

Venous Thromboembolism in Pediatric Age: A 15 Year Retrospective Review

Tromboembolismo Venoso em Idade Pediátrica: Estudo Retrospectivo de 15 Anos



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ABSTRACT

Introduction: Pulmonary thromboembolism and deep venous thrombosis occur in pediatric age, with unknown incidence, morbidity and mortality. Our aim is to review the epidemiology, clinical presentation, complementary diagnostic tests and prognosis of patients with pulmonary thromboembolism and deep venous thrombosis.

Material and Methods: Retrospective, descriptive and analytical study of pediatric patients admitted to a Level II hospital for pulmonary thromboembolism and deep venous thrombosis, between 2000 and 2014. Demographic characteristics, clinical history, comorbidities and risk factors were studied.

Results: Eleven patients (n = 7 pulmonary thromboembolism, n = 5 deep venous thrombosis, n = 1 both), 64% females and with 16 years old average, were admitted. All patients with pulmonary thromboembolism presented symptoms of chest pain and/or dyspnea, 25% syncope/palpitations and 25% fever. All patients with deep venous thrombosis reported localized pain at the site of obstruction, 83% edema/cyanosis of the affected limb and 17% fever. The study of positive thrombophilia was the most frequent risk factor in both entities. The mean value of D-dimers was 3252 ug/dL and 2660 ug/dL in pulmonary thromboembolism and deep venous thrombosis, respectively. All patients started anticoagulation, three required intensive care, two had sequelae and one died.

Discussion: All patients had at least one risk factor, and hereditary hypercoagulability was most commonly established.

Conclusions: The increased incidence in the pediatric population described in some studies can be attributed to an increased awareness of this pathology, medical advances and increasing survival of chronic diseases. There is a lack of evidence-based recommendations identifying patients at risk of thrombosis so that decisions can be made carefully, balancing the risk and benefit in each case.

Keywords: Child; Pulmonary Embolism; Venous Thrombosis

RESUMO

Introdução: O tromboembolismo pulmonar e trombose venosa profunda ocorrem em idade pediátrica com incidência, morbilidade e mortalidade desconhecidas. O objetivo foi rever epidemiologia, apresentação clínica, exames complementares de diagnóstico e prognóstico de doentes com tromboembolismo pulmonar e trombose venosa profunda.

Material e Métodos: Estudo retrospectivo, descritivo e analítico de doentes pediátricos internados num hospital de nível II por tromboembolismo pulmonar e trombose venosa profunda, entre 2000 e 2014. Estudaram-se características demográficas, história clínica, comorbilidades e fatores de risco.

Resultados: Foram internados 11 doentes (sete com tromboembolismo pulmonar, cinco com trombose venosa profunda e um com ambos), 64% do género feminino e idade média de 16 anos. Todos os doentes com tromboembolismo pulmonar referiam toracalgia/dispneia, 25% síncope/palpitações e 25% febre. Todos os doentes com trombose venosa profunda referiam dor no local da obstrução, 83% edema/cianose do membro afetado e 17% febre. O estudo da trombofilia positivo foi o fator de risco mais frequente nas duas entidades. O valor médio dos D-dímeros foi 3252 ug/L e 2660 ug/L no tromboembolismo pulmonar e trombose venosa profunda, respetivamente. Todos os doentes iniciaram anticoagulação, três necessitaram de cuidados intensivos, três apresentaram sequelas e houve um óbito.

Discussão: Todos os doentes tinham pelo menos um fator de risco associado e as condições de hipercoagulabilidade herdadas foram o fator de risco mais frequentemente encontrado nos nossos adolescentes.

Conclusão: O aumento da incidência na população pediátrica descrito na literatura pode ser atribuído à crescente sensibilização para esta patologia, aos avanços médicos e aumento da sobrevida de doenças crónicas. Escasseiam recomendações baseadas na evidência que identifiquem os doentes com risco de trombose, para que as decisões possam ser tomadas de forma cuidadosa, equilibrando o risco e benefício em cada caso.

Palavras-chave: Criança; Embolia Pulmonar; Trombose Venosa

INTRODUCTION

Venous thromboembolism (VT) includes deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) and is a potentially devastating pathology with a significant impact on the quality of life of paediatric patients as well as on associated hospital costs.¹ Considering a wider age range for paediatric attendance, the healthcare improvement, a longer survival from severe diseases and an in-

creasing awareness of vascular events, VT is becoming more and more recognised as a relevant paediatric issue.²

A PTE incidence of 0.07 per 10,000 children and adolescent aged between one month and 18 years has been described by the VT Canadian registry, corresponding to an incidence of 5.3 per 10,000 children admitted to hospital.³ An incidence of 0.07 to 0.14 / 10,000 children has been

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estimated in Europe, as well as a 2% mortality rate.⁴

VT pathophysiology is explained by the Virchow's triad, including venous stasis, endothelial injury/dysfunction and hypercoagulability, with a multifactorial aetiology and the presence of some underlying risk factors in most cases; only 5-10% of the patients in paediatric age groups were considered with an idiopathic condition, compared to 60% in adult patients.^{4,7}

Different classifications are used, including (i) first or recurrent episode, (ii) symptomatic vs. asymptomatic, (iii) acute vs. chronic, (iv) veno-occlusive vs. non-occlusive, (v) idiopathic vs. with underlying risk factors. The use of exogenous oestrogens, the use of central venous catheters, a reduced mobility and thrombophilia (including the presence of transient or persistent anti-phospholipid antibodies, acquired or inherited anticoagulant abnormalities, factor V Leiden or prothrombin gene G20210A mutations) have been included as prothrombotic risk factors. The term thrombophilia was introduced to describe the presence - usually inherited - of an increased predisposition for the occurrence of thrombotic events.²

The contribution of acute risk factors to the development of VT, in isolation as underlying a chronic disease, has been shown. Injuries and postoperative settings are frequent risk factors for its development in children and adolescent patients with no chronic disease. Other common risk factors include the presence of infectious diseases, the use of oral contraceptives, long-term parenteral nutrition and other inflammatory conditions.^{7,8} The use of central venous catheters, an underlying malignant disease and postoperative status (following heart surgery) were the most prevalent causes of VT described by the Canadian Childhood Thrombophilia registry,⁵ while infectious diseases and the use of central venous catheters were described by a recent US cohort study.⁶

Inherited and acquired thrombophilia and markers of coagulation activation have been considered as blood risk factors for paediatric VT. Inherited thrombophilia (as for instance factor V Leiden or prothrombin gene G20210A mutations) is frequently found in Caucasian populations, with an approximate prevalence of 5 and 2%, respectively. An elevated factor VIII activity with underlying significant infections and inflammatory states, anticoagulant deficiencies and disseminated intravascular coagulation underlying bacterial sepsis, the production of inhibiting antibodies in viral acute infections and para-infectious disorders with the development of anti-phospholipid antibodies are common examples of acquired thrombophilia in children.²

In fact, it is estimated that 60% predisposition to thrombosis is attributable to genetic factors.^{9,10} Patients with thrombophilia usually present with an initial thrombotic event under the age of 25 and an increasing chance of recurrence with patient's age, as well as with the association of other underlying risk factors. There is a low risk for thrombosis under the age of 15 due to this condition, with a 2 to 4% increasing annual risk onwards.¹²

The estimated risk based on adult populations with VT is shown in Table 1, showing the relevance of VT associated with risk factors due to inherited or acquired thrombophilia.²

A high level of suspicion for an acute VT episode should be taken into consideration with the presence of clinical thrombotic risks and a family history of early VT or other vascular disorders, as well as the presence of an history of known thrombophilia traits and clinical signs and symptoms, depending on the anatomical location and system involved and influenced by veno-occlusive characteristics and chronicity. The presence of unilateral limb painful oedema is the classical manifestation of DVT and signs and symptoms may include the presence of cervical and facial oedema and headache in case of involvement of superior vena cava. PTE usually presents with unexplained acute dyspnoea and underlying pleuritic chest pain, even though it may be asymptomatic or present with mild symptoms in children, mainly when limited segments of the pulmonary arteries are involved. In the case of involvement of renal veins, haematuria and thrombocytopenia are the typical clinical presentation and eventually with the presence of an abdominal mass and oligo-anuria (when bilateral). Chronic VT may be detected by accident in imaging requested due to other reasons, as in the presence of an asymptomatic thrombosis of dural venous sinuses or it may present with signs and symptoms of chronic venous obstruction or post-thrombotic syndrome secondary to limb venous thrombosis, including limb painful oedema, dilated superficial collateral veins, venous stasis dermatitis or skin ulceration.²

Complete blood count, coagulation, thrombophilia screening and beta-hCG blood test in post-menarche adolescents are included in paediatric VT workup. Thrombophilia screening panel and risk factors for VT used in paediatric evaluations and recommended by the Subcommittee for Perinatal and Paediatric Thrombosis of the International Society on Thrombosis and Haemostasis for the diagnosis of acute VT in children and adolescents are shown in Table 2.^{2,13}

Suspected distal or proximal DVT may be confirmed by Doppler ultrasonography and MRI or CT scan are frequently

Table 1 – Estimated risk of VT in selected thrombophilia traits

Thrombophilia	Estimated risk of VT (x Baseline)
Hyperhomocysteinaemia	2.5
Heterozygous prothrombin gene G20210A mutation	3
Heterozygous factor V Leiden mutation	2 - 7
Oral contraceptive + Heterozygous factor V Leiden mutation	35
Homozygous factor V Leiden mutation	80

Table 2 – Thrombophilia underlying an acute VT episode in the paediatric age

Thrombophilia
Inherited
Factor V Leiden polymorphism
Prothrombin gene <i>G20210A</i> polymorphism
Elevated lipoprotein (a) levels
Acquired or inherited
Anti-thrombin deficiency
Protein C deficiency
Protein S deficiency
Elevated factor VIII activity
Hyperhomocysteinaemia
Antiphospholipid antibodies
Disseminated intravascular coagulation
Resistance to activated protein C

needed for the identification of the involvement of perineal and abdominal veins. The use of spiral CT scan or ventilation/perfusion lung scintigraphy is usually used to confirm the presence of PTE.^{2,13}

Heparin and warfarin are the most widely used conventional anti-thrombotic agents and the target levels of anticoagulation should be based on recent paediatric recommendations. Hypercoagulability underlying this pathology is attenuated by these agents and therefore the risk of progression of the thrombus and embolism is reduced, relying on intrinsic fibrinolytic mechanisms that allow for a progressive dissolution of the thrombus.¹⁴

Even though around half of the venous thrombotic events are settled with 3-6-month traditional anticoagulation therapy, a risk of post-thrombotic syndrome remains, probably due to complete venous obstruction and local inflammatory disorders.¹⁵⁻¹⁷ While coagulation is reduced by anticoagulant therapy, fibrinolysis is increased by thrombolytic therapy due to an enhanced activation of plasminogen into plasmin.² Despite increasingly used, the indication for thrombolytic therapy in children have not yet been clearly established. Its use has been recommended by the American College of Chest Physicians in patients suffering from life, organ or limb-threatening venous thromboembolism even though it should not be used as routine.¹⁴ This therapy in a paediatric age is recommended by the American Heart Association when the benefits outweigh the risks.¹⁸

In addition, surgical thrombectomy in children with life-threatening thromboembolism is recommended by the American College of Chest Physicians. Inferior vena cava filter placement is recommended in children over 10 kg and presenting with lower limb thromboembolism and a contraindication for anticoagulation therapy.¹⁴

Acute complications of VT may arise from antithrombotic interventions or from the own thrombotic event, while long-term complications include the presence of recurrent VT, chronic hypertension in case of the involvement of the renal veins, variceal haemorrhage related to portal vein thrombo-

sis, chronic superior vena cava syndrome and development of post-thrombotic syndrome.¹⁶

This study aimed at a revision of the epidemiology, clinical presentation, diagnostic workup and outcome in paediatric patients with pulmonary thromboembolism and deep venous thrombosis. In addition, the presence of recognised potential risk factors for this pathology has been described in our group of patients.

MATERIAL AND METHODS

This was a retrospective, descriptive and analytical study of all the patients with VT (including DVT and PTE) aged under 18 and admitted to a level-II hospital throughout a 15-year period.

Data on children and adolescent patients admitted between 1 Jan 2000 and 31 Dec 2014 were collected: patient's gender, relevant personal and family history, in addition to VT-related variables including patient's age at diagnosis, presentation signs and symptoms, associated risk factors, comorbidities, treatment, clinical progression and complications.

Patients presenting with PTE confirmed by X-ray and those with DVT confirmed by ultrasound were considered. The presence of obesity was considered for BMI (body mass index) beyond the 97th percentile of the reference gender- and age-specific WHO (World Health Organization) curves. The study was approved by the Ethics Commission for Health of the *Centro Hospitalar Tondela-Viseu E.P.E.* and an informed consent was not required.

Data analysis

Data were collected and coded into a grid at an Excel[®], version 2011 (Microsoft Corporation, USA) software and using the SPSS[®], version 20 for Mac (SPSS, IL, USA) software for a descriptive analysis of a set of variables aimed at the characterisation of our group of patients, as well as to build up 95% confidence intervals (CI).

RESULTS

A total of 11 patients with VT were identified throughout the study period, corresponding to 13 in-hospital stays: seven patients with PTE, five with DVT and two patients with both pathologies, corresponding to three thrombotic events, two with PTE and one with DVT. Four events have occurred up to 2007 (31% of the patients) and nine onwards (69%) (Fig. 1), while this pathology has corresponded to 0.0004% of the hospital stays throughout this period.

Mostly female patients (64%) and a 16 year mean and median age at diagnosis (± 1.4), 95% CI 15.2 – 17.0, 13-17 year range were found.

All the patients presented with at least one associated risk factor (9% presented with one, 37% with two, 18% with three, 27% with four and 9% with five) (Table 3) and the presence of thrombophilia was the most frequently found risk factor in both entities, followed by obesity and the use of oral contraceptive drugs.

All the patients with hyperhomocysteinaemia presented

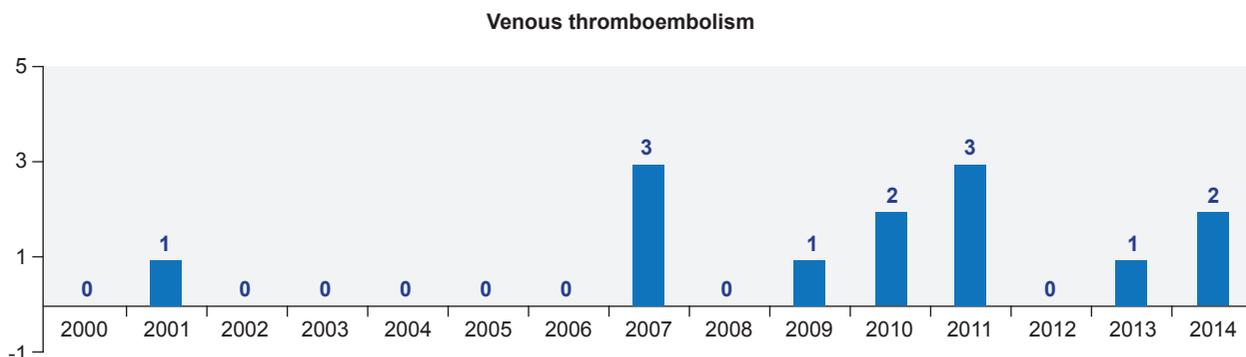


Figure 1 – Annual distribution of patients with VT

with a *MTHFR C677T* and *MTHFR A1298C* double-heterozygous mutation. In addition, two adolescents presented with concomitant thrombophilia: heterozygous *MTHFR C677T* mutation and protein S deficiency; double-heterozygous *MTHFR C677T* and *MTHFR A1298C* mutation and anti-thrombin deficiency.

Three patients presented with severe motor or intellectual disability related to paraplegia due to T9 spinal cord injury from a car accident, autism spectrum disorder and trisomy 21 syndrome.

Table 3 – Risk factors in patients with VT

Risk factors	n
Thrombophilia	10
<i>MTHFR</i> mutation	
Double heterozygous <i>MTHFR C677T</i> + <i>MTHFR A1298C</i> mutation	3
Heterozygous <i>MTHFR C677T</i> mutation	1
Heterozygous <i>MTHFR A1298C</i> mutation	1
Hyperhomocysteinaemia	2
Anti-thrombin deficiency	2
Protein S deficiency	1
Heterozygous factor V Leiden mutation	1
Heterozygous Prothrombin gene <i>G20210A</i> mutation	1
Antiphospholipid antibody syndrome	1
Personal history	
Obesity	6
Oral contraceptive	4
Severe motor or intellectual disability	3
Smoking habit	2
Recent surgery	1
Heart failure	1
Previous deep venous thrombosis	1
Traumatic injury	1
Recent extended trip	1
Family history	
Father and sister with an history of venous thromboembolism	1

As regards the patients with PTE ($n = 8$), one of whom with concomitant DVT, all presented with thoracalgia and dyspnoea at admission, 25% with syncope/palpitations and 25% with fever (Fig. 2). All the patients underwent a CT-scan for diagnostic confirmation and a bilateral pulmonary involvement has been found in five patients. The patient with concomitant DVT presented with iliac and femoral vein involvement.

As regards the patients with isolated DVT ($n = 5$), all presented with pain at the obstruction site, 83% with oedema and cyanosis in the affected limb and 17% with fever (Fig. 2). All the patients underwent Doppler ultrasound for diagnostic confirmation. Iliac and femoral veins were more frequently affected ($n = 3$) followed by tibial and popliteal veins ($n = 2$).

All the patients with VT presented with elevated D-dimer levels at diagnosis (Table 4).

A 14-day (range 1-25, 95% CI 8.8 – 18.8) and 8-day (range 3-24, 95% CI 3.4 – 16.4) mean length of stay has been found in patients with PTE and DVT, respectively. Three from the eight patients with PTE were transferred to a level III hospital due to the need for paediatric intensive care.

All the patients were initially treated with low-molecular-weight heparin (LMWH). Two patients with PTE were treated with tissue plasminogen activator thrombolytic agents and one patient presented with right ventricular failure. Upon the initial 5-10 day LMWH treatment, patients were concomitantly and subsequently in isolation on warfarin and in no patient the need for embolectomy or inferior vena cava filter placement was found. A 3-6-month treatment with warfarin was followed by patients in whom the risk factor had been solved. A 12-month duration has been used in patients with a chronic risk factor.

One patient with PTE and recurrent thrombotic events died during the acute stage due to non-compliance with medication and one patient with DVT progressed to a post-thrombotic syndrome.

DISCUSSION

Only adolescents were found in our group of patients. Two peak incidences are known to exist in paediatric age: infants and adolescents. A significant advance in the

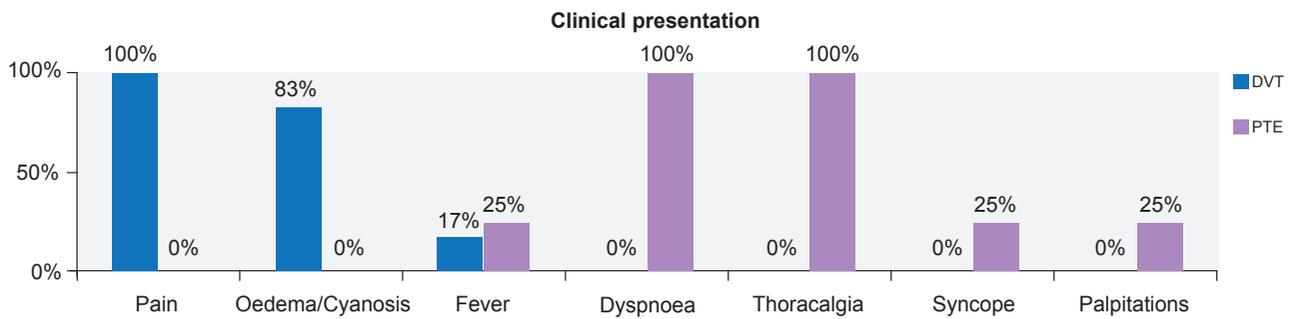


Figure 2 – Distribution of patients with DVT and PTE according to clinical signs and symptoms

Table 4 – Diagnostic workup in patients with PTE and DVT

Diagnostic workup	PTE	DVT
Leukocyte count > 15.0x10 ⁹ /L	12%	20%
Platelet count < 150,000/uL	0%	0%
Activated partial thromboplastin time	13%	17%
C-reactive protein > 4.0 mg/dL	88%	80%
D-dimer level (µg/mL)	Mean 3,252 Range 661 – 14,239 95% CI 1,303 – 7,048	Mean 2,660 Range 862 – 5,102 95% CI 862 – 5,102

knowledge of the physio-pathological mechanisms involved in VT has occurred over the past few decades.⁹ Most patients in the different studies involving children had some underlying clinical condition and the presence of a central venous catheter was most frequently described.¹⁰ At least one known risk factor for VT has been found in our patients. The confirmation of hereditary hypercoagulability conditions in a large percentage of patients with DVT and PTE has been the most significant advance in the knowledge of VT physiopathology and was the most frequently found in our group of patients.

Four from seven VT patients in our group were on oral contraceptive drugs and three from these presented with thrombophilia which was unknown until the event. The risk of VT relates to the dose of oestrogens, the type of progestin, patient’s age, family history and the presence of thrombophilia. The recommendations of the American College of Obstetrics and Gynecology were issued in 2010 by the Centers for Disease Control and Prevention, allowing for the consideration of the use of oral contraceptive drugs in patients with VT attributable to a reversible risk or on anticoagulation therapy. In addition, whenever a previous VT had occurred in a patient on oral contraceptives or pregnant, there was an absolute contraindication for hormone therapy. Despite the attention that was given to thrombophilia, no universal screening was ever recommended, due to its high cost, in addition to the fact that it may provide false reassurance, unnecessary anxiety, overtesting, additional family screening and significant and unnecessary expenditure as well as, when negative, a false reassurance regarding the development of thromboembolic events.¹⁹

A strong prevalence of obesity has been found in our

study (55%), in line with literature.²⁰ A 32% prevalence of overweight/obesity up to the age of 3 has been found in different Portuguese studies²¹ and 35% - 37% in children and adolescents.^{22,23} Considering that obesity is a recognised risk factor for VT and has been increasing worldwide at an alarming rate, this may have contributed to an increased incidence of thrombotic events in children.

Different risk factors were found in the patient with concomitant PTE and DVT, including a recent surgery, history of DVT, obesity and thrombophilia, in addition to non-compliance to medication.

There are recommendations for the assessment and classification of the risk of VT aimed at a stratified approach to its prophylaxis; this is the reason why healthcare professionals should be aware of the differentiation of this risk, even though there is still little evidence supporting any specific prophylactic approach in children/adolescents.^{24,25}

Our study showed that treatment has complied with the international recommendations and there was no need for embolectomy or inferior vena cava filter placement.

PTE is a potentially lethal condition although rare in the paediatric age. No multicentric studies on the progression of PTE in children have been carried out both national or internationally. A 10% global mortality rate has been described by both the registries in Canada and in The Netherlands, particularly in patients with PTE, showing a 9% (2/22) and 10% (1/10) mortality rate, respectively.^{3,4} A 9% (1/11) mortality rate has been found in our study, in line with literature.

Some limitations to our study are worth mentioning. The fact that our patients have attended only one institution and the small sample do not allow for any result extrapolation. All data were retrospectively collected from the patient’s

clinical record and a multicentric analysis should be included in a further study, with a control group of patients and a standard thrombophilia screening.

CONCLUSION

VT is a rare pathology in children. An increased incidence described in some studies may be due to an increasing awareness of this pathology, to medical and technological advances and to an increasing survival from chronic diseases. However, the incidence was probably underestimated as PTE is frequently a silent pathology or presenting with non-specific symptoms. This study was focused on the risk factors that should increase clinical suspicion.

In addition, the diagnostic and therapeutic approaches used in children are based on studies with adult patients and therefore there are little evidence-based recommendations in order to identify which paediatric patients are in risk of thrombosis and to allow for a careful decision with an adequate risk-benefit balance.

Further studies are needed to look for a reason for the increasing incidence of VT, which may be due to the longer survival of children with chronic disease, the increasing number of paediatric patients using central venous catheters and the increasing prevalence of obesity. The study on the progression of paediatric VT is crucial, including mortality, recurrent thrombotic events and pulmonary function. Finally, multicentric studies including the assessment of risk

factors and clinical presentation are needed and crucial to improved care of patients and the development of reliable and reproducible recommendations allowing for the evaluation of the chance of VT in paediatric patients.

OBSERVATIONS

This study was presented as oral communication to the 16^o Congresso Nacional de Pediatria, held in 22-24 Oct 2015, in Albufeira.

HUMAN AND ANIMAL PROTECTION

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

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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