

Rare thromboses of cerebral, splanchnic and upper-extremity veins

A narrative review

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Summary

Venous thrombosis typically involves the lower extremity circulation. Rarely, it can occur in the cerebral or splanchnic veins and these are the most frightening manifestations because of their high mortality rate. A third site of rare venous thrombosis is the deep system of the upper extremities that, as for the lower extremity, can be complicated by pulmonary embolism and post-thrombotic syndrome. The authors conducted a narrative review focused on clinical manifestations, risk factors, and treatment of rare venous thromboses. Local risk factors such as infections or cancer are frequent in thrombosis of cerebral or portal veins. Upper extremity deep-vein thrombosis is mostly due to local risk factors (catheter- or effort-related). Common systemic risk factors for rare venous thromboses are inherited thrombophilia and oral contraceptive use; chronic myeloproliferative neoplasms are closely associated with splanchnic vein thrombosis. In the acute phase rare venous thromboses should be treated conventionally with low-molecular-

weight heparin. Use of local or systemic fibrinolysis should be considered in the case of clinical deterioration in spite of adequate anticoagulation. Anticoagulation with vitamin K-antagonists is recommended for 3–6 months after a first episode of rare venous thrombosis. Indefinite anticoagulation is recommended for Budd-Chiari syndrome, recurrent thrombosis or unprovoked thrombosis and permanent risk factors. In conclusion, the progresses made in the last couple of decades in diagnostic imaging and the broadened knowledge of thrombophilic abnormalities improved the recognition of rare venous thromboses and the understanding of pathogenic mechanisms. However, the recommendations for treatment mainly derive from observational studies.

Keywords

Cerebral vein thrombosis, Budd-Chiari syndrome, extrahepatic portal vein thrombosis, mesenteric vein thrombosis, upper-extremity deep venous thrombosis

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Introduction

Venous thrombosis affects mainly the lower extremities but may rarely involve other venous districts, such as cerebral veins and sinuses, splanchnic and upper extremity veins. Possible reasons for the relative rarity of thrombosis in these sites, as compared to the lower extremities, include a less profound venous stasis (due to the absence of valves in the cerebral and splanchnic veins), and the high degree of mobility of the arms. Hence, venous thrombosis at these rare sites develops mainly due to hypercoagulable states and vessel wall injury. Examples are the predominance of female sex among patients with cerebral sinus thrombosis due to the use of oral contraceptives, and of indwelling catheters in subclavian vein thrombosis. The rarity of these thrombotic manifestations is the principal limitation for the accurate estimation of their incidences in the general population, and for the choice of the most effective treatment. However, recent progresses in vascular imaging have made early recognition of rare venous thromboses more feasible and contributed to ameliorate prognosis.

Cerebral sinus and vein thrombosis

Epidemiology and clinical manifestations

Because in the vast majority of patients thrombosis develops concomitantly in sinuses and veins, we will refer to the disease as cerebral sinus-venous thrombosis (CSVT). The incidence of CSVT is uncertain because of the absence of epidemiological studies. At variance with arterial stroke, CSVT affects mainly young adults and children, with an estimated annual incidence of 3–4 cases per 1 million adults and seven cases per one million neonates and children (1, 2). The most frequent locations of thrombosis are the superior sagittal (62% of patients) and the transverse sinus (40–45%), but in two-thirds of cases more than one sinus is involved. Symptoms are varied and related to the involved venous structure. When thrombosis involves the cortical veins, localised oedema and parenchymal infarction generally develop (1). The presence of large intracranial infarcts or haemorrhages lead to stupor or coma in 15% of patients with CSVT (1, 3, 4). Overall, intra-

cranial haemorrhage complicates 14–39% of CSVT (3, 4). The most common symptoms and signs are headache and papilloedema due to intracranial hypertension, seizures, focal neurological deficits and altered consciousness. Headache occurs in 90% or more of patients and papilloedema (30% of patients) may cause visual loss and, if the sixth cranial nerve is compressed, diplopia. Focal or generalised seizures develop in up to 40% of patients, as well as motor deficits, whereas symptoms such as dysarthria and aphasia are uncommon (3–5).

The onset of symptoms is subacute, developing from two days to one month in 50% to 80% of patients, and can be even longer in 10% to 20% of patients with isolated intracranial hypertension. Rarely, symptoms simulate those of arterial stroke, but a slower development, a tendency to fluctuate and the symptoms of intracranial hypertension and seizures are important clinical differences.

Prognosis of CSVT is favourable in more than 80% of cases (6), because poor neurological outcome is seen in 7–20% (3–5), and recurrence in only 2.2% of patients (3). Death is mainly caused by cerebral herniation in the acute phase and to underlying illnesses, e.g. cancer, during follow-up. Mortality rates, as high as 50% in older studies (7), has been recently estimated to range from 4.3% to 13% during the first month and from 7.7% to 17.7% after six months (6).

Diagnosis

Because of the wide spectrum of clinical presentations and the varying speed of onset of symptoms, diagnosis of CSVT is frequently overlooked or delayed, while early diagnosis and treatment are essential to minimise morbidity and improve survival. Indirect imaging signs include parenchymal abnormalities, such as venous infarcts, brain oedema, hydrocephalus and compression of the fourth ventricle; development of collateral venous network; changes in the mastoid region and erosion of middle air structures (8). Direct signs are those of interrupted venous flow or occlusion, and visualisation of the actual thrombus (8). The first recommended exam is a plain computerised axial tomography, with the main objective to rule out brain tumours. Contrast medium administration is essential, but other techniques such as magnetic resonance imaging, magnetic resonance venography or dynamic spiral computed tomography venography are required when contrast computed tomography is diagnostically insufficient (9). Ultrasound examination (transcranial Doppler or colour-coded duplex sonography through the temporal acoustic bone window) of the cerebral venous system has the great advantages of non-invasiveness, cost-effectiveness and wide availability of the technique. However, its accuracy is limited and at present ultrasound examination can only be recommended as complementary to other imaging techniques (8).

Risk factors

In children and neonates the main risk factors for CSVT are gestational or perinatal complications (24% of cases), dehydration (25%), head infections (18%) and thrombophilia (32%) (2). While until the mid 1970s CSVT affected equally adult men and women, in the last few decades it has shifted to a disease affecting predominantly women of childbearing age (1). Indeed, two-thirds of adult patients are women. Responsible of the sex disparity is the increasing use of oral contraceptives, as reported by several case-control studies, eight of which were recently reviewed in a meta-analysis that showed an almost six-fold increased risk of CSVT in oral contraceptive users (10). Whether or not – in analogy with deep-vein thrombosis of the lower limbs – oral contraceptives containing desogestrel or gestodene as progestagen, are associated with a higher risk of CSVT than those containing levonorgestrel, is not certain in the absence of specific studies. No data are available on the risk of CSVT and hormone replacement therapy. Inherited thrombophilia is another established risk factor for CSVT (► Table 1), the relative risk being approximately four-fold and 10-fold increased in the presence of factor V Leiden or prothrombin G20210A mutation (10–12). There is a synergistic interaction between oral contraceptives and inherited thrombophilia due to the aforementioned gain-of-function mutations, and also to the metabolic abnormality hyperhomocysteinaemia (11). The relationship between the risk of CSVT and the lack-of-function deficiencies of the naturally occurring anticoagulants antithrombin, protein C and protein S, as well as that associated with the acquired thrombophilia due to the presence of antiphospholipid antibodies, are less established because of the relatively small number of patients investigated so far and the low prevalence of these coagulation abnormalities in patients and controls. Another risk factor for CSVT exclusive of women is, more than pregnancy, puerperium (13). In low-income countries, it is the most frequent risk factor for CSVT, accounting for 31% of cases (5). Especially the first three weeks after delivery are associated with an increased risk of CSVT, because of the persistence of the hypercoagulable state induced by pregnancy (13–15). Other risk factors for CSVT are listed in Table 1.

Therapy

To date, prognosis of CSVT is favourable owing to the early identification of the disease that allows treatment in the acute stage. Early anticoagulant treatment with fixed doses of subcutaneous low-molecular-weight heparin (LMWH) (according to the patient's body weight) or adjusted doses of intravenous or subcutaneous unfractionated heparin (UFH) (maintaining the activated partial thromboplastin time ratio between 2.0 and 3.0) is also crucial to limit thrombus extension. Although three small controlled trials (16–18) and one meta-analysis (19) failed to show a significant advantage of heparins over placebo, heparin treatment in the acute stage followed by oral anticoagulants is recommended (20). Heparin

Table 1: Risk factors for cerebral sinus and vein thrombosis in adults. The percent estimates are the ranges from single studies (3–5, 11, 12) and revision papers (10).

Cerebral sinus and vein thrombosis	
Local risk factors (%)	
● Acquired	
Brain tumors	2
Central nervous system infections	2–5
Ear, mouth, face, and neck infections	8–14
● Circumstantial	
Head trauma, neurosurgery, lumbar puncture, jugular catheter	1–2
Systemic risk factors (%)	
● Inherited	
Antithrombin deficiency	1–7
Protein C deficiency	3–6
Protein S deficiency	3–8
Factor V Leiden	3–12
Prothrombin G20210A	11–21
● Acquired	
Cancer	3–10
Myeloproliferative neoplasms	1–3
Antiphospholipid antibodies	4–17
Behcet disease	1
Autoimmune diseases	8
Paroxysmal nocturnal haemoglobinuria	1
Hyperhomocysteinemia	4–29
Inflammatory bowel diseases	2–3
L-asparaginase and other drugs	1–2
● Circumstantial*	
Oral contraceptives	10–77
Hormone replacement therapy	4–7
Pregnancy or puerperium	2–31

* percentage calculated on the number of women.

rin is not contraindicated in patients with concomitant intracranial haemorrhage, but it should be used cautiously in patients with large haemorrhagic infarcts at diagnosis (21). There is no adequate evidence supporting the use of such other treatments as local or systemic thrombolysis, that are associated with a high risk of intracranial bleeding and should be considered in patients who deteriorate despite adequate anticoagulation (20). Anti-oedema treatment with intravenous osmotic diuretics or acetazolamide is required in 20% of patients (20). In case of severe intracranial hypertension, lumbar puncture to lower the cerebrospinal fluid pressure and reduce headache and papilloedema, or decompressive surgery to avoid or reverse cerebral herniation can be considered (20). Oral anticoagulant therapy with vitamin-K antagonists

(VKAs) follows the initial heparin treatment, but its optimal duration is not established. A minimum of three months in the presence of transient risk factors and indefinite anticoagulation in the presence of strong and persistent risk factors (i.e. severe thrombophilia, malignancy) are recommended (20, 21).

Splanchnic vein thrombosis

Epidemiology and clinical manifestations

The term splanchnic vein thrombosis (SVT) encompasses occlusions of the hepatic veins (Budd-Chiari syndrome) or the veins forming the portal vein system. Budd-Chiari syndrome (BCS), extrahepatic portal vein obstruction (EHPVO), and mesenteric vein thrombosis (MVT) are three different diseases but the concomitant involvement of more than one venous district is frequent.

BCS is defined as the obstruction of the hepatic venous outflow at any level, spanning from the small hepatic veins to the junction of the inferior vena cava and the right atrium. Outflow obstruction caused by hepatic veno-occlusive disease or hepatic disorders associated with congestive heart failure are not included in this definition (22). The annual incidence of BCS is less than one per million individuals (23, 24). BCS is considered primary in the presence of thrombus or web, and secondary in the presence of endoluminal material other than thrombus (tumours or parasitic mass) or of extrinsic compression (abscesses, cysts, tumours) (22). Membranous webs that obstruct the terminal portion of the inferior vena cava can be either congenital or, more likely, the late sequelae of inferior vena cava thrombosis (25). These are rare causes of BCS in the Western countries, but account for the large majority of cases in Oriental and South African cohorts (23), caused by recurrent bacterial infections and filariasis. However, the improvement in hygienic and sanitary conditions in India has made isolated inferior vena cava obstruction much rarer than in the past (26). In Western countries, two thirds of the patients are women (27, 28), whereas in Asia there is a slight prevalence of males (23). Symptoms of BCS depend on the extent and rapidity of the hepatic outflow obstruction, as well as on the degree of liver decompression via collateral blood flow. Accordingly, presentation can be fulminant, acute, subacute or chronic (22). Fulminant BCS is rare (5% of cases) and is associated with a rapid onset, extensive hepatocellular necrosis and hepatic encephalopathy; the acute form accounts for 20% of cases, with rapid development of ascites and hepatic necrosis with little or no formation of venous collaterals. The subacute or chronic forms are the most common, occurring in 60% of patients (29). The remaining 15% of patients are and remain asymptomatic, perhaps because the hepatic outflow is preserved by a patent hepatic vein or large collaterals (30). However the prevalence of the asymptomatic forms was notably lower (3%) in a recent survey (31). Hepatomegaly, splenomegaly, right upper abdominal quadrant pain and ascites occur in the majority of patients, whereas mild jaundice and slight elevation of the amino-

transferases are seen only in a minority of patients and in the chronic forms (27, 28, 31). The mortality rate at six months is 10% (31). After 10 years of follow-up, the survival of patients with BCS is 57–62%, and prognosis is worse in the 14% of cases with concomitant EHPVO (27, 32, 33).

EHPVO is defined as the obstruction of the extra-hepatic portal vein that may occur with or without the involvement of the intra-hepatic portal, splenic or superior mesenteric veins, formation of portal cavernoma and development of portal hypertension. Isolated occlusion of the splenic or superior mesenteric vein and portal vein thrombosis associated with chronic liver disease or tumour are not included in EHPVO (34). In the 1980s the annual incidence of portal vein thrombosis was estimated at less than four per million individuals (35), but a recent autopsy study found EHPVO in approximately three individuals per thousand (36). Presentation of EHPVO can be acute or chronic. Acute thrombosis is characterised by abdominal pain, fever and diarrhoea, with no evidence of portal hypertension. When the mesenteric veins are also obstructed, there is a substantial risk of intestinal ischaemia and bowel infarction. However, EHPVO may also be asymptomatic, and diagnosed incidentally. The chronic form (34, 37, 38) is characterised by portal cavernoma, portal hypertension with splenomegaly, and a frequency of bleeding from esophageal varices as high as 12% patient-years (39). The overall survival of patients with portal vein thrombosis is 54% after 10 years, but in the absence of cancer, cirrhosis and thrombosis of the mesenteric vein it is 81%, with a mortality rate at one year of 5% (40).

The annual incidence of superior MVT is 2,7 per 100,000 individuals (41), and its presentation can be acute, subacute or chronic (42). Symptoms of acute and chronic forms mimic those of EHPVO, that occurs concomitantly with MTV in 65–72% of patients (43). Acute thrombosis is associated with a definite risk of bowel infarction in 23–33% of patients, with an early mortality rate of 20–30% (41, 43). The rate of recurrent thrombosis is 9.1%, in most cases in the absence of anticoagulant therapy (44).

Diagnosis

The key imaging findings of BCS are occlusion of the hepatic veins, inferior vena cava, or both. Other typical findings are caudate lobe enlargement that may compress the inferior vena cava, liver enhancement due to portal and sinusoidal stasis and, in the subacute and chronic forms, intrahepatic collateral vessels and hypervascular nodules (45). Doppler ultrasound has a sensitivity as high as 89% in EHPVO and near 100% in BCS, whereas in MTV sensitivity is much smaller because the quality of the test is often limited by overlying bowel gas (46–48). Contrast-enhanced computed tomography and magnetic resonance imaging are the techniques of first choice and, in case of uncertain diagnosis, hepatic venography and liver biopsy are warranted (22, 45, 49). Venography allows for pressure measurements, while liver biopsy helps to rule out other liver diseases (22).

Risk factors

Risk factors for SVT can be local or systemic (► Table 2). Multiple risk factors are present in 10–46% of patients with BCS (28, 31, 50, 51) and in 10–64% of those with portal vein thrombosis (38, 40, 50–52). A local precipitating factor is rarely present in patients with BCS (28, 50, 51), but is found in 21–60% of those with portal vein thrombosis (37, 38, 52), mainly liver cirrhosis, hepatocarcinoma or other abdominal tumours, inflammatory diseases and abdominal surgery (Table 2). EHPVO develops in 5–8% of patients after splenectomy, especially in those with underlying myeloproliferative neoplasms or haemolytic anaemia (53, 54).

The leading cause of SVT are myeloproliferative neoplasms, diagnosed in half of the patients with BCS and in one third of those with EHPVO (31, 40, 50–52, 55, 56). The JAK2 V617F mutation, the main molecular marker of the Philadelphia-negative chronic myeloproliferative neoplasms, is found in nearly all patients with polycythemia vera and in about half of those with essential thrombocytopenia (57). The close relationship between myeloproliferative neoplasms and SVT is confirmed by the high prevalence of the JAK2 V617F mutation among patients with BCS and EHPVO (31, 52, 58–60) (Table 2). Among patients with SVT and JAK2 V617F positivity as the sole marker of haematologic disease at the time of thrombosis, the rate of development of an overt myeloproliferative neoplasm during follow-up is 52% (60). Enhanced platelet and leukocyte activation and plasma hypercoagulability associated with JAK2 V617F positivity have been postulated as pathogenic mechanisms of thrombosis (61, 62). In the absence of myeloproliferative neoplasms, the mutation is extremely rare in patients with venous thrombosis other than those of the splanchnic district (60, 63). Preliminary data show that the mutation is found in the endothelial cells of patients with BCS and polycythemia vera, suggesting a possible contribution of endothelial abnormality to the prothrombotic state (64).

Inherited thrombophilia is found in patients with SVT, although diagnosis of deficiencies of antithrombin, protein C, and protein S is difficult in patients with liver function impairment (56, 65). A high prevalence of prothrombin G20210A mutation but not of factor V Leiden has been consistently reported in patients with EHPVO (52, 56, 65, 66), whereas factor V Leiden is more common in those with BCS (31, 51). Case-control studies found an eight-fold increased risk of EHPVO for prothrombin G20210A mutation (56) and 11-fold increased risk of BCS for factor V Leiden (51). A recent meta-analysis showed a four-fold and three-fold increased risk of EHPVO for prothrombin G20210A and factor V Leiden, respectively (66).

Established circumstantial risk factors for BCS are pregnancy, puerperium and the use of oral contraceptives (67, 68). A case-control study showed that oral contraceptives were associated with a 2.4 increased risk of BCS (68), but more recent estimations on currently used hormone preparations are needed.

Reports on the risk factors associated with MVT were mostly anecdotal until recently, when an autopsy series and a population-based study were published (41, 69). The former showed the presence of abdominal cancer in 22% and liver cirrhosis in 17% of

Table 2: Risk factors for Budd-Chiari syndrome and portal vein thrombosis in adults. The percent estimates are the ranges from single studies (24, 27, 28, 31, 38, 40, 50–52, 56, 58, 65, 67) and revision papers (55, 59, 60, 66).

	Budd-Chiari syndrome	Portal vein thrombosis
Local risk factors (%)		
● Acquired		
Cancer	6–7	13–24
Cirrhosis	8–14	17–18
Abdominal infection	7	10
Liver abscess	2	3–5
Inflammatory bowel diseases	3–8	1–4
Pancreatitis	-	6–19
Cholecystitis	-	2–7
Appendicitis	-	1
Tuberculous lymphadenitis	-	3
Membranous web	1–4 (West) – 30 (East)	-
Neonatal omphalitis	-	1–6
● Circumstantial		
Abdominal surgery	2–23	10–30
Splenectomy	2	7
Cholecystectomy	-	3–12
Gastrectomy	-	3
Liver transplantation	-	2
Abdominal trauma	10	1–3
Systemic risk factors (%)		
● Inherited		
Antithrombin deficiency	2–5	1–2
Protein C deficiency	2–9	1–9
Protein S deficiency	3–7	1–5
Factor V Leiden	4–26	3–8
Prothrombin G20210A	3–8	3–22
● Acquired		
Myeloproliferative neoplasms	23–49	6–33
JAK2 V617F (with overt myeloproliferative neoplasms)	57–100	78–100
JAK2 V617F (without overt myeloproliferative neoplasms)	44	27
Antiphospholipid antibodies	1–11	3–13
Behcet disease	4–9	
Autoimmune diseases	10–13	1–4
Paroxysmal nocturnal haemoglobinuria	2–19	1–2
● Circumstantial*		
Oral contraceptives	15–50	15–30
Hormone replacement therapy	14	3
Pregnancy or puerperium	4–16	2–3
* percentage calculated on the number of women.		

cases. The latter showed thrombophilia markers in 67%, a local factor (surgery or inflammation) in 25%, cancer in 24%, and use of oral contraceptives in 6% of patients.

Therapy

In the acute phase patients should be treated promptly with LMWH or UFH followed by oral anticoagulant therapy with VKAs, sodium restriction, diuretic therapy and paracentesis if necessary. In the case of clinical deterioration despite anticoagulation, patients should be considered for such invasive procedures as angioplasty with or without stenting, transjugular intrahepatic portosystemic or surgical portosystemic shunt (22, 49). In patients with BCS, systemic thrombolytic therapy with tissue plasminogen activator is of little value, whereas catheter-directed thrombolysis seems to be effective in acute and partially occlusive thrombosis (70). Local thrombolysis may also be effective in patients with EHPVO and MVT (71–73). Transjugular intrahepatic portosystemic shunt is minimally invasive, has a low morbidity and mortality, improves survival of patients with BCS (74) and has been used also for patients with non-cavernomatous EHPVO (75). However, owing the 23% of perioperative mortality (32) and the unknown improvement in patients' survival, surgical shunting is rarely performed (31). Failure of the aforementioned interventions occurs in 10–20% of patients with BCS (31, 49), who are therefore candidates for liver transplantation.

Also acute EHPVO and MVT require prompt anticoagulation. There is limited evidence that oral anticoagulant therapy with VKAs favours recanalisation and reduces the recurrence rate, without increasing the risk and severity of variceal bleeding (39, 52, 76). A recent prospective study showed that at one year of follow-up the recanalisation rate in patients with initial obstruction of the portal vein, superior mesenteric vein, and splenic vein receiving anticoagulant therapy with VKAs was 38%, 61% and 54%, respectively (52). The optimal duration of anticoagulant treatment is unknown, but a minimum of 3–6 months for EHPVO and life-long for BCS or EHPVO in the presence of permanent risk factors are suggested (21, 22, 34, 37).

Upper-extremity deep vein thrombosis

Epidemiology and clinical manifestations

The most common cause of upper-extremity deep vein thrombosis (UEDVT) is the use of indwelling central venous catheter or pacemakers. Central catheterisation is complicated by thrombosis, often asymptomatic, in 67% of adults and 34% of children (77). Excluding catheter-related cases, UEDVT has an annual incidence of two cases per 100,000 individuals, and accounts for 5–10% of all cases of venous thrombosis (78–80). Another strong risk factor for UEDVT is cancer. Catheter- and cancer-related UEDVT are sec-

ondary events and account for approximately 70% of all UEDVT (80). The remaining 30% are primary UEDVT, including those due to Paget-Schroetter syndrome or effort thrombosis, which are triggered by strenuous muscular activity and hyperabduction of the arms (mainly the dominant). A predisposing factor is the thoracic outlet syndrome, due to the compression of the neurovascular bundle in the area of the neck just above the first rib. The underlying anatomic features are cervical ribs, anomalous first ribs, and congenital narrow scalene triangles (81). The most frequently involved venous segment in secondary and primary UEDVT is the subclavian vein.

The short-term complications of UEDVT are pulmonary embolism and superior vena cava syndrome, occurring in 5% and in 21–23% of patients (82, 83). This latter complication is characterised by dyspnea, headache, dysphagia, neck pain, cough, nausea and facial swelling, and develops most frequently in patients with mediastinal tumours that cause invasion of the venous wall with or without associated thrombosis. The long-term complication of UEDVT is the post-thrombotic syndrome, occurring after two years in up to 27% of patients and characterised by chronic pain, swelling, and heaviness of the arm (84, 85). The annual incidence of recurrent UEDVT is lower than that observed in patients with lower-limb deep-vein thrombosis, ranging after five years from 2 to 11% (79, 86, 87). The clinical presentation of UEDVT is similar to that of deep-vein thrombosis of the lower limbs, with swelling (by far the most common sign present in approximately 80% of patients), functional impairment, weakness and discomfort of the arm and/or hand. Paresthesia, cyanosis and pain can also be present. Symptoms may worsen with lifting or hyperabduction of the arm. Because of the congestion of the superficial veins, the superficial venous network of the arm and upper anterior thorax may become visible.

Diagnosis

Duplex ultrasound examination is the first diagnostic investigation when UEDVT is suspected, because of its simplicity, reliability and non-invasiveness. Diagnostic accuracy is high, with sensitivity and specificity ranging from 78% to 100% and 82% to 100%, respectively (88). However, the proximal subclavian vein (as well as the brachiocephalic vein and superior vena cava) are poorly visualised by ultrasound, because they lie below the clavicle. Hence, the diagnostic gold standard remains digital subtraction venography that is reserved to patients with a strong clinical suspicion of UEDVT when duplex ultrasound is not diagnostic. Computed tomography and magnetic resonance angiography are valid alternatives. When the thoracic outlet syndrome is suspected, abnormalities of the clavicle, subclavius and scalenus anticus muscles, first rib and costoclavicular ligament should be looked for. Cervical radiographs for the presence of anomalous first rib and extra (cervical) rib, and dynamic magnetic resonance angiography (with and without hyperabduction) should be performed in order to evaluate whether or not the subclavian vein is compressed (81).

Risk factors

Recently, a large population-based case-control study showed an approximately eight-fold increased risk of UEDVT in patients with cancer. The risk was 18 times higher in patients with central venous catheter and 11 times higher in patients with metastatic malignancy (82). The left-side insertion of the catheter is associated with a 3.1-fold increased risk of UEDVT than the right-side (89). In analogy to lower-limb deep-vein thrombosis, other established risk factors for UEDVT are surgery, immobilization (e.g. plaster and arm trauma). Strenuous muscular activity of the arm is reported in approximately one fourth of patients and is associated with a two-fold increased risk of primary UEDVT (82, 86, 90, 91). On the other hand, the thoracic outlet syndrome is rarely present in patients with primary UEDVT, being diagnosed in only two of 27 (7%) patients (79).

Whereas oral contraceptives are not associated with an increased risk of secondary UEDVT, their role in primary UEDVT is controversial (82, 86, 92). Recently, two large studies of more than 100 patients with primary UEDVT showed that the risk is not (86) or is slightly (82) increased in oral contraceptive users. The same studies found a synergistic effect between oral contraceptives and the presence of thrombophilia, with a nine- to 14-fold increased risk in carriers of factor V Leiden or prothrombin G20210A mutation. The two mutations are associated with an approximately three-fold increased risk of primary (82, 86) and five-fold increased risk of secondary UEDVT (93).

Since the early 1990s a number of cases of UEDVT occurred after assisted reproductive techniques complicated by ovarian hyperstimulation syndrome (94). The subclavian and axillary veins, jugular veins and cerebral sinuses are more often involved. A possible explanation for this particular location is that women with ovarian hyperstimulation syndrome produce a peritoneal fluid with a very high oestrogen concentration, that is collected into the lymphatic system and drained into the upper extremity veins in close proximity to the internal jugulars. Very high oestrogen concentrations would cause excessive local coagulation activation leading to on-site thrombus formation (95).

Therapy

Treatment of primary UEDVT does not differ from that recommended for deep-vein thrombosis of the lower limbs, i.e. subcutaneous LMWH followed by oral anticoagulation with VKAs adjusted to maintain an international normalised ratio (INR) range between 2.0 and 3.0 (96). Early catheter-directed thrombolytic therapy and surgical options for decompression of the thoracic outlet syndrome are not routinely recommended (96) and perhaps may be reserved to professional athletes or musicians who must recover very quickly, or to patients with disabling neurogenic sequelae (97–99). Duration of oral anticoagulant therapy after a first episode of UEDVT is of at least three months and the indication of in-

definite duration is very rare because of the low recurrence rate of primary UEDVT (21, 79, 86, 87, 96).

In the last decade special attention has been placed on the prevention and treatment of catheter-related UEDVT in patients with cancer. The use of novel materials and coating substances led to a substantial reduction in the rate of catheter-related UEDVT, estimated at present 5% of radiologically confirmed events (100). Antithrombotic prophylaxis with heparin or VKAs has no effect on the risk of catheter-related UEDVT (100–102). Treatment of catheter-related UEDVT consists of anticoagulant therapy; thrombolytic therapy and removal of catheter are not routinely recommended (89, 96). The decision should be made considering the patient's conditions, response to anticoagulation, catheter function, and need of a central venous access (89, 96). The safety of allowing the catheter to remain on-site was recently demonstrated by a prospective study on 74 cancer patients with catheter-related UEDVT treated with heparin followed by VKAs, that showed no episodes of line failures neither extension or recurrence of thrombosis (103).

Conclusions

Venous thromboses occurring in sites other than the lower extremities are rare but clinically relevant diseases. Thrombosis of the cerebral, splanchnic and upper-extremity veins are diagnosed more frequently than in the past owing to the progress in diagnostic imaging. In young women on oral contraceptives who present with a sudden and strong headache or abdominal pain, CSVT or SVT should be considered as possible causes; a canoeist with a swollen arm after an unusual effort may have UEDVT. Caregivers should be able to recognise symptoms and signs, prescribe the appropriate diagnostic workup and the optimal treatment to limit mortality and morbidity. Since venous thrombosis is a multifactorial disease, local and systemic risk factors should be looked for to better understand the pathogenic mechanisms. The great advances made in molecular medicine allowed to recognise the important role of the gain-of-function mutations in coagulation factor V and prothrombin that, alone or in combination with other systemic or local risk factors, contribute to the occurrence of rare venous thromboses. Improved knowledge on risk factors for a disease does not automatically mean a better therapy. Owing to the rarity of these thromboses, there are no randomised trials of adequate sample size addressing the optimal duration of anticoagulant therapy and choices are often based on opinions of experts. The frequent decision to continue anticoagulant therapy life-long in order to prevent recurrences of thrombosis in critical organs such as the brain and the liver does not appear sensible, because in rare venous thromboses the risks of recurrence and long-term complications (i.e. disability in CSVT and post-thrombotic syndrome in UEDVT) are relatively low and do not outweigh the risk of bleeding induced by long-term anticoagulant therapy. Long-term therapy should be considered in patients with unprovoked thrombosis, those with severe hypercoagulable states (antithrombin deficiency,

antiphospholipid antibodies, combined abnormalities) or myeloproliferative neoplasms, and in those with recurrence of thrombosis.

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