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Is JAK2-Mutation Associated with Extensive Clot Burden in Cerebral Venous Thrombosis?

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Abstract

Cerebral Venous Thrombosis (CVT) is a, rare form of stroke which is usually associated with acquired and genetic risk factors. The presence of JAK2 or JAK2-V617F mutation is a novel genetic biomarker increasing which has been shown to increase the risk of arterial and venous thrombosis, especially in patients with myeloproliferative disease. We present a case of a patient with extensive CVT affecting intracranial venous sinuses and extending to the neck vessels and possible JAK2 associated polycythemia vera who had a good therapeutic response to a direct oral anticoagulant.

Introduction

Cerebral Venous Thrombosis (CVT) is an uncommon form of neurovascular disorder which occurs in less than 1% of all patients with stroke [1]. Hereditary thrombophilia is an essential cause of CVT especially in children and young adults. A meta-analysis confirms that genetic mutation in the factor V-Leiden and the prothrombin genes are likely to predispose patients to CVT [2]. The presence of a mutation in JAK2 (JAK2-V617F) is another novel genetic abnormality which has been shown to increase the risk of venous and arterial thrombosis among genetic carriers [3-11].

The occurrence of thrombotic events in patients with JAK2 mutation is due to their predisposition to Myeloproliferative Disorders (MPD) such as polycythemia vera and essential thrombocytosis [6]. If affecting the venous systems, splanchnic venous thrombosis is the most common manifestation [7]. At the same time, CVT is a relatively rare phenomenon [3-5,8-11]. While a few cases of CVT associated with both JAK2 positive and negative MPDs have been reported in the literature, most treatment focused on heparin and vitamin K antagonists. There have been none documented on the potential role of DOAC. We report a case of a young adult patient who had an extensive cerebral venous sinus thrombosis as a first manifestation of JAK2 positive polycythemia vera and excellent response to DOAC.

Case Presentation

A previously well, 20-year-old male presented with a 10-day history of headache along with right-sided neck pain, photophobia and diplopia. No infective or other systemic symptoms were reported. There was no history of any thrombophilia or stroke in the young in the family. His examination at the emergency department revealed normal vital signs, including normal higher cortical functions. There was evidence of mild left abducens nerve involvement, but no papilledema was noted. Motor, sensory, cerebellar and meningeal testing were normal. His gait was normal. The plantar response was flexor, bilaterally.

An initial cranial CT scan and angiography of the aortic arch to the vertex did not show any abnormality. His initial blood workup including full blood examination, coagulation profile, electrolytes, and inflammatory markers were normal. In particular, his hemoglobin was in the range of 159 g/L to 179 g/L while hematocrit was at 0.49 to 0.51. Platelets were within the normal range. Thrombophilia screen consisting of protein C, protein S, Factor V Leiden, prothrombin G20210A and antithrombin along with lupus antibody and anti-cardiolipin serology yielded negative results. Homocysteine levels were marginally elevated. Somatic mutation of the Janus Kinase 2 (JAK2) V617F using real-time PCR was detected. A full workup for malignancy was likewise non-contributory.

A brain MRI with magnetic resonance venography was performed and showed extensive

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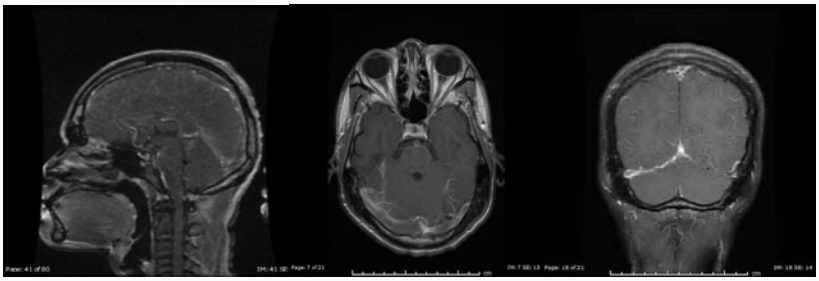

Figure 1: Sagittal, axial and coronal MRI with MRV images showing filling defects involving the uperior sagittal sinus, right jugular bulb, sigmoid and the transverse sinus.

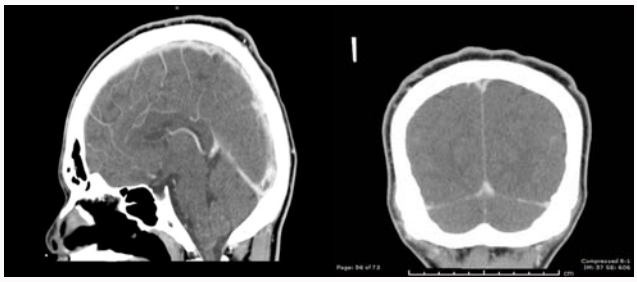

Figure 2: Sagittal and coronal CT venography images showing substantial resolution of the thrombosis leaving minimal residual at the superior aspect of the posterior sagittal sinus.

thrombosis involving the right sigmoid, right transverse, straight and superior sagittal sinus. An ultrasound of the neck likewise revealed thrombi involving the right and left internal jugular veins with lengths of 2 cm and 3.4 cm, respectively. No venous infarctions were noted. The patient was commenced on Enoxaparin for ten days and was subsequently transitioned to Dabigatran 150 mg two times a day. Acetazolamide was also started to relieve pressure-related symptoms. The patient was discharged with headache improvement and resolution of associated craniopathy. A repeat CT venography was done nine months after the diagnosis showed substantial resolution of the previous thrombosis leaving a minimal residual thrombus in the superior sagittal sinus. MRV and CTV images are shown in Figure 1 and 2, respectively.

Discussion

To date, this is the first reported case in the literature of a patient with extensive cerebral venous sinus thrombosis as a first manifestation of JAK2 positive myeloproliferative disorder with significant response clinically and radiologically after treatment with a DOAC.

In this patient, the presence of Polycythemia Vera (PV) is likely but not definite as he fulfils two (hemoglobin >165 g/L and presence of JAK2V617F mutation) of the three major criteria using the World Health Organization parameters [12]. The occurrence of CVT as the first manifestation of a JAK2 positive Myeloproliferative Disorder (MPD) is uncommon. In a retrospective cohort study of more than 150 patients with CVT, it has been reported that only ten patients had JAK2 mutation with approximately half having a normal full blood examination and only one associated with PV [3]. Another study involving 87 patients with CVT reported only one case of JAK2 mutation, which was not associated with PV but essential thrombocytopenia [11]. De Stefano et al. also identified four cases of CVT with MPD-associated- JAK2 mutation [9]. It is known that patients with MPD have a predisposition to arterial and venous thrombotic events with the latter commonly occurring in unusual locations such as in the splanchnic and the cerebral circulation [13]. The presence of JAK2V617F mutation in patients with CVT and without overt evidence of MPD also raises suspicion on whether this parameter itself is the causative aetiology for thrombosis [10,11]. Increased thrombotic risk for patients with normal full blood examination in the presence of JAK2 mutation have been hypothesized to be due to leukocyte activation aggregating with circulating platelets rather than the high blood counts [14].

Could the presence and burden of JAK2V617 phenotype be contributory to the increased thrombi burden in this patient? Godeneche et al. [5] described five cases of CVT, all associated with occlusion in more than two cerebral venous locations. Another study reported a case of CVT associated with JAK2 mutation and revealed thrombosis involving the superior sagittal, sigmoid and both transverse sinuses [15]. Mutreja et al. [16] also described the stormy course of an adult case with CVT of the superior sagittal sinus, torcula and bilateral cavernous sinuses who later on tested positive for JAK2 mutation. It has been proposed that the presence of this genetic mutation may be suggestive of a high thrombotic burden, but this was refuted by another study involving 22 Indian patients with CVT and JAK2 positivity with only one patient having multiple sites affected [5,8]. Whether the presence of this mutation is related to the severity of cerebral venous thrombus is still debatable. Apart from the presence of the mutation, the quantity of allele burden has also been studied to be related to increased Venous Thromboembolism (VTE) risk. Borowczyk et al. [17] demonstrated that when the JAK2 allele burden is higher than 25%, the risk of VTE increases 7.4 fold, and if higher than 50% 8.8 fold.

It is also interesting to note that despite the significant thrombotic burden in the index patient, the patient had minimal residual deficits. A similar case of a young adult with CVT involving the superior sagittal, transverse and sigmoid sinus also presented with minimal neurological manifestation [18]. Wang et al. conclude that pediatric patients with CVT usually present with non-specific clinical manifestations increasing misdiagnosis rates [19]. Whether the presentation at a young age or the early manifestation resulting in lesser cerebral damage is attributable to the benignity of the clinical manifestation remains speculative.

Another highlight of this study is the patient's favourable response to the Direct Oral Anticoagulant (DOAC), Dabigatran. Clinical guidelines recommend the use of the Vitamin K antagonist for patients with provoked and unprovoked CVT [20]. There is convincing evidence that DOACs such as Dabigatran, Apixaban and Rivaroxaban achieved successful recanalization in patients

with acquired CVT [20-24]. The RESPECT-CVT trial is the only randomized controlled trial to date that provides evidence on the use of a direct thrombin inhibitor in CVT [20]. Of the sixty patients in the Dabigatran arm, only five cases of genetic thrombophilia with no specific mention on the JAK2 mutation status was reported. No recurrent VTEs were seen in the treatment group and 60% achieved improvement in cerebral venous recanalization [20]. Other studies likewise focused on the success of DOACs on various acquired aetiologies [23,24].

This study stresses the role of Dabigatran, and potentially other DOACs as long-term anticoagulation for CVT associated with JAK2 mutation. Chen et al. [15] provided evidence on the use of Warfarin and concomitant antiplatelets in patients with JAK2 related ET and concomitant CVT. Other more extensive studies with similar clinical genotype do not provide specific information on long-term anticoagulation [3,8,25]. Given the presence of the mutation and lack of other known risk factors, anticoagulation may be indefinite. The role of DOACs in the prevention of this particular thrombophilia is likely explained by JAK2 induced thrombin up regulation and augmentation in factor Xa production as a result of the activation of the heparinase protein complex mainly affecting the erythropoietin receptor [26,27]. More studies are imperative to determine treatment response to DOACs among patients with VTEs related to genetic thrombophilia.

Apart from anticoagulation, secondary prophylaxis is imperative since the presence of thrombosis increases the risk for subsequent thrombosis. Follow up to determine development of overt MPD should be done. Among 19 patients with the JAK2 V617F mutation without overt MPD, only 4 developed overt MPD after thrombosis [9]. If MPD is confirmed, treatment of the underlying disease is most appropriate with cytoreductive therapy using hydroxyurea. The JAK2 inhibitor, ruxolitinib, while proven beneficial in reducing spleen size and constitutional symptoms, has not been confirmed to reduce the quantity of mutant allele burden [17].

Conclusion

This study highlights the significance of JAK2 mutation in the thrombogenesis associated with cerebral venous thrombosis and provides evidence on its potential role in increasing clot burden. We also highlight the potential role of direct anticoagulants in CVT associated with this clinical phenotype which is likely explained by JAK2 induced up regulation of thrombin and factor Xa as a result of alterations in the erythropoietin receptors. DOACs also provide a more convenient option for patients and is associated with lesser interactions, unlike VKA, the standard of care treatment.

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