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Testing for thrombophilia in mesenteric venous thrombosis – Retrospective original study and systematic review

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A B S T R A C T

The aim was to perform a local study of risk factors and thrombophilia in mesenteric venous thrombosis (MVT), and to review the literature concerning thrombophilia testing in MVT. Patients hospitalized for surgical or medical treatment of MVT at our center 2000–2015. A systematic review of observational studies was performed. In the local study, the most frequently identified risk factor was Factor V Leiden mutation. The systematic review included 14 original studies. The highest pooled percentage of any inherited thrombophilic factor were: Factor V Leiden mutation 9% (CI 2.9–16.1), prothrombin gene mutation 7% (CI 2.7–11.8). The highest pooled percentage of acquired thrombophilic factors were JAK2 V617F mutation 14% (CI −1.9–28.1). The wide range of frequency of inherited and acquired thrombophilic factors in different populations indicates the necessity to relate these factors to background population based data in order to estimate their overrepresentation in MVT. There is a need to develop guidelines for when and how thrombophilia testing should be performed in MVT.

Introduction

Although described already in 1895 by Elliot [1], mesenteric venous thrombosis (MVT) was not defined in detail as a clinical entity until 1935 by Warren and Eberhardt [2].

The portal venous system drains blood from the gastrointestinal (GI) tract, spleen, pancreas, and gallbladder to the liver. The portal vein (PV) is formed by the union of the superior mesenteric vein (SMV) and splenic vein (SPV), hence the alternative name splenic-mesenteric confluence [3]. At the level of the porta hepatis, the PV divides into the right and left PV. Finally, after further branching, the terminal portal venules empty into the hepatic sinusoids to supply the liver, thereafter emptying, via any of the three hepatic veins, into the inferior vena cava (IVC) [4].

The common definition of MVT as a single entity is thrombosis within the superior mesenteric vein (SMV) with or without involvement of the portal (PV) or splenic vein (SPV) [5]. Involvement of more than one venous segment is frequent and the most common veins involved are PV, SMV, followed by SPV and the inferior mesenteric vein (IMV) [5–9].

Venous thromboembolic (VTE) involvement of the aforementioned veins is a life-threatening disease due to the risk of mesenteric ischemia with a mortality ranging between 12 and 20% [8,10–13]. Importantly, MVT comprises 5–15% of all causes of mesenteric ischaemia [14,15].

As for any other VTE events, predisposing pro-thrombotic states known as Virchow's triad are associated with thrombus formation; endothelial injury, stasis, and hypercoagulability [16]. Often, simultaneous occurrence of at least two of these events is needed to cause a VTE event [17].

Physiological factors differ between the mesenteric veins, limbs veins, and the pulmonary circulation, increasing MV susceptibility to prothrombotic factors. Firstly, MV blood is rich in both nutrients and intestinal toxins. Secondly, blood flow is subjected to fluid shifts; changes in viscosity could occur after large meals, during periods of fasting, diarrheal illness, and dehydration. Also the splenic vein has the potential to be rich in inflammatory cells, such as monocytes, dendritic cells, and macrophages due to its close anatomic location to the reticuloendothelial system [18].

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Furthermore, organs in the vicinity of the MV might be affected by local processes such as inflammation (pancreatitis, cholecystitis, enteritis, diverticulitis) and malignancy (hepatic or pancreatic tumors) [18]. Malignancy with emphasis on myeloproliferative neoplasia (MPN) is the leading pro-thrombotic disorder associated with obstruction of MV, due to its systemic effect on the pro-thrombotic state [7,8,19,20]. Concerning local risk factors, malignant tumours within the portal venous distribution and cirrhosis are the major MVT contributors [21,22]. It's well known that tumours may locally invade the vessel wall, with resulting VTE [23].

The estimated overall incidences of MVT in Malmö, Sweden, in 1970–1982 and 2000–2006 were similar (2.7 per 100,000 person-years), with equal incidences for men and women. The highest incidence was seen in both elderly (70–79 years) men (12.0/100,000 person-year) and women (10.8/100,000 person-year) [20]. Still, these figures should be compared to the annual estimated incidence rate for all VTE, ranging between 104 and 183/100,000 person-years [24]. The most common sites for VTE are extremity deep vein thrombosis (DVT) and pulmonary embolism (PE). However, MVT is the third most common site of venous thrombosis, after PE or DVT [25]. In other words, MVT is the most common form of atypical venous thrombosis [8,26,27] and the third cause of VTE morbidity and mortality in Western counties [28].

A precipitating risk factor can be identified in up to 80% of patients with MVT [11]. Known risk factors are presented in Table 1.

A thorough investigation in patients suffering from MVT identified one or more systemic pro-thrombotic factors in 60–70%, and local factors in 30–40% [38–41]. Recently, autopsy series showed abdominal cancer in 22%, and liver cirrhosis in 17% of patients with MVT [11]. A population-based study reported thrombophilic factors in 67%, local factors such as surgery or inflammation in 25%, cancer in 24%, and use of ET in 6% of patients diagnosed with intestinal infarction [11,41]. The Swiss Inflammatory Bowel Disease Cohort Study showed a high (26.8%) prevalence of MVT in patients with inflammatory bowel disease (IBD) [42].

Thrombophilia is the term use to describe predisposition to venous and occasionally arterial thromboembolism due to haematological abnormalities [43–45]. However, in most of the cases there is an interaction with another inherited or acquired risk factor triggering the development of VTE [37,46,47]. When an individual with a genetic predisposition is exposed to a clinical setting associated with acquired thrombophilia, the risk for VTE increases beyond that for the normal population [43].

Inherited or acquired thrombophilic conditions have been reported in patients with MVT, irrespectively of the presence of a local risk factor. The prevalence of inherited thrombophilia in MVT patients has been estimated to 36–55% [10,11,39].

In a study from Malmö, Sweden, the prevalence of Factor V Leiden (FVL) mutation was 45% in patients with MVT [48]. Studies have also shown a high prevalence of other inherited thrombophilic factors in patients with MVT, such as prothrombin G20210A (PT) gene mutations, deficiencies of antithrombin (AT), protein C (PC), and protein S (PS) [24,49,50].

As patients with MVT have an increased prevalence of both acquired and inherited thrombophilic risk factors, several authors have expressed different opinions concerning the clinical utility of thrombophilia testing in MVT (Table 2).

The aim of the present study was to (I) study risk factors for MVT in a large retrospective study, and (II) evaluate the role of thrombophilia testing in a systematic review.

Table 1
Risk factors for mesenteric venous thrombosis (MVT) [29–37].

Risk factors
Liver cirrhosis
Inflammation
Infections
Autoimmune diseases
MPN
JAK2 V617F mutation
PNH
Surgery
Malignancy
Inherited and acquired thrombophilia
Pregnancy or the post-partum period
Estrogen Therapy
Hospitalization
Central venous catheter
Trauma
Immobilization
Congestive heart failure
Nephrotic syndrome
IBS
Hyperviscosity syndromes (Waldenström's macroglubinemia)
AIDS

MPN, Myeloproliferative neoplasms; JAK2 V617F, Janus-activated kinase gain-of-function substitute of valine to phenylalanine at position 617; PNH, paroxysmal nocturnal hemoglobinuria; IBS, Inflammatory bowel syndrome; AIDS, Acquired immunodeficiency syndrome.

Methods

Retrospective original study

All patients hospitalized at Skåne University Hospital for surgical or medical treatment of MVT between 1st January 2000 and 31st December 2015 were identified based on the ICD, 10:th edition, codes I81 and K55, and *AuriculA* (register for anticoagulation in *Region Skåne* 2007–2015). Patients included between 2000 and 2006 have previously been reported [11]. Computed tomography (CT) images of all patients with PV thrombosis were scrutinized to evaluate whether the thrombosis involved the superior mesenteric vein. Medical records were analyzed retrospectively. Primary MVT was defined as spontaneous, idiopathic thrombosis of the mesenteric veins, not associated with any other disease or aetiological factor. Patients with symptoms, mainly abdominal pain, of less than 4 weeks' duration were classified as having acute MVT. Those with symptoms for more than 4 weeks, but without bowel infarction, or those with MVT diagnosed incidentally on abdominal imaging, were considered to have chronic MVT. The term “trombophilia” was used as a common denominator for factors that may provoke MVT, such as coagulation disorders, cancer, previous or concomitant VTE, and ET. Testing for thrombophilia includes inherited thrombophilic factors (FVL mutation, PT gene mutation, and deficiencies of PC, PS, antithrombin [AT]) and acquired thrombophilic factors (JAK2 V617F mutation, lupus anticoagulant [LA] and cardiolipin antibodies [CA]).

Swedish currency (SEK) was converted to Euro, using www.oanda.com.

This study was approved by the Regional Ethical Review Board in Lund, Sweden (Dnr 2015/143).

Systematic review

A systematic literature search was performed in PubMed, EMBASE and Scopus from 2006 to September 1, 2016, by combining the Medical Subject Headings “mesenteric venous thrombosis”, “MVT”, “splanchnic vein thrombosis” and “prothrombotic”, “hypercoagulability”, “thrombophilia”, and NOT “Budd Chiari”. The review was performed according to the PRISMA statement (www.prisma-statement.org) (Fig. 1). Study selection and data abstraction was performed by MZ. After exclusion of duplicates from the three database sources, screening and exclusion based on titles and abstracts was performed. Reviews, editorials, commentaries,