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CASE REPORT

Unexpected papilledema in a young male with Type 1 diabetes

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Key Clinical Message

In young patients with T1D, neurological manifestations of cerebral hypertension should suggest the possibility of a cerebral venous sinus thrombosis (CVST). In these patients an inherited prothrombotic risk factor, including factor V Leiden G1691A gene mutation, should be considered during an event of thrombosis. Improving the glycemic control is the first factor that should be controlled in a patient who carries a genetic prothrombotic risk factor. Anticoagulant treatment should be started as son as CVST has been diagnosed. Long-term antithrombotic treatment with tinzaparin 175 IU/kg/day, a low-molecular weight heparin (LMWH), could be reliable and well tolerated, although an indefinite special follow-up, including neurological controls, is advisable even in asymptomatic patients.

Keywords

Cerebral venous sinus thrombosis, inherited thrombophilia, low-molecular weight heparin treatment, papilledema, type 1 diabetes.

Introduction

In young people with type 1 diabetes (T1D), the most common cause of acute neurological deterioration is cerebral edema. Therefore, intracerebral vascular thrombosis, subarachnoid hemorrhage, meningoencephalitis, and ischemic stroke should also be considered, all of which are often associated with an episode of acute diabetic ketoacidosis (DKA) in patients with T1D.

Papilledema (or papilloedema) is optic disk swelling, and detection of bilateral papilledema is related with causes that increase intracranial pressure (Table S1). Thus, an evaluation with a computed tomography (CT) and magnetic resonance images (MRI) studies of the brain should be quickly performed. In general population, the incidence of cerebral venous thrombosis is approximately three to four cases per million affecting mainly patients <40 years old. It is three times more prevalent in women mostly during pregnancy or taking hormonal contraceptive drugs, and special attention should be given to identifying carriers of inherited thrombophilia. However, cerebral venous sinus thrombosis (CVST) is an uncommon form of presentation of stroke affecting young patients [1]. Therefore, in a study performed in children and young adults (<18 years old), an incidence of CVST of 6.7 per million per year was reported [2]. In addition, in a meta-analysis, it was observed that only two of 149 children with CVST were found to have diabetes without acute hyperglycemia or DKA [3]. Finally, the largest study of CVST, the international Study on Cerebral Vein and Dural Sinus Thrombosis, included 624 patients in a prospective observational, multicenter and multinational study, found an inherited prothrombotic condition in 22% of patients [4]. Here, we report a case of asymptomatic presentation of a CVST in a youth with T1D identified after detection of a bilateral papilledema in a routine outpatient retinography.

Case History and Examination

A 15-year-old boy with T1D since the age of nine was presented on a routine visit with a fasting glucose of 12.43 mmol/L and HbA1c of 76 mmol/mol, serum total cholesterol of 3.37 mmol/L, and thyroid-stimulating hormone of 3.66 mUI/L. He was asymptomatic and his physical examination showed a weight of 79-kg with a height of 174-cm and blood pressure (BP) of 139/78 mmHg with a heart rate of 93 bpm. He was afebrile, and his head and neck, abdomen, and extremities were also normal. Others results from urinalysis (including microalbuminuria and ketones), complete blood cell counts, and liver and kidney functions were all normal. A year before, the retinal exploration was normal (ophthalmology report). Insulin treatment was glargine 38 units at bedtime plus aspart before each meal (≈11, 12 and 11 Units; total insulin 0.91 Units/kg/day). Four weeks before, he presented an acute gastroenteritis accompanied by an intermittent frontal headache without showing any warning signs (neurological, ophthalmological, etc.). The headache did not stop his normal routine including school activities. He was treated with minor analgesics (paracetamol) and progressively improved over a 2 week period. It was interpreted as minor in relation to a likely acute viral gastroenteritis. The patient was encouraged to reinforce diabetes education, and a new retinography was requested, when a bilateral papilledema was unexpectedly diagnosed (Fig. 1, panel A left and right). Immediately, the patient was sent to the emergency department where a CT and MRI studies without contrast were unremarkable (Figure S1). Subsequently, sagittal and axial reformatted images from the contrast-enhanced magnetic resonance venography (MRV) showed, in both the superior sagittal sinus and the right transverse sinus, the presence of filling defects compatible with sinus thrombosis (Fig. 2, panel C and D, arrows).

Differential diagnosis

The clinical presentation of an episode of cerebral thrombosis may be mainly due to two pathophysiological mechanisms in the brain. Therefore, the CVST quickly increases the pressure in veins and brain capillaries. In addition, the thrombosis "per se" has inflammatory actions that generate a perivascular cerebral edema, which again increases capillary pressure and in conjunction with the inflammation on the vessels increases the likelihood of cerebral hemorrhage. Thus, a wide clinical variability can be observed in the presentation of a CVST.

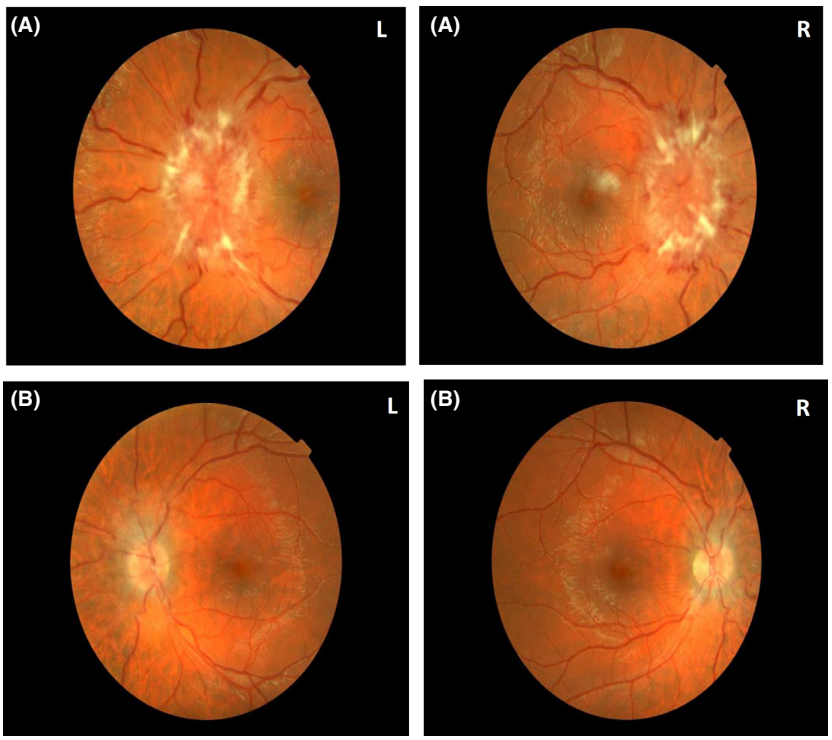

Figure 1. Retinography showing an unexpectedly diagnosed bilateral papilledema (panel A, left and right). A new retinography demonstrated a dramatic improvement of papilledema after 6 months (panel B, left and right).

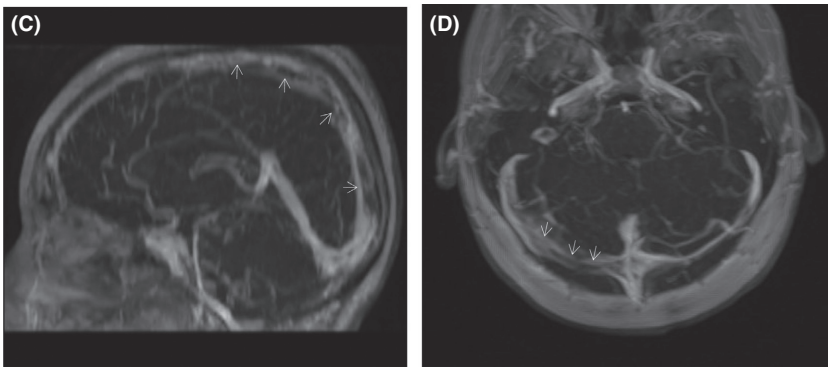

Figure 2. Filling defects in both superior sagittal sinus and right transverse sinus, findings consistent with thrombosis are shown (panel C and D, arrows).

Symptoms may be mostly derived from those produced by intracranial hypertension (p.e. papilledema) and others resulting from a focal neurological deficit. Finally, the clinical course may be acute, subacute and more latent, or chronic, considering the time evolution. Four main syndromes can be observed such as isolated intracranial hypertension syndrome (90%), focal neurological abnormalities (44%), seizures (30–40%), and encephalopathy which are more likely in elderly patients.

In the case described here, a bilateral papilledema was suddenly observed in a young boy with T1D in a routine outpatient visit. The patient was asymptomatic, although his metabolic control was bad (HbA1c~10%); however, he was stable without glycemic variability. Quickly, neurological explorations were made including the result of a lumbar puncture, and no findings resulted. In addition, ophthalmological examination was found to be normal, and a careful evaluation of retinography images noted that no diabetic retinopathy lesions were present. The patient's medical history revealed that only an episode of headache without symptoms of neurological deficiency was noted, associated with an episode of gastroenteritis. This was treated with minor analgesics and did not stop his daily life and had gradually improved at to the date of the consultation. Headache may be present in up to 90% of patients with CVST and can be generalized or focused and often increases with Valsalva maneuver or exercise [5]. Initially, on the day of the consultation, CT and MRI studies without contrast showed no orbitary or brain lesions. However, after a MRV the presence of thrombus both in the superior sagittal sinus and the transverse sinus was observed. Therefore, while MRI may give a good signal of deep veins or sinuses on T1-weighted images and in brain tissue near to venous thrombosis, MRV provides the best evaluation of partially clogged sinuses, as in this case.

One or more risk factors can usually be identified in over 85% of patients with CVST (Table S2) [4, 6]. Risk factors for thrombosis are usually divided into inherited (thrombophilia) and acquired. At evaluation, a complete investigation of primary hypercoagulability by inherited risk factors was carried out. Levels of antithrombin III and protein S and C were normal. American Heart Association defines as high-risk thrombophilias homozygosis for either factor V Leiden or G20210A mutations [7]. However, whereas the mutation G20210A of prothrombin gene was absent, a state of thrombophilia was diagnosed because the patient was a heterozygous carrier of the factor V Leiden G1691A mutation.

In addition, acquired precipitating factors are frequently found in patients with thrombosis, increasing the risk of genetic prothrombotic states. Therefore, a thorough investigation of clinical and analytical data of acquired prothrombosis risk factors was made. In developed countries, the more common of these include oral contraceptives (~22-fold risk of CVT), pregnancy and puerperium, but this was not applicable to this patient [4]. The presence of "antiphospholipid antibodies" such as anti-β_2-glycoprotein I, anticardiolipin antibodies, and lupus anticoagulant was negative, and homocysteinemia level was normal. Other frequent factors including head trauma, cancer, exogenous hormones and drugs, localized and systemic infections [including parameningeal locations], hematologic disorders, chronic inflammatory diseases, and neurosurgical procedures were discarded. Therefore, of relevance in this patient, a probably viral infection, bad control of T1D, and a heterozygous carrier of the factor V Leiden were identified. This mutation is quite frequent in Caucasians and can be found in 5% of the general population of European descendents, but increases up to 11–21% in patients with venous thromboembolism [8]. Thus, subjects with the factor V Leiden G1691A mutation have a risk of deep vein thrombosis seven times higher than subjects without the mutation. Coagulation disorders have been reported in 39 of 123 (32%) children with CVST, while an inherited

prothrombotic condition was found in 22% and specifically the G1691A mutation was observed in three patients [2]. Currently, there is limited information about the relationship between the presence of factor V Leiden mutation in T1D and venous thrombosis incidence. However, in a few case reports of venous thrombosis in patients with T1D a heterozygous carrier of factor V Leiden mutation has been found. In these cases, chronic or acute poor glycemic control appeared to be the reason that precipitated the episode of thrombosis [9, 10]. Our patient showed bad metabolic control, although stable and without glycemic variability, at the time of diagnosis. However, one episode of probable acute viral gastroenteritis 4 weeks previously, either "per se" through stimulating inflammatory mechanism or through altering the metabolic control, could have affected the weak balance/imbalance primary procoagulant state.

Diabetes and cerebral sinus thrombosis

In this type of patient, differential diagnosis should include several neurological disorders frequently associated with T1D, like cerebral edema with increased intracranial pressure, meningoencephalitis, cerebral infarction, CVT, and subarachnoid hemorrhage, all these mainly associated with DKA [11, 12].

Risk factors for CVT are those that affect blood stasis, changes in the vessel wall, and changes to the composition of blood (Virchow triad). In diabetes, there is a predisposition to present dehydration, hyperosmolarity and pH reduction, altered platelet and leukocyte functions, and dyslipidemia. All these factors contribute to microperfusion and endothelial damage and would establish a prothrombotic environment in the setting of a poorly controlled metabolic state of diabetes [13]. In addition, diabetes increases fibrinogen levels and decreases the mechanism of fibrinolytic activity with a decrease of tissue activator plasminogen (t-PA), increases plasminogen activator inhibitor 1 (PAI-1), increases concentrations of thrombin–antithrombin complexes, factor VIII activity, and soluble tissue factor and alpha-2 macroglobulin levels [13]. All these factors establish a procoagulant status. It is possible that during the episode of acute gastroenteritis that the patient presented some weeks before, hyperosmolarity and hyperglycemia and/or transient ketoacidosis might have occurred; however, this could not be verified.

Hyperglycemia might be considered a marker for brain injury in patients with CVT. Therefore, in patients with aneurysmal subarachnoid hemorrhage, hyperglycemia was shown to be correlated with the magnitude of the hemorrhage [14]. In addition, it has recently been found that hyperglycemia on admission is a strong predictor for poor clinical outcome in patients with CVT, even without a previous history of diabetes mellitus [15]. However, whether tight glucose control can improve, the outcome of these patients needs to be observed in a specific randomized clinical trial.

Treatment

Treatment with anticoagulants may reduce thrombus propagation, appearance of other venous infarcts, and neurological impairment in patients with CVST. Thus, anticoagulant treatment should be started as soon as CVST has been diagnosed. Initial anticoagulation is advised with adjusted-dose unfractionated heparin or weight-based low-molecular weight heparin, regardless of the possible presence of intracerebral hemorrhagic lesions [7, 16, 17]. As necessary, management of seizures, severe headache, and increased intracranial pressure may require a neurological and neurosurgical approach. In this patient, tinzaparin 175 UI/kg/day was started, and 6 months later a new retinography demonstrated a dramatic improvement of papilledema (Fig. 1, panel B left and right). However, at this time in the control with MRV the persistence of thrombus in the transverse sinus was observed, although fewer in number and smaller in size. Therefore, treatment with tinzaparin was subsequently extended for another 6 months (12 months). The young man remained asymptomatic during all this time.

In addition, the suboptimal metabolic control at the time of diagnosis (10% HbA1c) was improved after appropriate intensification of lifestyle in our nursing clinic, and by adjusting his bolus-basal insulin pattern to preprandial capillary plasma glucose between 80 and 130 mg/dL and postprandial capillary plasma glucose <180 mg/dL, and after 3 months treatment the HBA1c was 7.2%, very close to the 7% control goal set by the standards of medical care in diabetes of the American Diabetes Association (ADA) [18].

Patient's perspective

In a meta-analysis that grouped 1180 patients with CVT, the mortality rate at 30-days was 5.6%. The main cause of death was transtentorial herniation. A complete or partial recovery occurs within a few months, although 10% have persistent neurological deficits at 12 months [19]. Concern for anticoagulation treatment in CVST results from the possibility that venous infarcts to become hemorrhagic. However, the evidence from two randomized and controlled trials comparing treatment with intravenous unfractionated heparin and the low-molecular weight heparin vs placebo supports the quickly use of

anticoagulant therapy [20, 21]. It is possible that even improvement of obstruction and venular pressure could reduce the risk of further hemorrhage. Thus, after an initial period of treatment with heparin, it is advisable to continue anticoagulation with oral anticoagulation with vitamin K antagonists.

However, we have no direct specific evidence for anticoagulation in CVST, but guidelines recommend these for deep vein thrombosis and pulmonary embolism. The AHA/ASA 2011 recommends oral vitamin K antagonist during 3–6 months for provoked and 6–12 months for unprovoked in patients with CVST. In addition, the AHA/ASA 2011 recommends identifying patients with high risk to recurrent CVST and should include those with severe thrombophilia (homozygosity for prothrombin gene mutation 20210 or factor V Leiden; combined thrombophilias; deficiencies of antithrombin, protein C, or protein S; or antiphospholipid antibodies). These patients should be considered for indefinite anticoagulation therapy.

Due to the clinical particularity of our patient, we considered tinzaparin treatment for the first 6 months. The clinical follow-up of the AHA/ASA 2011 Scientific Statement advises a control imaging 3–6 months after diagnosis [7]. At this time (6 months), a new retinography already demonstrated a dramatic improvement of papilledema, but in MRV control some persistent thrombus, although fewer in number and smaller in size, was observed. Thus, we chose to extend tinzaparin for a further 6 months (12 months). After 12 months of heparin treatment, we considered discontinuing anticoagulation treatment in our patient. Mainly, because he had no associated clinical complications and presented a full resolution in thrombus images in a new MRV control at 12 months, and secondly, he was not a homozygous but a heterozygous carrier of factor V Leiden mutation. However, we thought that the thrombotic process could have injured the cerebral venous bed (factor 1 and 2 of Virchow), and this fact together with being a carrier of factor V Leiden and having a T1D with improper handling could increase the risk of a new thrombotic event. Therefore, at the end of treatment in this young patient, we were uncertain of the following: how long we should continue the treatment for and what the antithrombotic treatment should be? We made the decision to stop the treatment at 12 months. However, if you decide to continue antithrombotic treatment for an extended period, it is advisable that warfarin be chosen to target international normalized ratio of 2.0–3.0 instead of tinzaparin. Currently, these and other questions cannot be answered based on medical trial evidence and can only be answered based on expertise. Lastly, we established a specific monitoring regime for this boy: first, reinforcing education in diabetes and the implications of his self-control in achieving better blood glucose levels. Hyperglycemia is the first factor that should be controlled in a patient who carries an unmodifiable genetic prothrombotic factor. Second, this patient must continue special surveillance, including neurological controls, even if he becomes asymptomatic. At the moment, after 2 years of follow-up he remains asymptomatic without any new recurrent episodes.

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Authorship

JAP: contributed to the study design, data collection, analysis, and interpretation and wrote the paper. RB, ACS, and FV: all contributed to analysis and interpretation.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Differential diagnoses of Papilledema.
Table S2. Risk factor for several sinus thrombosis.
Figure S1. Computerized Tomography (CT): demonstrates no orbitary defects.