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EPIDEMIOLOGY, ETIOLOGY AND DIAGNOSIS OF VENOUS THROMBOSIS

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Abstract: Venous thromboembolism (VTE) is one of the most frequent multifactorial diseases. It manifests clinically by deep vein thrombosis (DVT) and pulmonary embolism (PE) leading to death in about 6%. It is important to emphasize, that 50% of the patients do not present any symptoms. The prevalence is influenced by age and ethnics. Both, hereditary (Factor V Leiden, G20210A prothrombin gene mutation, deficiencies of protein C, S or antithrombin) and acquired risk factors (estrogen replacement, cancer, cardiovascular disease, surgery, trauma, immobility, use of central venous catheters, autoimmune disease such as anti-phospholipid syndrome) contribute to VTE. The risk increases dramatically by the addition of hyperhomocysteinemia or the combination of several risk factors. Since VTE is a dynamic process able to manifest clinically or to resolve completely, the identification of persons at increased risk is mainly important for early diagnosis and treatment. The diagnostic strategy including clinical scores and laboratory tests (D-dimer measurement) as initial steps to confirm the suspicion of VTE may exclude patients who do not need further, sometimes invasive imaging tests (venography, compression ultrasonography combined or not combined with colour Doppler imaging, magnetic resonance imaging). Laboratory tests for suspected inherited thrombophilia should be performed six months after clinical presentation.

Key words: venous thromboembolism; deep vein thrombosis; diagnostic score strategy

EPIDEMIOLOGY

Pulmonary embolism (PE) and deep venous thrombosis (DVT) constitute the two clinical manifestations of venous thromboembolism (VTE) that occur in approximately 100 persons per 100,000 each year for the first time in the United States, considering that most of the population studied is Caucasoid [1]. The incidence rises from less than 5 cases per 100,000 persons below 15 years of age to approximately 500 cases (0.5%) per 100,000 persons at 80 years of age. Approximately one third of the patients with symptomatic VTE manifest PE, whereas two thirds manifest DVT alone. VTE and DVT are distinct but related aspects of the same dynamic disease process. Some authors report an annual incidence that increases from 1 per 100,000 during childhood to 1 per 100 in old age [2]. Death occurs in approximately 6% of DVT cases. Ethnics seems to be an incidence factor since DVT appears higher among Caucasians [3, 4] and African Americans than among Hispanic persons and Asian-Pacific Islanders [5]. In the United States rate of VTE seems to be higher in the East region: 52.2/100,000 and lowest in Alaska, with the lower rates in American Indian and Alaska native compared to Caucasians [6]. The incidence of DVT increases rapidly with age in an apparently linear form suggesting a constant incidence and cumulative prevalence especially in those older than 65 years [7]. It also seems to affect more commonly women although data are limited [8, 9]. In a recent meta-analysis study about incidence of DVT Fowkes FJ et al. found that studies had been mainly conducted in the USA or Sweden: the weighted mean incidence of first DVT in the whole general population was 5.04/10,000/year with no difference between males and females, but increased with age from 2-3/10,000/year at age 30-49 to 20/10,000/year in persons over 70 years old [10].

Other authors report DVT as one of the main causes of maternal death in the Western world mainly because of PE as a complication [5, 7, 11]. In pregnant women DVT is the end result of inherited and acquired risk factors sometimes interrelated. In case of personal history of thrombosis woman considering pregnancy should be screened for risk factors in order to prevent thrombophilia. A hypercoagulable state in pregnancy may result in PE but also in miscarriage and intrauterine growth restriction [16, 17]. The risk is increased by smoking, prior VTE and inherited thrombophilias [18].

In postmenopausal women another risk factor associated with VTE is oral estrogen replacement therapy (OR = 3.5, 95% IC 1.8-6.8): compared with non users, oral but not transdermal oestrogen replacement seems to be associated with a risk

Table 1. Incidence of deep venous thrombosis (DVT) in different populations.

Incidence/year	Country	Author
48/100,000 (97% caucasian)	Worcester,Mass.USA	Anderson FA Jr. et al. 1991 [3]
48/100,000	Minnesota,USA	Silverstein MD et al. 1998 [11]
182/100,000 (autopsies)	Sweden	Hansson PO et al. 1997 [12]
1/1000	USA	Rosendaal FR 1997 [2]
100/100,000	USA	White RH et al. 2003 [5]
230/1000,000 293/1000,000 139/1000,000 60/1000,000	California,USA -White -African American -Hispanic -Asian or Pacific Islander	White RH et al. 1998 [13]
23/100,000	USA (caucasian)	Kroegel C et al. 2003 [14]
16.1/100,000	Alaska,USA American Indians and Alaska native	Hooper WC et al. 2002 [6]
1/1000	USA	Heit JA 2002 [15]
5.04/10,000 (2-3 to 20/10,000)	Meta-analysis (mostly USA and Sweden publications)	Fowkes FJ et al. 2003 [10]

Table 2. Incidence of idiopathic VS secondary venous thromboembolism (VTE).

Idiopathic	Surgey	Trauma	Immobilization	Cancer	Author
47%	25%			25%	Cushman M [22]
				15%	Anderson Jr. FA [3]
26%		12%	59%	18%	Heit, JA [24]
41%	23%	2%	15%	18%	White RH [5]
25%	24%	12%	59%	18%	Heit JA [23]
		36-60%			Ennis RS [36]
			48%	27%	Hingorani A [37]
			37%		Kierkegaard A [35]
	22-35%	60%			Attia J [31]

for VTE [19, 20]. Reports about oral contraceptives refer that the increase in the prevalence of VTE episodes seems to be proportional to the increased use of oral contraceptives in the last decade regardless of the type of progestin contained in the different preparations [21].

Mortality rate of DVT has a strong association with risk factors such as: cancer, cardiovascular disease, states following surgery or trauma, immobility at home or long hospitalisation [22-25] Table 2.

Advanced cancers particularly associated with VTE are those of brain, lung, breast, pelvis, ovary, rectum, gastrointestinal tract and pancreas. Specially is to be mentioned the strong association between thalidomide therapy and DVT in patients with multiple myeloma [26-28].

Cardiovascular diseases, mainly myocardial infarction are associated with DVT and congestive heart or respiratory failure with VTE. They cannot be considered as independent risk factors since they are commonly also associated with age, hospitalisation / immobilization and venous stasis [29].

States of VTE or DVT following surgery (10-30%) are mainly associated with cardiovascular: coronary-artery bypass, abdominal operations: gynaecologic, urologic, orthopaedic operations: elective total hip (20% - 26%) or knee replacement and neurosurgery (22% - 35%) [30, 31].

Major trauma or multiple trauma associated with VTE includes mainly fractures of the hip and the lower extremities, it can be present in almost 50% of the cases, proximal DVT can be documented in 12 % to 60%. Also 40% of the patients in whom injury was in chest, abdomen or even the

face presented DVT. The incidence of DVT in acute spinal cord injury patients is likely in excess of 50%-80% [31, 32, 33].

Incidence of DVT has also been reported in 13 % of bedridden non-surgical patients [34]: In autopsies of patients on bed rest for less than one week before death 15% of venous thrombosis is reported, this incidence increases in patients on bed rest for longer periods to up to 80% [35].

ETIOLOGY

Recognition of VTE as a multifactorial disease, as important and frequent as diabetes [38], which can be improved and prevented by identification of risk factors (50% of the cases are reported as idiopathic), has provided significant insights into its epidemiology [39, 40].

The etiology of DVTE can be divided in two main groups: hereditary or acquired, but there are not sufficient studies about incidence of each of them published (Table 3).

The frequency of the so called hereditary thrombophilias varies within the studied groups, Factor V Leiden and G20210A mutation in the prothrombin gene are common in white healthy populations and extremely rare in Asians and Africans. The frequency is higher in patients with DVT, in these patients the coinheritance with other thrombophilias is common [41]. The addition of hyperhomocysteinemia, that also can be caused by a genetic disorder (metabolism of homocysteine is affected) or by deficiency of vitamins B6 or B12 or folic acid, renal failure, hypothyroidism, etc, to one of these factors increases dramatically the risk of DVT [42].

The prevalence of DVT in families with deficiencies of protein C, protein S or antithrombin was 13-25% by the presence only of Factor V Leiden, 19-57% among patients with only one of the three deficiencies and 73-92% among subjects who coinherited one of the deficiencies and factor V Leiden [41].

Heterozygous factor V Leiden is detected in about 5% of population, commonly in North European descendents and in some people from the Middle East; the homozygous form is less than 1%. In Hispanic populations and in Asian, African and native American populations it is very rare. Heterozygous persons with factor V Leiden have an increased risk for the first DVT of 5 to 7-fold, but very often have additional risk factors that contribute if they develop DVT. Homozygous factor V Leiden increases the risk of DVT up to 25 to 50-fold [43].

There are not sufficient studies published considering the different anatomical locations of DVT like the hip region, upper extremity, mesenteric, calf, cerebral, etc. Cogo et al. determined the distribution of VT in symptomatic patients at the Clinica Medica, University of Padua, Italy by interpreting 542 venograms performed in consecu-

Table 3. Deep venous thrombosis. Etiology.

Idiopathic: 50% of the cases.		
Hereditary thrombophilia:	Factor V Leiden	
	Protein S or C deficiency	
	Antithrombin III deficiency	
	Polymorphism in the prothrombin gene	
	Heterozygous carriers of G20210A	
	Dysfibrinogenemia	
	Homozygous homocystinuria	
	Rare mutations (Factor Va etc.)	
Acquired:	Secondary to Cancer (Mama, Ovarian, Colon, Lung, Brain and Pancreas)	
	Pregnancy and puerperium	
	Oral contraceptives	
	Secondary to hemophilic treatment (F VIII elevated)	
	Secondary to chemotherapy	
	Use of central venous catheters	
	Secondary to hip arthroplasty	
	Secondary to surgery or major trauma	
	Home nursery (immobilization)	
	Long hospitalization time	
	Long travel	
	Acquired blood conditions:	antiphospholipid antibodies (lupus anticoagulants, anticardiolipin antibodies)
		hyperhomocysteinemia
		thrombocytosis
		heparin associated thrombocytopenia

Table 4. Distribution of DVT [57].

Location	% of cases
Proximal veins	88
Calf-veins	12
Popliteal vein	10
Popliteal and superficial femoral veins	42
Popliteal,superficial/ common femoral vein	5
Entire proximal deep venous system	35
Superficial femoral	0
Common femoral	0
Iliac vein	0

tive patients with suspected VT, the distribution of VT is shown in Table 4.

The association of DVT and VTE to the hip region was already mentioned above. As for the upper extremity deep vein thrombosis (UEDVT) there is a direct association to the use of central venous catheters (CVC), where PE is present in one third of the patients [44]. The reported incidence of 2/100,000 persons/year is referred either to effort thrombosis (Paget-Schroetter Syndrome) or idiopathic UEDVT [45]. Other associated risk factors are: pacemaker, history of neoplasia, where the incidence ranges from 2-40%, or previous lower extremity DVT and potential risk factors reported are: size and catheter position, and perhaps site of insertion [37, 46]. It is important to be mentioned that specially in children the incidence of UEDVT is in almost 50% of the cases associated to CVC, most of them are clinically silent and can predispose to PE or post thrombotic syndrome [47].

Mesenteric VT is uncommon but should be considered in patients over 55 years referring abdominal pain since most of the cases are operated because of misdiagnosis. It is mostly associated to postoperative states, cirrhosis and portal hypertension as well as intra-abdominal processes. [48, 49]

Cerebral venous thrombosis (CVT) appears to be rare but its identification has increased due to more accurate diagnostic studies like nuclear magnetic resonance. Death rate is below 10% and 80% of the patients recover completely [50]. In children CVT is a multifactorial disease resulting from a combination of prothrombotic risk factors (50%): factor V Leiden, protein C or S deficiency and elevated lipoprotein (a) and/or underlying clinical condition (70%): infections, vascular trauma, immobilization, malignancies, autoimmune diseases, etc. [51]

Isolated calf DVT rarely cause leg symptoms, 80% of the symptomatic cases involve proximal veins and rarely cause clinically important PE [52].

Most of the DVT start in the calf veins and resolve spontaneosly. The presence of symptoms are associated with the extent and location of the thrombosis. Most symptomatic patients have occlusive proximal thrombosis at the time of presentation. It is important to emphasize that VTE is a dynamic process, and that the balance between progression and resolution of the process may change, resulting in clinical manifestations of remissions or exacerbations [53].

Travel as a risk factor for DVT is discussed elsewhere in this issue.

Primary anti-phospholipid syndrome (APS) is a thrombophilic state characterized by recurrent arterial thrombosis: cerebral ischemia and transient ischemic attacks and DVT of the lower limbs with or without PE, recurrent miscarriages and fetal death. There is an estimation of 35,000 new cases each year in the USA associated with DVT in younger population than the typically affected by thrombosis. Ophtalmologic features are present in 15-55% of these patients [54]. Overall, the prevalence of thrombosis in patients with APS is about 30%. The prevalence of obstetric complications is about 15 to 20%. The presence of lupus anticoagulants has an odds ratio for current miscarriages and fetal death from 3-4.8 and that of anticardiolipin antibodies from 0.86 to 20 [55].

In some cases there is the development of a post-thrombotic syndrome after DVT, characterized by pain, heaviness and swelling of the leg that gets worse by walking or standing, with a cumulative incidence from 17-29% after 8 years of follow up. The severe form is characterized by skin and subcutaneous changes varying from varicose eczema to ulceration with a cumulative incidence of 2-5% after 5 years [56].

Diagnosis

Since the mechanisms involved in the DVT are not yet completely understood, the accurate identification of the disease must first made by clinical suspicion or physical examination, and then confirmed by laboratory and/or imaging tests. Thereafter, an effective prophylaxis or treatment can be implemented for each individual case in time [40].

In order to realize the laboratory and/or imaging tests to confirm the diagnosis of DVT it is recommended to make first a clinical setting and to remember that as much as 50% of the patients do NOT present symptoms or signs. DVT may first be suspected simply by the history of one or more risk factors present (see Table 3.)

The so called diagnostic gold standards tools for DVT and PE were venography and pulmonary angiography, both are invasive tests, costly and not devoid of risks. By venography the thromboembolic risk is about 1.9% [58] and the mortality rate secondary to pulmonary angiography, reported only in very ill patients, is of 0.2%.These studies are also very difficult to interpret and there is frequent disagreement between even expert readers [59]. It must also be considered that isolated VTE of muscle veins of the calf may not be visible in venography studies [60]. For the reasons mentioned above, pulmonary angiography is not anymore indicated and venography only in few very selected cases (see below).

Table 5. Clinical model for predicting pretest probability for DVT (Wells et al.)

Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis,or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 days or major surgery, within 4 weeks	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	-2
In patients with symptoms in both legs, the more symptomatic leg is used	
SCORE > or = 3 = high pretest probability	
SCORE 1-2 = moderate pretest probablity	
SCORE of zero or less = low pretest probability	

The noninvasive method more used as diagnostic procedure for DVT is, in combination with the pre-test DD assay, the compression ultrasonography (CUS) which has shown a high accuracy for the diagnosis of symptomatic proximal vein thrombosis, although its sensitivity for nonocclusive or calf vein thrombi is much lower. Because of the possible extension of these thrombi to pulmonary emboli, serial testing must be considered during a 7 to 14 day period in order to rule out the disease even in cases with a low clinical pretest probability and a normal result of CUS. Compression ultrasonography proved to have a sensitivity of 97% and a specificity of 98%, using venography as the gold standard, for symptomatic proximal DVT, shows a DVT in around 50 to 60% of the patients with proven PE, but the position of this diagnostic method for PE is on debate [60-63].

The CUS combined with colour Doppler imaging is known as duplex sonography (DUS). The main criterion for diagnosing DVT is lack of compression of a deep vein. This diagnosis can be confirmed by direct visualization of thrombus on ultrasound or by abnormal venous flow on Doppler examination. DUS is very accurate among symptomatic patients but its sensitivity decreases when they are asymptomatic. The limitations of these techniques include inability in most situations to image directly pelvic VT and difficulty in diagnosing acute events superimposed upon chronic DVT. It is not recommended for upper extremity DVT diagnosis [64, 65].

Most authors recommend a systematic 3-month follow-up in order to allow detection of delayed events and establish a true diagnosis . This strategy is associated with a lower thromboembolic risk (approximately 2%). It also would be of great use that each Institution develops and validates its own diagnostic algorythms for suspected DVT/PE [59, 62, 64].

Among the studies required in selected cases are the following:

Contrast Venography.
Despite its limitations (not useful by total vein obstruction, difficult interpretation, uncomfortable, possible allergy or phlebitis) it can show fresh thrombus and demonstrate collaterals. It is necessarily indicated in selected patients with massive or recurrent DVT that require catheter directed thrombolysis or thrombectomy, venous angioplasty or venous stenting [64].

Magnetic Resonance Imaging (MRI) can provide very precise and detailed information about the venous system. It is specially useful in assessing suspected pelvic VT and in defining upper extremity vein thrombosis, for detecting thrombus in the central thoracic veins such as brachiocephalic veins [64, 65].

In all cases of DVT/E the principal aim is to confirm or exclude the diagnosis, so besides clinical assessment, non invasive diagnosis tests have emerged in the recent decades. Some authors consider that D-dimers (DD) measurement should be the initial step to confirm the suspicious of VTE. The potential value of this test as exclusionary for VTE in an era of increasing negative imaging test results has been appreciated in the last decade [66]. Plasma DD is a degradation product of cross-linked fibrin and its plasma levels increase in patients with acute VTE [67].

There are also several studies that propose scores strategies to exclude DVT. Most of them agree by considering that patients with a normal DD concentration by rapid ELISA(<500 fibrin equivalent units [FEU]mg/L) and non-high probability score according to Wells et al. [68] should not need further testing. Those with normal DD concentrations and a high probability score need a ultrasonogram. Serial ultrasonography should be

Table.6.

High priority test	Conditions or states
Increased resistance to activated protein C	Pregnancy, oral contraceptives, lupus anticoagulant, oral anticoagulants, stroke, increased F VIII levels, autoantibodies against protein C
Factor V Leiden (homozygous, heterozygous)	Same as above
G20210A prothrombin gene mutation (homozygous, heterozygous)	Recurrent VTE first before 50 years of age, thrombosis in unusual anatomic sites, affected first degree relative, unprovoked VTE at any age, oral contraceptives, pregnancy, unexplained miscarriage in 2nd or 3rd trimester, surgery, trauma, older age (70,71)
Increased level of homocysteine	Deficiencies of folic acid, vitamin B12 or B6, older age, renal failure, smoking (72)
*Increased level of Factor VIII	Stress, exertion, pregnancy, oral contraception, older age, acute phase response
**Presence of lupus anticoagulant (antibodies antiphospholipides) and IgG anticardiolipin antibodies	APS: DVT lower limbs with or without PE, arterial thrombosis, obstetric complications: recurrent miscarriages, fetal death (55,73)

Intermediate priority Test	Conditions or states
Decreased protein C activity	Liver disease, childhood, oral anticoagulants, vitamin K deficiency, disseminated intravascular coagulation (DIC), autoantibodies against protein C
Decreased level of free protein S antigen	Liver disease, childhood, oral anticoagulants, vitamin K deficiency, DIC, pregnancy, oral contraceptives, nephrotic syndrome, autoantibodies against protein S
Decreased antithrombin activity	Liver disease, heparin therapy, DIC, nephrotic syndrome
**Increased titer of anticardiolipin antibodies	Infectious diseases, obstetric complications (55, 73)

Low priority (very rarely diagnose inherited thrombophilia) Test	Conditions or states
Dysfibrinogenemia (normal or low fibrinogen level and prolonged thrombine time)	Recent birth, liver disease, DIC
*Increased level of fibrinogen	Acute-phase response, pregnancy, older age, atherosclerosis, smoking
*Increased F IX activity	-
*Increased F XI activity	-
Homozygosity for C677T mutation in methylenetetrahydrofolate reductase gene	Hyperhomocysteinemia, idioptahic DVT (74)
*genetic basis for test results unknown	
** no genetic basis for test results	

done in patients with an abnormal DD concentration, in more of 50% of them DVT/E has been detected. The diagnostic strategy including DD and clinical scores (Table 5), reduces in almost 30% of the cases the need for ultrasonograms. DD test have a negative predictive value of 97.2% (quatitative-latex DD) [61, 69].

It must be considered that although DD is very specific for fibrin, fibrin is produced in other conditions such as inflammation, infection, necrosis or cancer, so its specificity and positive predictive value for VTE is poor. So DD is unlikely to be useful in very elderly patients or in those with suspected VTE [59].

There are two groups of DD tests for clinical use : ELISAs tests (rapid enzyme-linked immunosorbent assays) have a high sensitivity (92-98.4%), but a low specificity, and Latex agglutination tests have a lower sensitivity (85 a 98.8%), but are more specific [59, 66].

With the identification of factor V Leiden and the G20210A mutation in the prothrombin gene (1993 and 1996 respectively) the diagnosis of inherited thrombophilia in patients with DVT has increased. Seligsohn U et al. suggest that decisions regarding laboratory tests should be made according to a set of priorities and considering individualized likelihood of inheritance [41] Table 6.

It is important to consider that the optimal time to perform tests in most patients are six months after the thrombotic event in relation to decide if anticoagulation therapy has to be continued or not. Results of tests performed before this period can be misleading because low antithrombin levels, and elevated levels of factor VIII may be caused by the thrombosis itself. At six months, all high priority tests and test for antithrombin activity should be performed in patients in whom there is a high suspicion of inherited thrombophilia [41].

CONCLUSION

Although today there are highly specific and sensitive laboratory and imaging tests, diagnosis of thrombosis remains a clinical issue supported by personal history and physical investigation. A clinical score comprising the results of clinical history and physical examination can facilitate the decision about necessity and course of diagnostic procedures with respect to availability of laboratory and/or imaging techniques. DVTE is one of the most frequent multifactorial diseases. It's development or serious complications can be prevented in many cases by identification of persons at increased risk, early diagnosis and treatment.

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