

Inferior Vena Cava Malformations and Deep Venous Thrombosis

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We carried out a prospective study of 116 patients under 50 years of age who had deep venous thrombosis of the lower extremities to determine whether the presence of congenital anomaly of the inferior vena cava (IVC) was a risk factor for the disease. All patients were investigated by Doppler echography. Some 37 patients who had iliac vein occlusion also underwent phlebography. In 10 patients in whom the IVC was difficult to image, magnetic resonance angiography or computerized axial tomography was carried out. In all patients, studies of antithrombin, protein C and protein S deficiency, factor V Leiden, prothrombin G20210A, antiphospholipid antibodies, and acquired risk factors were also performed. Of the 37 patients who had iliac vein occlusion, 6 had an IVC anomaly. Two of these patients had antiphospholipid antibodies, while another had prothrombin G20210A. Two patients with an anomaly had recurrent thrombotic occlusion. In conclusion, congenital IVC anomalies were present in 16.2% (95% confidence interval, 6.2%-32%) of young patients with iliac thrombosis.

Key words: *Inferior vena cava malformation. Vena cava hypoplasia. Deep venous thrombosis.*

Anomalías de la vena cava y trombosis venosa profunda

Estudio prospectivo de 116 pacientes menores de 50 años con trombosis venosa profunda (TVP) de los miembros inferiores, en el que se valora la presencia de anomalías de la vena cava inferior (VCI) como factor de riesgo de la TVP. Se practicó a todos una eco-Doppler; cuando tenían afección iliaca se realizaba también flebografía, y cuando el drenaje a la VCI era deficiente, se completaba el estudio con resonancia magnética o tomografía computarizada. En todos los pacientes también se realizaron las siguientes determinaciones: antitrombina, déficit de proteína C y S, factor V Leiden, protrombina G20210A y anticuerpos antifosfolipídicos. También se valoraron los factores de riesgo adquiridos.

De los 37 pacientes con afección iliaca, 6 presentaron anomalías de VCI: 4 hipoplasias y 2 duplicaciones. Todos ellos eran menores de 30 años, 2 tenían anticuerpos antifosfolipídicos y 1 protrombina G20210A. Dos presentaron recidiva trombotica tras la suspensión de la anticoagulación. En conclusión, el 16,2% (intervalo de confianza [IC] del 95%, 6,2-32) de los pacientes con trombosis iliaca presentaba anomalía de la VCI.

Palabras clave: *Anomalías de la vena cava. Hipoplasia vena cava. Trombosis venosa profunda.*

INTRODUCTION

Deep venous thrombosis (DVT) is an illness of clinical interest, due to the associated morbidity and mortality and its social and health care consequences. The etiology in young patients has shown it frequently associated with congenital or acquired coagulation

abnormalities, immunologic diseases, and neoplasias.^{1,2} However, recent radiological advances derived from computerized axial tomography (CT) and magnetic resonance imaging (MRI) have identified vena cava malformations as a new etiologic factor to be considered.³⁻⁷

In adults, inferior vena cava (IVC) has 3 segments of different embryologic origin, prerenal, renal, and postrenal, as a result of the fusion and partial reabsorption of 3 pairs of vessels that depend on the posterior cardinal veins in the embryo. This complicated evolutionary process can give rise to anatomic malformations that impede vein drainage and favor the development of thrombosis.⁸

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The objectives of the present study are to describe the presence of IVC malformations as a risk factor in DVT of the lower extremities in young patients and learn about the clinical characteristics of its presentation.

PATIENTS AND METHOD

We studied 116 patients aged <50 years (60 men and 56 women) with DVT of the lower extremities, prospectively enrolled from January 1992 thru January 2004 in the Hospital Clínico Universitario de Valencia, Valencia, Spain. Following clinical suspicion of DVT, all underwent Doppler echography, and phlebography when iliac veins thrombosis was suspected as blood flow could not be imaged or was poor, and there was a loss of cyclical respiratory variations in the common femoral vein. If phlebography showed contrast interruption in the inferior vena cava, thread-like drainage and/or presence of collaterals (lumbar, paravertebral, abdominal, or pelvic) leading to atypical contrast drainage, in general via the azygos-hemiazygos system, we performed contrast CT or angio-MRI to determine inferior cava anatomy and rule out tumors and concomitant illnesses.

Thrombophilia testing determined values of antithrombin III, protein C, protein S, baseline homocystein, activated protein C resistance test, factor V Leiden, prothrombin G20210A, and presence of antiphospholipid antibodies (APLA). The methodology used in analyses is described elsewhere.² We also determined epidemiologic data on possible trigger cofactors and relevant clinical characteristics.

RESULTS

Of 116 patients studied, 55 presented thrombosis beginning in the femoral veins; in 54% of these, thrombosis extended to the popliteal vein and in 45% to the most distal veins. In 24 patients, thrombosis started in the popliteal vein thrombosis and extended to more distal veins. All these patients (n=79) underwent echo-Doppler only.

The remaining 37 patients had iliac vein thrombosis and underwent phlebography. Thrombosis was unilateral in 31 patients; in 20 of these it extended to the popliteal vein and in 11 to more distal veins. Thrombosis was bilateral in 6 patients; in 3 it extended to the femoral veins and in 3 to the popliteal veins.

In 10 patients with iliac vein DVT, contrast CT or angio-MRI was needed to visualize IVC correctly. We found 6 abnormalities: 2 hypoplasias in the prerenal segment, 2 in the renal and prerenal segments (the collateral vein system substituted for missing segments), and 2 duplications of inferior vena cava.

In all cases of hypoplasia we found thrombosis of the portion of the cava distal to this and in cases of duplication we found thrombosis of the cava of the side affected.

TABLE 1. Characteristics of Patients With Vena Cava Malformations*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, years	20	27	27	27	27	30
Gender	Woman	Man	Man	Man	Woman	Woman
Location of thrombosis	Bilateral iliac to femoral veins	Bilateral iliac veins to left popliteal vein	Bilateral iliac veins to both popliteal veins	Bilateral iliac veins to left popliteal	Unilateral left iliac vein	Unilateral left iliac vein
Cava malformation type	Prerenal hypoplasia	Prerenal and renal hypoplasia	Prerenal hypoplasia	Prerenal and renal hypoplasia	Double vena cava with left renal vena drainage	Double vena cava with right renal vena drainage
Associated malformation	No	No	No	No	Left renal vena hypoplasia	Renal vein hypoplasia and right renal agenesis
Method of diagnosis	CT	MRI	MRI	MRI	MRI	MRI
Thrombophilia testing	APLA	PT G20210A	APLA	Negative	Negative	Negative
Other factors	Oral contraceptives	Exercise	Infection	Polytraumatism	Caesarian section	Oral contraceptives
Continued anticoagulant treatment	Yes	No	Yes	No	Yes	Yes
Recurrent thrombotic occlusion	No	Yes	No	Yes	No	No

*APLA indicates antiphospholipid antibodies; CT, computerized axial tomography; MRI, magnetic resonance imaging; PT, prothrombin.

TABLE 2. Comparison of Clinical Characteristics of Patients With Malformations of Vena Cava According to Different Authors*

	Rugeri (2001)	Siragusa (2001)	Chee (2001)	Obernosterer (2002)	Presente (2004)
No. patients studied	75	21	60	97	116
Population age, years	<30	<21	20-40	Mean 51±19	16-50
DVT unilateral/bilateral	2/2	1/1	1/3	4/1	2/4
No. malformations, %	4 (5.33%)	2 (9.52%)	4 (6.7%)	5 (5.15%)	6 (5.17%)
Cava hypoplasia	4	2	3	5	4
Double vena cava			1		2
Mean age DVT	19	26	27	25	26
Gender M/F	3/1	1/1	2/2	3/2	3/3
Thrombophilia testing	No	2 FV Leiden	1 FV Leiden	1 deficiency ps	3 PT G20210A, 2 APLA

M indicates male; F, female; DVT, deep venous thrombosis.

Principle characteristics of patients with the cava malformations described are in Table 1. Table 2 compares these with patients of earlier series.³⁻⁶

Patient 1

A 20-year-old woman taking oral contraceptives for the previous 4 months presented lumbar and hypogastric pain and edema of both lower extremities after exercise. Phlebography revealed thrombosis of both iliac veins and absence of representation of vena cava. Thoracic-abdominal CT found hypoplasia in the intrahepatic prerrenal segment of the IVC, dilatation of the azygos and hemiazygos system, and thrombosis in the postrenal segment of the cava. Thrombophilia blood testing highlighted the presence of APLA (anticardiolipin IgG, IgA, and IgM). After overcoming the acute process, the patient remained asymptomatic after 4 years' anticoagulation. The APLA became normal in 6 months.

Patient 2

A 27-year-old man presented lumbar pain and edema in both lower extremities after intensive exercise. Phlebography showed DVT of both iliac veins, extending to the popliteal vein in the left leg. The MRI revealed hypoplasia in the prerrenal and renal segment with abundant collateral circulation in the lumbar veins and dilatation of the azygos vein. We found thrombosis in the postrenal cava. Prothrombin G20210A was found. The patient received 6 months' anticoagulation, presenting recurrent thrombotic occlusion 2 years later.

Patient 3

A 27-year-old man with antecedents of testicular edema and left varicocele suddenly suffered intense testicular and lumbar pain and edema of both lower

extremities. Phlebography showed affection in both legs extending from the popliteal to the common iliac veins. The MRI, revealed hypoplasia of the prerrenal segment in the hepatic portion and dilatation of the azygos vein. The distal portion of the cava was thrombotic. Thrombophilia testing found presence of APLA. The patient underwent 3 years' anticoagulation without presenting recurrent thrombotic occlusion.

Patient 4

A 27-year-old man presented bilateral DVT following severe polytraumatism. Phlebography revealed thrombosis of both common iliac veins and extension of the left leg thrombus to the popliteal vein. The MRI, showed hypoplasia of the prerrenal and renal segments of the vena cava with drainage of the renal veins into the azygos system. We found thrombosis in the postrenal portion of the cava. Thrombophilia testing was negative. The patient received 6 months' anticoagulation and presented recurrent thrombotic occlusion 1 year later.

Patient 5

At 3 days after a caesarian section, a 27-year-old woman presented thrombosis from the external left iliac vein to the popliteal vein. In MRI, we found double inferior vena cava with drainage of the left cava (which presented thrombosis) in the homolateral hypoplastic renal vein. Thrombophilia testing was negative. The patient received 20 months' anticoagulation without presenting recurrent thrombotic occlusion.

Patient 6

A 30-year-old woman taking oral contraceptives presented DVT from the popliteal vein to the iliac of the affected limb following a period of rest due to a

sprain in her right leg. The MRI, showed double inferior vena cava with drainage of both in the right renal vein, which was hypoplastic. The right cava, which continued into the venous system of the right leg, presented thrombosis accompanied by right renal agenesis. Thrombophilia testing was negative. The patient received 12 months' anticoagulation without recurrent thrombotic occlusion.

DISCUSSION

In the present study we found that 16.2% (95% confidence interval, 6.2-32) of patients <50 years with iliac vein thrombosis presented inferior vena cava malformation. Given that only 31.8% of the patients had iliac vein thrombosis, cava malformation represented a risk factor in 5.1% of the population studied.

Earlier studies also based on younger populations³⁻⁷ report a 5%-9.52% range. None of these studies evaluated prevalence of IVC malformation in the population as they did not study vena cava in all patients but only analyzed its influence as a thrombotic risk factor on causing retrograde stasis. In all studies, age of presentation of first thrombosis is <30 years and incidence is similar in men and women. Only Gayer et al's retrospective study⁷ reports that 8 of the 9 malformations diagnosed affected men.

In all the studies, the most frequent malformations are hypoplasia in the prerrenal and renal segment, followed by those in the postrenal segment and presence of double inferior vena cava. In the embryo, the prerrenal segment consists of the hepatic and right subcardinal veins; the renal segment consists of the subcardinal and right supracardinal veins; and the postrenal segment consists of the right supracardinal vein. This complicated evolutionary process can give rise to many anatomic variants. In 1920, Huntington et al⁸ described 15 theoretically possible forms combining lesions of the 3 pairs of embryonic veins. With the advances in angiography, Chuang et al⁹ described malformations found in routine practice and observed that hypoplasia of the prerrenal segment and double inferior vena cava were the most frequent. Shah et al,¹⁰ in their review of the literature on malformations and thrombosis from 1961 to 1969, observed that hypoplasia in the prerrenal segment represented 93.8% of diagnosed malformations; in the infrarenal segment this was 3.7%; and in the renal segment, 2.4%. Few studies^{6,7,11} consider double inferior vena cava to be the cause of DVT, perhaps because it causes retrograde stasis less often. In the 2 patients in the present study, the vena cava homolateral to the thrombotic limb drained in a hypoplastic renal vein, which contributed to increasing stasis.

Compensatory drainage thru the thoracic-lumbar, pelvic, and abdominal veins can cause symptoms in the thorax, hypogastrium, lumbar, and genital regions, prior to those typical of DVT of the lower extremities, as found in some of the patients described. Early detection could warn of the presence of cava malformations in young patients.

Some authors believe cava malformation alone can provoke DVT,⁵ but the fact that lifelong asymptomatic malformations occur,⁹⁻¹¹ the findings of the present study and of those reviewed⁴⁻⁶ and the status of thrombosis as a multifactorial illness,¹² suggest the presence of associated factors, both congenital and acquired.

Apparently, the most appropriate approach to treatment is >6 months' anticoagulation while the principal factor provoking thrombosis continues. In the present study we found recurrent thrombotic occlusion only in patients whose anticoagulation treatment was suspended. However, more research is needed to corroborate this observation.

In conclusion, we should suspect the presence of inferior vena cava malformation in patients <30 years with DVT of the lower extremities when the iliac veins are affected. The possibility of recurrent thrombotic occlusion is high in these patients when anticoagulation treatment is withdrawn.

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