

Unusual Sites Thrombosis: From Mechanism to Clinical Practice

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Venous thromboembolism (VTE) is well known as a multifactorial disease with high morbidity and mortality. Although VTE can potentially involve any site of the venous system, most common manifestations are surely deep vein thromboses (DVT) of the lower limbs and pulmonary embolism (PE). Nowadays, modern imaging systems make diagnosis of DVT easy also in unusual sites. Among atypical DVT, those that frequently occur are upper extremities deep vein thrombosis (UEDVT) and retinal vein occlusion (RVO), both are underdiagnosed but important for their complications (e.g. high pulmonary embolism risk for UEDVT) or impact on quality of life (e.g. Visual loss in RVO). Other atypical thromboses are splanchnic vein thromboses (SVC) as portal vein thrombosis (PVT), hepatic (HVT) or mesenteric vein thrombosis (MVT), and cerebral vein thrombosis (CVT). VTE results from multiple interactions between inherited and acquired risk factor. Basic mainstay still remains Virchow's triad: blood stasis, endothelium damage and hypercoagulable state. Inherited risk factors for VTE are well known today as deficiency of clotting inhibitors (i.e. C Protein or S Protein or Antithrombin III) or prothrombotic point mutation in factor V gene (G1691A better known as factor V Leiden), and in factor II (Prothrombin G20210A). Factor V Leiden (FVL) and Prothrombin G20210A (PTM) are the most commonly inherited risk factors for VTE, present respectively in 20% and 10% of the VTE affected population and in about 3% of general healthy population. About 1/3 of typical VTE (lower limbs DVT or PE) occurs in patients carrying inherited thrombophilia. Transient situations associated with increased risk of typical or unusual VTE are neoplasm, surgery, trauma, prolonged bed rest, hormone replacement therapy, oral contraceptives, and pregnancy. Importance of each risk factor in different subtypes of clinical manifestations may be different. Surely, we hypothesize presence of specific risk factors for each specific VTE site.

UPPER EXTREMITIES DEEP VEIN THROMBOSIS

UEDVT are certainly less investigated and studied than lower limbs. UEDVT accounts about 10% of all venous thrombosis [1,2]. Most frequent cause of UEDVT is the insertion of indwelling venous catheters (i.e. secondary

UEDVT) and/or cancer [3,4]. Idiopathic UEDVT, including Paget-Schroetter or effort syndrome, accounts about 20-30% of all UEDVT cases and may be aggravated by anatomical abnormalities conditioning vein compression known as thoracic outlet syndrome (TOS), often difficult to diagnose [3] (Fig. 1). Transient risk factors, such as immobilization, trauma or surgery are less associated to UEDVT in comparison of lower limbs DVT in part explained by valve absence and, therefore, less blood stasis in arm's veins [2].



Fig. (1). Effort left subclavian-axillary thrombosis in young male with additional cervical rib.

Inherited thrombophilia are present in about 15-20% of all cases, although not so much investigated [5]. Martinelli *et al.* showed a 5 fold increased risk for factor V Leiden, 6 fold for prothrombin G20210A mutation and 5 fold for clotting inhibitors deficiency (C or S protein or antithrombin III) taken together. No significant association with hyperhomocysteinemia was found [1].

RETINAL VEIN OCCLUSION

Retinal vein occlusion (RVO) is a frequent vascular disease localized in the eye, that is only second to diabetic retinopathy. RVO is a very important cause of visual loss or blindness from middle age to elderly. Incidence rises from 1 per 1.000 in 40 yrs patients to 50% and more in patients

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older than 65 yrs [6]. RVO is classified according to occlusion site (branch RVO, central RVO, hemicentral RVO). Exact pathogenesis is still unclear: Virchow's triad and atherosclerosis are still today the pathophysiologic mainstay. Strong association with diabetes or hypertension is well known. Open angle glaucoma and ocular hypertension are the most commonly associated local risk factors. The role of inherited thrombophilia has lack of consensus and seems to be consistent just with juvenile RVO [7]. A recent metanalysis by Janssen *et al.* showed that only hyperhomocysteinemia and antiphospholipids antibodies have significant association with RVO and, maybe, the more important risk factor might be atherosclerosis [6] as confirmed (just for hyperhomocysteinemia) also by Pinna *et al.* [8]. Ocular fundus is basilar for diagnosis and shows typical widespread retinal hemorrhages, cotton wool spots, retinal oedema and venous dilatation.

SPLANCNIC VEIN THROMBOSIS

Abdominal vein thrombosis, such as portal vein thrombosis (PVT), mesenteric vein thrombosis (MVT) or hepatic vein thrombosis well known as Budd-Chiari syndrome (BCS), are unusual but nowadays quite reevaluated diseases for their life-threatening effects. Their incidence is largely underestimated. Because of the poor specificity of presenting symptoms diagnosis is difficult but facilitated today by modern imaging approaches. Acquired risk factors may vary according to thrombosis site range from cancer or intra-abdominal flogosis (common for MVT) to liver cirrhosis with portal hypertension, hepatocarcinoma or myeloproliferative disorders (common in PVT). Role of inherited thrombophilia was investigated by few studies and is still a matter of discussion [9].

Janssen *et al.* in a case-control study showed a higher prevalence of FVL or C protein deficiency in patients with BCS and patients with PVT than in controls with no differences [10]. Oral contraceptives was an important acquired risk factor for both BCS and PVT [2]. These data were different from recent data reported by Primignani *et al.* that found a high incidence of PTM gene variant and clotting inhibitors. More recently, Amitrano *et al.* showed higher incidence of FVL, PTM and MTHF C677T mutation in patients with MVT than in controls [11]. These scattered data need to be confirmed by further studies.

CEREBRAL VEIN THROMBOSIS

Until the middle of the last century, CVT was thought to be a very uncommon disease with uncertain clinical correlates and poor prognosis. This opinion was also changed because of the modern imaging support that makes the diagnosis of CVT easier and well-timed (Fig. 2). Past majority of CVT was related to systemic infection or sepsis and about 50% were idiopathic. Today idiopathic CVT decreased to 30% because of the a better knowledge of risk factors as inherited or acquired thrombophilia and use of oral contraceptives [12] while a reduced number of septic cases as trigger factors for CVT are reported [13].

A recent meta-analysis by Dentali *et al.*, with 17 studies investigated, showed a strong association of CVT with FVL or PTM mutation and hyperhomocysteinemia, although inadequate data on clotting inhibitors deficiency or antiphospholipid syndrome are present in the Literature [14]. The role of

other thrombophilic abnormalities (i.e. factor VIII, reduced factor XII and so on) remains to be clarified [15, 16]. Goals of pharmacological treatments include treatment of underlying disease if known (e.g. sepsis), relief of endocranial hypertension and, of course, control of thrombosis and its recurrences.

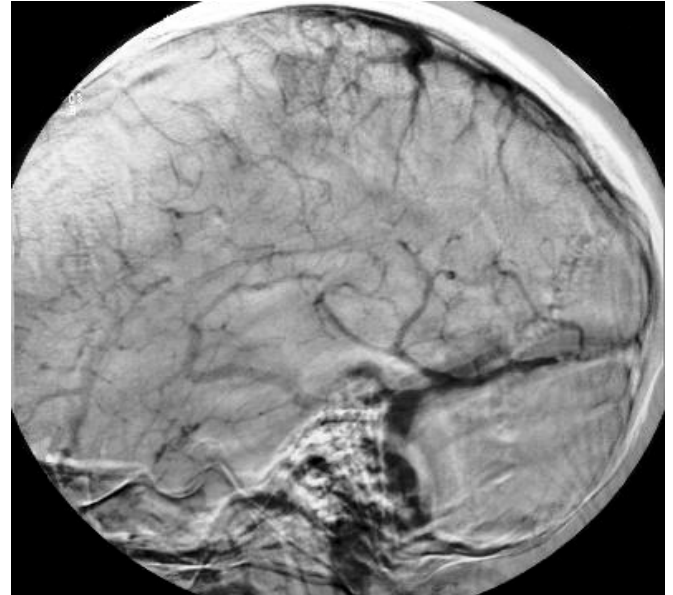


Fig. (2). Straight sinus thrombosis with frontal lobe oedema in 20 yrs old patient with prolonged history of headaches.

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