach of *Anisakis* allergy, and *Anisakis*-related eviction measures, while raising awareness to this problem.

Material and Methods: Literature search in the MEDLINE and Scopus databases, regarding *Anisakis* allergy.

Conclusion: Assessment of sensitization to *Anisakis* should be included in the workup study of urticaria/angioedema and anaphylaxis, as there is a rise in consumption of raw and undercooked fish. Ingestion of previously frozen and properly cooked fish appears to be safe for most patients who are allergic to *Anisakis*.

Keywords: Anaphylaxis; Anisakiasis; Anisakis; Food Hypersensitivity; Hypersensitivity; Urticaria

RESUMO

Introdução: A ingestão de *Anisakis* é uma causa frequente de alergia a pescado, em países onde o hábito de ingerir estes alimentos crus/pouco cozinhados faz parte das tradições gastronómicas. Apesar do aumento na frequência de ingestão de peixe cru/marinado/pouco cozinhado que se verifica em Portugal, a prevalência de anisquiase e alergia ao *Anisakis* continua a ser considerada como sendo baixa. O nosso objectivo foi rever os mecanismos fisiopatológicos da alergia a *Anisakis*, a abordagem clínica e diagnóstica, e as medidas de evicção de *Anisakis*. Em simultâneo, pretendemos consciencializar para este problema de saúde crescente.

Material e Métodos: Foi efetuada uma pesquisa e revisão bibliográfica nas bases de dados MEDLINE e Scopus, sobre alergia ao *Anisakis* e anisquiase.

Conclusão: A avaliação da sensibilização ao *Anisakis* deve ser incluída no estudo inicial da urticária/angioedema e anafilaxia, dado que o consumo de peixe cru e malcozinhado está a aumentar. A ingestão de peixe previamente congelado e sujeito a uma cocção correta parece ser segura para a grande maioria dos doentes alérgicos ao *Anisakis*.

Palavras-chave: Anafilaxia; Anisakis; Anisquiase; Hipersensibilidade; Hipersensibilidade Alimentar; Urticária

INTRODUCTION

The ingestion of *Anisakis* is a common cause of allergic reactions to seafood in countries with high fish consumption, particularly in those in which ingestion of undercooked/raw seafood is part of their gastronomic traditions.^{1,2} Even though the specific prevalence and incidence rates are unknown, gastro-allergic anisakiasis (parasitosis caused by nematodes of the genus *Anisakis*). *Anisakis* allergy and asymptomatic sensitization are particularly common in countries in which raw fish (e.g. Japan), or undercooked/marinated fish (e.g. Italy and Spanish Basque Country) are an important part of the traditional gastronomy.¹ Despite having one of the highest fish consumption rates *per capita* in the European Union (EU), Portugal is currently considered as having a low prevalence rate of *Anisakis* allergy.³ Whether this results from a reduced awareness/underdiagnosis, or a low prevalence rate granted by the 2004's EU regulations on hygiene of foodstuffs,⁴ remains largely unknown. Nonetheless, the growing trend of ingestion of raw fish (i.e. *sushi* and *sashimi*), undercooked (e.g. *tataki*) and marinated fish (e.g. *ceviche*) may require a paradigm shift, namely one that moves towards a more thorough evaluation of idiopathic allergic reactions that may be related, even if remotely, to the

ingestion of fish.

We aimed to review current pathogenic mechanisms, the clinical and diagnostic approach to *Anisakis* allergy, and *Anisakis*-related eviction measures, while raising awareness to this problem.

MATERIAL AND METHODS

A literature search was made in the MEDLINE® and Scopus® databases using the PubMed and Google Scholar search engines. Conjugated keywords used included: '*Anisakis*', '*Anisakiasis*', '*Gastro-allergic anisakiasis*', '*urticaria*', '*anaphylaxis*'. The search was limited to articles published during the past 10 years, but relevant clinical and observational studies published before, and those regarding oral provocations with *Anisakis* extracts and allergen components were also cited. No language restrictions were included. A narrative review was performed based on all relevant literature encountered.

DISCUSSION

Microbiology and life cycle

Most allergic reactions related to *Anisakis* have been

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Recebido/Received: 07/02/2021 - Aceite/Accepted: 23/06/2021 - Publicado Online/Published Online: 04/04/2022 - Publicado/Published: 01/07/2022

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found to be caused by the so called *Anisakis simplex* complex, which includes *A. simplex*, *A. pegreffii* and *A. berlandi*.⁵ However, other members of the *Anisakidae* family, such as the *Pseudoterranova* genus, may also induce disease.⁶ Humans are accidental hosts for these nematodes. Infection occurs following ingestion of viable larvae present in raw, or even undercooked seafood. The life cycle of *Anisakis* is summarized in Fig. 1. While fish are quite often parasitized, cephalopods [the taxonomic group (class) that includes for

instance octopuses, squids and cuttlefishes] are infrequent hosts for *A. simplex*.⁷

Humans may suffer from different diseases caused by the *A. simplex* complex. Anisakiasis is a parasitic infection that may involve gastric, intestinal or extra-gastrointestinal mucosae and that may or may not include allergic symptoms, depending on the patient's immune response.⁵ Patients with no evidence of current infection may also display allergic symptoms.⁵

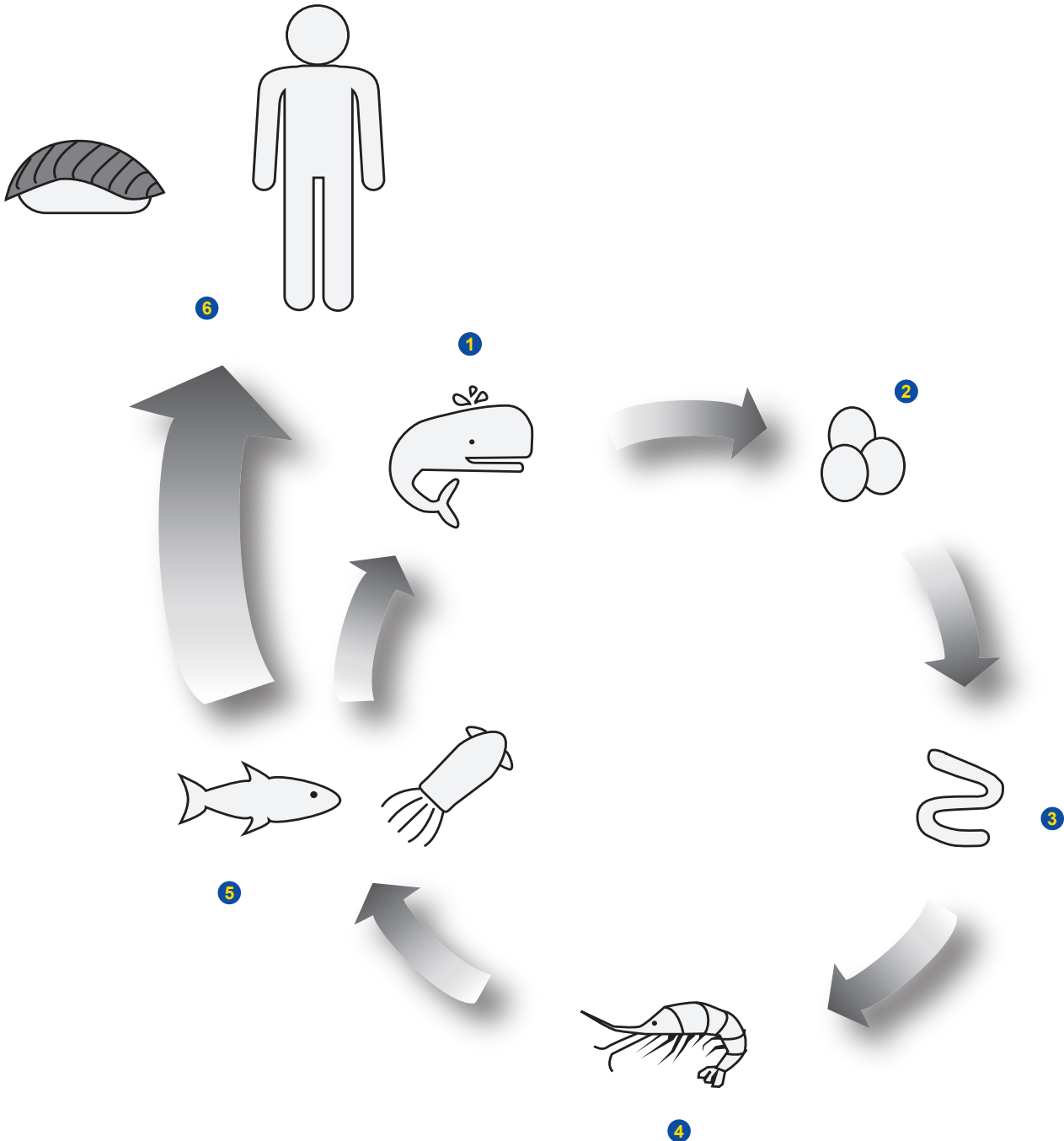


Figure 1 – Life cycle of *Anisakis*. 1: Eggs are released into the gastric lumen of the definitive host and are later excreted with faecal matter; 2: Hatching occurs at the ocean floor, where stage 2 larvae emerge; 3: Stage 2 larvae are ingested by planktonic crustaceans (e.g. krill) and other invertebrates, and develop into L3; 4: Infested zooplankton is ingested by fish, cephalopods and cetaceans (which may also ingest the former); 5: Stage 3 larvae (L3) of the *Anisakis* complex reach the adult stage at the gastric mucosae of large marine mammals such as cetaceans or pinnipeds; 6: Humans ingest viable larvae, present in raw or undercooked seafood.

Epidemiology

Little is known about the true global burden of anisakiasis. Sensitization rates seem to be increasing worldwide, reaching a seroprevalence of 27.4%² and 29.8%⁸ in the Spanish general population and in patients showing urticaria and/or food allergy in Japan, respectively. These numbers are even more significant among chronic urticaria patients, ranging between 14% and 63%.^{9,10} True allergy to *Anisakis* may be more prevalent than seafood allergy *per se* in countries with a high burden,⁸ ranging from 4.5% to 15% of cases of suspected seafood allergy.^{9,11} Nevertheless, these results should be interpreted with caution as they report data from different populations.

In Portugal, a study by Falcão *et al* showed a sensitization prevalence rate of 5.5% among children with relapsing acute urticaria¹² but studies on the actual prevalence rate among both children and adults are lacking. In fact, Portugal is considered a low burden country as far as allergy to *Anisakis* is concerned, notwithstanding the fact that cod and most of the fish on Portuguese shores are often parasitized¹³⁻¹⁵ and that the notification of *Anisakis* in fish has been increasing.¹⁶ This may be due to the absence of gastronomic traditions involving the ingestion of undercooked/raw fish but also due to compliance with the aforementioned EU regulations. However, at least two clinical cases of anisakiasis diagnosed during gastroscopy have been reported by Portuguese authors, in the last few years. These have been associated with the ingestion of undercooked scabbard (*Aphanopus carbo*)¹⁷ and *sushi*.¹⁸ Whether the increased exposure of the Portuguese population to parasitized fish is actually associated with an increase in the incidence of sensitization and allergy to *Anisakis* is still unknown. This surely results from a lack of studies on this matter but awareness of the issue may also be lacking.

Pathophysiology

Both gastrointestinal anisakiasis and ectopic anisakiasis (i.e., involving the oral cavity, lungs, peritoneal cavity) may present without allergic symptoms. Pure gastrointestinal anisakiasis usually presents with mild-to-severe abdominal pain, hours to days following ingestion of live larvae.¹⁹ *Anisakis* can penetrate the mucosal lining through release of proteases.²⁰ Local innate immune responses induce the formation of an eosinophilic and/or neutrophilic granuloma surrounding the larvae. Eosinophilic inflammation sustained by local mastocytosis leads to abdominal pain. Parasites usually perish after a few days, due to the deleterious effects of eosinophil major basic protein, inducible nitric oxide synthase, peroxidases and eosinophil-derived neurotoxin.¹⁹

Adaptive immunity and namely the Th1/Th2 balance plays a vital role in the course of the disease. As it seems, patients with pure gastrointestinal disease present with a less adapted strictly Th1-driven immune response,²¹ often requiring surgical, or endoscopic removal of parasites.¹⁷⁻¹⁹ On the other hand, a more Th2-driven immune response induces release of polyclonal immunoglobulin (Ig) E, which further activates mast cells. Mast cell mediators induce

massive and quick constriction of gastrointestinal and bronchial smooth muscle leading to intense vomiting, profuse diarrhea and cough, which may, by itself, eliminate larvae.²¹ However, patients in which the Th2 response lacks proper regulation may also display urticaria, angioedema or even anaphylaxis due to massive mast cell activation. Such acute manifestations may recur on reexposure, creating the false impression that patients suffer from chronic rather than relapsing acute urticaria/angioedema, or anaphylaxis.^{21,22}

Clinical manifestations

Gastrointestinal anisakiasis may involve the gastric and/or intestinal mucosae. Strict gastric involvement usually presents with acute epigastric pain, nausea and vomiting, with or without fever within 24 hours following the ingestion of undercooked/raw fish.²³ Presentation of intestinal anisakiasis is usually delayed from 48 hours up to until one week following exposure, and usually includes abdominal pain, diarrhea with mucus and/or blood, and fever.²⁴ More severe cases may present with intestinal obstruction, appendicitis or peritonitis.²⁵ The latter may occur due to migration through the intestinal wall and into the peritoneal cavity and such migration may also occur into the pleural cavity.²⁶

Allergic manifestations from exposure to *Anisakis* may occur because of ingestion, cutaneous or even respiratory exposure.¹ Gastroallergic anisakiasis presents with similar gastrointestinal manifestations but may be associated with urticaria/angioedema, bronchospasm or even anaphylactic shock.²⁵ Occupational cutaneous or respiratory exposure may induce urticaria, rhinitis and conjunctivitis, or even anaphylaxis.²⁷⁻²⁹

Diagnosis

Diagnosis of urticaria or anaphylaxis related with *Anisakis* may be underreported in countries in which the prevalence rate is unknown, as many of those allergic to *Anisakis* may display symptoms only once or twice a year, despite having a high fish consumption.^{30,31} Moreover, clinical manifestations may appear more than 24 hours following ingestion of infested fish, which makes it more difficult to recognize in low prevalence areas.³²

When approaching patients with suspected allergy to *Anisakis*/gastro-allergic anisakiasis, one should keep in mind that the patient may be currently infected. These patients usually present significantly higher total IgE levels during the acute reaction.¹⁷ Physical removal of the worm through endoscopy or surgery is usually curative.^{17,23} In spite of the absence of international consensus, a reasonable approach for patients presenting with urticaria/angioedema or anaphylaxis with accompanying gastrointestinal manifestations and acutely high total IgE with a recent history of ingestion of undercooked/raw fish may include an endoscopic study. A larger proportion of patients may display only recurrent urticaria with/without angioedema upon exposure, mimicking chronic urticaria, or even bronchospasm or anaphylaxis following exposure to the live parasite, in the absence of evidence of gastrointestinal infection.¹ In fact,

the prevalence rate of allergy to *Anisakis* has been reported in some series to be around 67%¹ and 10%²⁰ of patients suffering from chronic idiopathic urticaria and idiopathic anaphylaxis, respectively. Both specific IgE and skin prick tests (SPT) for *Anisakis* may be used for the assessment of sensitization and display similar sensitivities.¹ Nonetheless, a positive specific IgE or a positive SPT do not make the diagnosis of allergy to *Anisakis*, as asymptomatic sensitization should be considered.

Asymptomatic sensitization has been associated with *Anisakis* specific IgE (sIgE) below 3.5 kU/L.³³ However, patients with values above that cutoff may not be truly allergic and the opposite may also occur.³⁴ Elevated specific IgE for *Anisakis* may occur due to cross-sensitization with other invertebrates, due to the presence of panallergens (i.e. allergens which are present in closely related organisms from a phylogenetic point of view; examples: casein in mammalian milk, tropomyosin from the exoskeleton of arthropods and crustaceans.) - tropomyosin (*Ani s 3*), present in mites and crustaceans,^{35, 36} or paramyosin (*Ani s 2*), present in *Ascaris* - that are usually present in allergenic extracts.³⁷

Several methods have been proposed to avoid misdiagnosing true allergy. In order to exclude cross-reactivity with *Ascaris*, Brusca and col. have proposed a diagnostic algorithm based on a ratio between sIgE for *Anisakis* over sIgE for *Ascaris* above 4.2, as diagnostic of true sensitization to *Anisakis*, following exclusion of sensitization to tropomyosin.³⁴ Besides *Ani s 3*, *Ani s 1* is also commercially available in Portugal, while other allergen components have been extensively used for research purposes.^{33, 35, 38} Serine proteases (i.e. *Ani s 1*, and *Ani s 7*), paramyosin (i.e. *Ani s 2*), a protein with unknown function (*Ani s 12*) and hemoglobin (i.e. *Ani s 13*) are considered major allergens, as they are found in 85%, 100%, 88%, 57% and 64% of *A. simplex* infections, respectively.³⁹⁻⁴¹ *Ani s 13* seems to be more sensitive and specific than *Ani s 1* or *Ani s 7*, while showing absence of cross-reactivity with *Ascaris* hemoglobin.⁴²

Until this moment, no double-blind oral food challenge trials have shown that ingestion of individualized allergens/dead larvae lead to symptoms. In fact, previous studies have shown that truly allergic patients tolerate the ingestion of dead/unviable larvae, displaying no allergic reactions.⁴³⁻⁴⁵ Such reports were based in oral challenges with 11⁴³ to 20⁴⁵ previously frozen encapsulated larvae that had been obtained from gastroscopic procedures, or from 20 to 40 mg (equivalent to 105 to 201 larvae, respectively) of previously frozen lyophilized encapsulated larvae obtained from parasitized fish.⁴⁴ However, self-reported reactions on patients under eviction measures have cast a potentially reasonable doubt on the ability of allergens to penetrate through highly permeable gastrointestinal mucosae, causing recurrent acute urticaria.⁴⁶ In fact, *Ani s 1*, *Ani s 4*, *Ani s 5*⁴⁷ and *Ani s 11*-like protein (*Ani s 11.0201*)³⁸ do retain *in vitro* IgE-binding ability following prolonged exposure to high temperatures. Nonetheless, strong *in vivo* evidence of reactions following ingestion of properly frozen and cooked fish is still lacking. There is, however, evidence that trans-

cutaneous and airborne exposure to allergens of *Anisakis* may induce cutaneous, respiratory, or even multisystemic reactions, as mentioned above.²⁷⁻²⁹

Management

Several *Anisakis* eviction measures have been proposed and are currently regulated by the EU.⁴ Different recommendations have been proposed for patients with anisakis allergy, with varying degrees of restrictiveness.

Viable larvae are not usually found in frozen fish.⁴⁸ As such, less restrictive measures include ingestion of fish that has been frozen at -35°C for more than 24 hours, or -20°C for more than 72 hours - preferably deep-frozen at deep-sea.⁴⁵ This simple measure seems to be enough to ensure that patients with previous gastro-allergic anisakiasis and, or urticaria remain symptom-free.^{5, 31} While strict eviction of non-frozen and undercooked fish may be enough to avoid reactions in most patients,⁴⁹ ingesting only fish that has been cooked for at least 10 minutes at a 60°C temperature is strongly recommended. Smoked, or marinated fish should also be avoided since these are not usually previously frozen, nor heated, nor processed in a way that would kill live larvae. Ingestion of portions nearest to the tail of large specimens should be preferred, as muscle nearest to the digestive system often possesses larvae.²⁰ Concerning canned fish, reports on safety are ambiguous as the presence of larvae depends of the specific process of conservation - those heated before canning seem to be safe, however industrial tuna in olive oil preparations have been associated with self-reported reactions.¹¹ Moreover, some authors propose lowering the risk of exposure to *Anisakis* through consumption of farmed fish,^{7, 50} or species that are usually not heavily parasitized (e.g. wild gilthead seabream, *Sparus aurata*),⁵¹ while following the aforementioned preventive measures, after making it clear to the patient that it may be impossible to predict whether allergic reactions will recur.

Restrictive measures for the prevention of allergic reactions may include avoidance of all seafood, regardless of fish processing methods, with obvious deleterious effects to general health and wellbeing of those allergic to *Anisakis*. This option is based on self-reported cases of allergic reactions following ingestion of previously frozen, aquaculture fish and, or canned fish,⁵² which have been purportedly explained by the ability of *Anisakis* allergens to retain IgE-binding abilities, even following freezing and treatment with high temperatures.⁴⁷ Nonetheless, compliance with restrictive eviction recommendations may be low in patients that appreciate seafood, as most present a low frequency of allergic reactions.³⁰

Recommendations for the prevention of allergic reactions require an individual risk-benefit assessment, since most patients remain reaction-free when less restrictive preventive measures are followed but may be required for those that sustain recurrent reactions.⁴⁹ Oral food challenges may support the diagnosis and may help to establish specific recommendations. This procedure seems to be

safe, since the large majority of patients do not display positive challenges following the ingestion of non-viable/dead larvae.⁴⁴ However, standardization is still lacking.

Standardization is also lacking in the proper approach to acute gastric and intestinal infection. Nevertheless, endoscopic and surgical approaches have been successfully used.²³ Moreover, some authors also suggest a course of albendazole (400 - 800 mg qd, during six to 21 days) but evidence on its efficacy is also lacking.²⁶

CONCLUSION

Anisakis allergy may be an underdiagnosed cause for urticaria/angioedema and anaphylaxis in Portugal, due to a rise in consumption of undercooked, raw or marinated fish. The authors recommend that patients presenting allergic symptoms related to the ingestion of fish – especially if undercooked or raw – be studied for IgE mediated sensitization to *Anisakis*. The correct approach to acute infection by *Anisakis* lacks a broad consensus but performing endoscopic studies on patients presenting with urticaria, gastrointestinal symptoms and high total IgE hours to days after the ingestion of undercooked/raw fish might be reasonable approach.

While ingestion of previously frozen and properly cooked fish seems to be safe in the vast majority of patients in whom IgE mediated allergy was confirmed, better diagnostic markers may be needed in order to prevent potential systemic reactions in the remainder few.

AUTHORS CONTRIBUTION

TAR: Main author. Literature research, conception and draft of the paper.

DS: Contributed to the draft and critical review of the paper.

PROTECTION OF HUMAN SUBJECTS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration issued by the World Medical Association and updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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