Beyond the usual workup: severe hypertriglyceridemia as a potential cause of cerebral venous thrombosis

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ABSTRACT

Hypertriglyceridemia and cerebral venous thrombosis are well-recognized complications of asparaginase therapy for B-cell acute lymphoblastic leukemia. Hypertriglyceridemia has also been associated with an increased risk of thrombosis in conditions such as Behçet's disease and has been implicated in a pediatric case of cerebral venous thrombosis, suggesting a possible link between hypertriglyceridemia and cerebral venous thrombosis. We present the case of a patient with acute delirium and amnesia, revealing a venous infarction caused by cerebral venous thrombosis of the sinus rectus. Classical causes, including hereditary thrombophilia, were excluded. Notably, the patient's blood appeared lactescent at admission, and laboratory testing revealed severe hypertriglyceridemia. The patient improved significantly with heparin, dietary modifications, and ciprofibrate. This case suggests that severe hypertriglyceridemia should be considered as a potential trigger of cerebral venous thrombosis and that including a lipid panel in cerebral venous thrombosis work-ups could be considered, allowing subsequent specific therapeutic interventions.

Key words: hypertriglyceridemia, hyperlipidemia, cerebral venous thrombosis.

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Introduction

Cerebral venous thrombosis (CVT) represents a rare form of stroke. It most often affects young people with risk factors for thrombophilia: estrogen-progestogen contraception, smoking, constitutional thrombophilia, or local infectious foci. The thrombogenic potential of dyslipidemia was highlighted and attracted considerable interest in the 1990s and until 2010.[1-6] After, publications have been rarer until a regain of interest in 2021.[7,8] Several potential mechanisms have been discussed, involving the intrinsic, extrinsic, and common pathways, as well as the inhibitory feedback control of hemostasis.

Interestingly, treatment with asparaginase used in acute B-cell lymphoblastic leukemia has well-known side effects including hypertriglyceridemia (HTG) and CVT, although no link between these two side effects has been clearly established.[9] Furthermore, it has been shown that HTG contributes to the risk of thrombosis in Behçet's disease.[10] Finally, a case of CVT attributed to severe genetic HTG in a child has been reported.[11] Despite this, dyslipidemia remains largely overlooked in the etiological workup of CVT.

In this article, we describe the case of a 43-years-old patient who presented with CVT and whose tests revealed severe HTG with no other potential cause.

Case Report

A 43-years-old man, working as a tiler, was referred to our neurology department for confusion associated with acute anterograde amnesia. Symptoms had begun three weeks earlier while he was traveling. He reported no exposure to toxic substances. His medical history was limited to obesity (body mass

index 32.1 kg/m²) and a remote episode of lumbar radiculopathy. Family history was notable for obesity and dyslipidemia in his father.

Neurological examination was unremarkable except for marked anterograde amnesia. There were no clinical signs suggestive of systemic disease. The patient reported no abdominal pain, no deterioration in general condition, and ear, nose and throat examination were normal. Brain computed tomography revealed hypodensity involving the head of the left caudate nucleus and, to a lesser extent, the left thalamus and perithalamic white matter, without pathological contrast enhancement.

Lumbar puncture showed clear, acellular cerebrospinal fluid, with mild elevation of cerebrospinal fluid (CSF) protein (0.76 g/L) and normal CSF glucose. Routine laboratory investigations were largely unremarkable, except for moderately elevated liver enzymes (AST 68 U/L, 1.7× upper limit of normal; ALT 170 U/L, 4.2× upper limit of normal) and serum creatinine of 109 µmol/L. Toxicological screening was negative.

Brain magnetic resonance imaging demonstrated CVT involving the sinus rectus, complicated by multi-territorial venous infarctions (Figure 1).

As part of the etiological assessment, a computed tomography scan of the chest, abdomen, and pelvis was performed, showing no suspicious lesions, but revealing a 36-mm dilation of the pulmonary artery trunk and steatotic hepatomegaly. Given the dilation of the pulmonary artery trunk, a ventilation scintigraphy was performed and yielded normal results.

A comprehensive thrombophilia workup was negative, including testing for antiphospholipid syndrome (anticardiolipin antibodies, anti-β2-glycoprotein I antibodies, and lupus anticoagulant), antithrombin, protein C and protein S deficiencies, factor V Leiden (c.1601G>A) and factor II (c.97G>A) variants, as well as plasma homocysteine level, which was within the normal range (14.1 µmol/L). Additional investigations showed negative HIV, Hepatitis B and C serologies, hyperbetaglobulinemia on serum protein electrophoresis, and normal antinuclear and extractable nuclear antigen antibodies. Notably, the serum had a milky appearance.

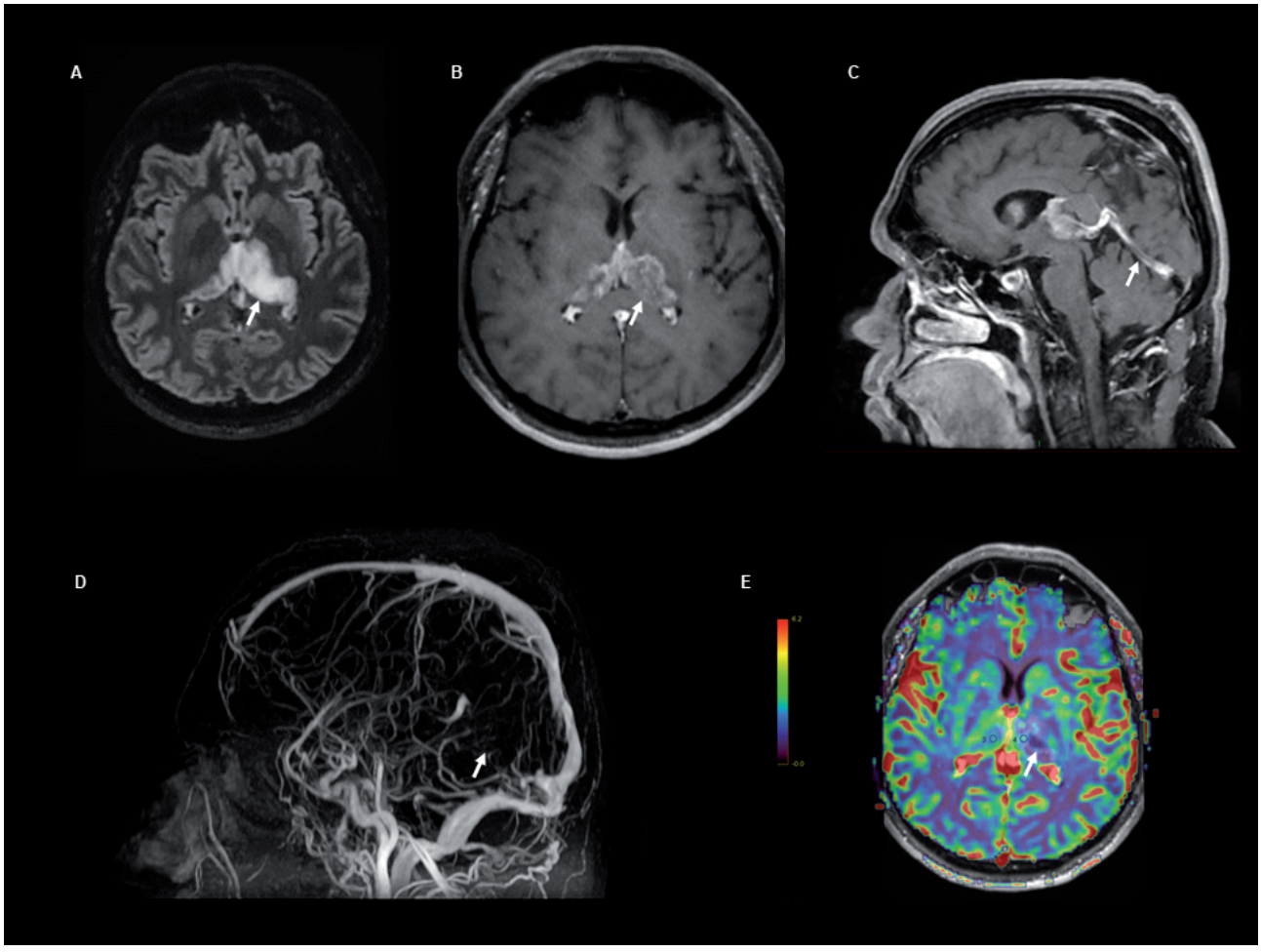

Figure 1. Brain imaging of the patient. A) T2-weighted FLAIR sequence displaying bilateral thalamic hyperintensity; B, C) T1-weighted gadolinium enhanced sequences revealing delayed thalamic contrast enhancement due to blood–brain barrier breakdown (B) and filling defect within the straight sinus (C); D) Magnetic resonance venography depicting lack of flow within the straight sinus; E) Magnetic resonance perfusion imaging displaying a decreased cerebral blood volume in the infarcted thalami.

In this context, a lipid profile was performed and initial results revealed severe HTG with triglycerides (TG) at 24.42 g/L (27.75 mmol/L, laboratory reference ranges: 0.44-1.47 g/L (0.50-1.67 mmol/L), total cholesterol at 4.2 g/L (10.86 mmol/L), non-HDL cholesterol at 3.92 g/L (10.14 mmol/L), and HDL-cholesterol at 0.28 g/L (0.73 mmol/L). Serum lipase levels were within the normal range. No secondary cause of this severe HTG was identified, including hypothyroidism, nephrotic syndrome or Cushing's syndrome. On physical examination, eruptive xanthomas were observed on the palm of the right hand, along with bilateral xanthelasma and bilateral corneal arcus (arcus juvenilis).

Therapeutic anticoagulation with low-molecular-weight heparin was initiated and subsequently switched to dabigatran after antiphospholipid syndrome had been excluded. A broth-based diet was started, combined with hyperhydration using sodium chloride, followed by dietary counseling and initiation of ciprofibrate therapy. At discharge, lipid parameters had markedly improved, with TG at 3.12 g/L (3.56 mmol/L), LDL cholesterol at 1.4 g/L (3.63 mmol/L), and HDL cholesterol at 0.3 g/L (0.78 mmol/L).

The patient's clinical condition improved significantly and rapidly. Neuropsychological evaluation performed three months later showed persistent moderate impairment of executive and attentional functions, including deficits in attention mobilization and selectivity, impaired inhibitory control, and secondary impact on verbal episodic memory. One year later, the patient reported no residual complaints; however, relatives noted persistent behavioral changes, including increased irritability, a slightly more caustic temperament, and psychomotor slowing in daily activities. The patient was subsequently lost to follow-up, and the scheduled check-up at the dyslipidemia reference center, organized on several occasions, was not attended by the patient.

Discussion

In our patient, the absence of other identified prothrombotic factors strengthens the hypothesis that severe HTG may have contributed to the thrombotic event. While causality cannot be established, the absence of alternative triggers and the severity of HTG in our patient strongly support a contributory rather than incidental role.

Severe HTG is a rare dyslipidemia defined by a concentration of TG >8.8 g/L (10 mmol/L).[12] Triglyceride-rich lipoproteins containing apolipoprotein B (apoB) are chylomicrons synthesized by the intestines (exogenous origin) and very low density lipoprotein (VLDL) synthesized by the liver (endogenous origin). The TGs of these lipoproteins undergo hydrolysis by a key enzyme, lipoprotein lipase (LPL), into non esterified fatty acids (NEFA) and glycerol, leading to the formation of TGs-depleted lipoproteins as chylomicrons-remnants, VLDL-remnants and low-density lipoprotein (LDL). NEFA can be stored by adipose tissue or used for hepatic production of VLDL. The depleted lipoproteins are captured by peripheral or hepatic receptors (LDL-R and LRP) via the specific binding with apolipoprotein E (apoE) present on the surface of these lipoproteins.[9,13,14]

Diminution or absence of LPL lead to severe hypertriglyceridemia, and can be partially attributed to a genetic predisposition.[9,11,14] The unfunctional LPL activity, with accumulation of chylomicrons and remnant particles, can in addition be associated with microcirculatory occlusion, endothelial dysfunction, inflammation and oxidative stress leading to many complications as acute pancreatitis, atherosclerotic cardiovascular diseases, peripheral and cardiac autonomic neuropathy.[15]

Routine lipid profile consists of measuring total cholesterol, TG, HDL-c, LDL-cholesterol, and the aspect of serum, which was lactescent for our patient (normally clear). Specific other assays, such as the measurement of the apoB, apoE, and apolipoprotein CII (apoCII), apolipoprotein CIII (apoCIII) respectively activator and inhibitor of LPL, in addition to the measurement of post-heparin LPL activity, genetic analysis of LPL and its precursors, are necessary for the diagnosis of severe hypertriglyceridemia.[11,13,16]

Most available data on dyslipidemia and thrombosis risk concern deep vein thrombosis of the lower limbs, and their extrapolation to CVT must be interpreted with caution, given the specific hemodynamic and endothelial characteristics of the cerebral venous system. On the other hand, CVT shares core mechanisms of venous thrombosis, including endothelial dysfunction, hypercoagulability, and venous stasis and several potential mechanisms may be proposed to explain a link between HTG and CVT. First, increased levels of lipolysis products derived from triglyceride-rich lipoproteins, promote cellular stress and endothelial inflammation, thereby facilitating platelet adhesion and activation.[11,17,18] The frequent co-occurrence of obesity and/or metabolic syndrome, which are associated with chronic inflammation, may further exacerbate this phenomenon. In addition, HTG is associated with increased blood viscosity, one of the components of Virchow's triad that predisposes to thrombosis.[19] Furthermore, an increased expression of procoagulant factors and a reduction in anticoagulant factors have been demonstrated in the context of HTG, including elevated levels of factors VII, VIII, IX, and X, reduced activated protein C, and increased fibrinogen levels.[20] These associations, initially identified in observational studies, have been challenged by studies focusing on genetically determined lipid profiles.[21-23]

More recent studies using refined lipidomic analyses have reignited the debate, notably by demonstrating an association between certain lipid subtypes or specific metabolites, such as fatty acid unsaturation, and an increased risk of deep vein thrombosis.[5,6] Conversely, some phosphatidylcholines or large VLDL particles appear to be protective.[24,25] In addition, several studies suggest that inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the main target of statins, is associated with a slight reduction in the risk of deep vein thrombosis, whereas inhibition of apoB or apoCIII, and activation of LPL, may increase this risk, suggesting complex pleiotropic effects.[23] Taken together, these mechanisms provide biological plausibility for a link between HTG and venous thrombosis.

From a therapeutic perspective, meta-analyses suggest a modest reduction in the risk of venous thrombosis with statin therapy (odds ratio approximately 0.8-0.9), with a more pronounced effect when combined with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. Notably, this benefit appears to be independent of LDL reduction, which may reflect an effect on endothelial function or the coagulation cascade.[26,27] In contrast, fibrates are associated with an increased risk of venous thrombosis (odds ratio around 1.6), possibly related to unfavorable modulation of certain coagulation factors and increased venous stasis. In particular, activation of peroxisome proliferator-activated receptor α (PPARα) by fibrates has been associated with modulation of coagulation

factors, increased PAI-1 expression, and potential alterations in venous tone, which may contribute to a prothrombotic environment.[28-30] Importantly, the effects of lipid-lowering therapies on venous thrombosis may not rely on triglyceride levels per se and rather reflect drug-specific pleiotropic mechanisms. Although fibrates have been associated with an increased risk of venous thrombosis, their use was considered appropriate in our patient case given the severity of hypertriglyceridemia and the effective therapeutic anticoagulation. An individualized risk-benefit assessment is mandatory.

Thus, unlike arterial risk, the relationship between plasma lipids and venous thrombosis may be less direct, involving specific lipid species, lipoprotein particle characteristics, and downstream metabolic effects which may explain the discrepancies between studies. Plasma triglyceride concentration represents an aggregate marker of multiple triglyceride-rich lipoprotein species, and the specific lipid subfractions are not available in standard care. Measurements of apoB or apoC-III would have provided valuable insight into the atherothrombotic and venous thrombotic risk profile of our patient but were not performed.

Conclusions

Pathophysiological evidence and the case of our patient, who had no other notable risk factors apart from dyslipidemia and obesity, suggest a potential contributory role of severe HTG in the development of CVT. We recommend assessing patients with CVT for clinical signs of hypertriglyceridemia and relevant family history. A lipid profile should be obtained when these factors raise suspicion, to enable identification and appropriate management of underlying dyslipidemia, particularly when no other cause of CVT is found. In our patient, the lactescent aspect of the serum was already suggestive and readily apparent at the time of initial blood sampling.

Despite its inherent limitations, this case highlights an extreme metabolic phenotype that may help uncover underexplored mechanisms linking triglyceride-rich lipoproteins to cerebral venous thrombosis and illustrates the complexity of lipid–thrombosis interactions beyond traditional lipid measurements. Further studies integrating clinical phenotyping, lipidomic profiling, and genetic data are warranted to better delineate the role of triglyceride-rich lipoproteins in CVT.

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