



## Original Article

# Dural Venous Sinus Thrombosis and Papilledema Related to *JAK2* Mutation: A Case Series

Laura Donaldson<sup>1</sup> , Arjan S. Dhoot<sup>2</sup> and Edward Margolin<sup>1,3</sup> 

<sup>1</sup>Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada, <sup>2</sup>Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada and <sup>3</sup>Department of Medicine, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

**ABSTRACT: Background:** Dural venous sinus thrombosis (DVST) is an important cause of papilledema. Patients diagnosed with DVST should undergo work-up for underlying hypercoagulable state, including genetic causes. One important prothrombotic mutation is in the *JAK2* gene, which is a driver of myeloproliferative neoplasms including polycythemia vera (PV). We aimed to determine the prevalence of *JAK2* mutation in patients presenting to neuro-ophthalmology clinic with DVST and papilledema. **Methods:** Retrospective case series of patients seen in a tertiary neuro-ophthalmology practice who presented with papilledema due to DVST and were investigated for presence of *JAK2* mutation. **Results:** Four out of 15 patients with DVST (26%) were found to have *JAK2* V617F mutation which led to subsequent diagnosis of PV in 2. One additional patient had a known diagnosis of essential thrombocytosis. We describe the clinical presentation of these four patients with papilledema and *JAK2* mutation. **Conclusions:** A significant proportion of patients with papilledema secondary to DVST will harbor mutations in the *JAK2* gene. Clinicians should be aware of this mutation as early testing will facilitate timely diagnosis and treatment of myeloproliferative disease to improve prognosis and reduce risk of recurrent thrombotic events.

**RÉSUMÉ : Thrombose des sinus veineux durs, œdème papillaire et mutations du gène *JAK2* : une étude de série de cas. Contexte :** La thrombose des sinus veineux durs (TSVD) est une cause importante d'œdème papillaire. Les patients chez qui l'on a diagnostiqué une TSVD doivent par ailleurs subir un bilan pour dépister un état d'hypercoagulabilité sous-jacent, y compris pour des causes génétiques. On le sait, une importante mutation pro-thrombotique se trouve dans le gène *JAK2* et constitue une cause des néoplasmes myéloprolifératifs, par exemple la polyglobulie de Vaquez (PV). Nous avons donc cherché à déterminer la prévalence des mutations du gène *JAK2* chez des patients admis dans une clinique de neuro-ophthalmologie et atteints d'une TSVD et d'un œdème papillaire. **Méthodes :** Une série rétrospective de cas de patients vus dans une clinique de neuro-ophthalmologie tertiaire qui présentaient un œdème papillaire attribuable à une TSVD ; ces patients ont été examinés pour dépister la présence de mutations du gène *JAK2*. **Résultats :** Quatre des quinze patients atteints d'une TSVD (26 %) ont présenté des mutations du gène *JAK2* V617F, ce qui a conduit à un diagnostic ultérieur de PV chez deux d'entre eux. Soulignons qu'un autre patient avait déjà reçu un diagnostic de thrombocythémie essentielle. Nous avons donc décrit la situation clinique de ces quatre patients présentant un œdème papillaire et des mutations du gène *JAK2*. **Conclusions :** Une proportion significative de patients souffrant d'un œdème papillaire consécutif à une TSVD sera porteuse de mutations dans le gène *JAK2*. Les cliniciens doivent ainsi être conscients de ces mutations car un dépistage précoce facilitera le diagnostic et le traitement en temps utile de la maladie myéloproliférative, ce qui permettra d'améliorer le pronostic des patients et de réduire le risque d'événements thrombotiques récurrents.

**Keywords:** Dural venous sinus thrombosis; Papilledema; *JAK2* mutation; Polycythemia vera

(Received 5 September 2021; final revisions submitted 5 December 2021; date of acceptance 7 December 2021; First Published online 15 December 2021)

## Introduction

Papilledema is a common reason for referral to neuro-ophthalmology clinic and typically manifests with bilateral optic disc edema and normal or near-normal afferent visual function. Idiopathic intracranial hypertension (IIH) is the most common cause of papilledema in young women with elevated body mass index.<sup>1</sup> However, even patients fitting this typical demographic should undergo neuroimaging in the form of an MRI brain with venography (MRV). This helps to confirm the diagnosis of raised

intracranial pressure (ICP) through visualization of indirect neuroimaging signs of increased ICP. The most sensitive of these is stenosis of the dural venous sinuses, present in nearly all patients.<sup>2</sup> Venography also allows identification of critical nonidiopathic causes of elevated ICP such as dural venous sinus thrombosis (DVST).

DVST is an important cause of increased ICP and was identified in 11% of patients with the presumed initial diagnosis of IIH in one large series.<sup>3</sup> In addition to papilledema, DVST can present with a

**Corresponding author:** Edward Margolin, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON M5N 1E3, USA. Email: [Edward.Margolin@uhn.ca](mailto:Edward.Margolin@uhn.ca)

**Cite this article:** Donaldson L, Dhoot AS, and Margolin E. (2023) Dural Venous Sinus Thrombosis and Papilledema Related to *JAK2* Mutation: A Case Series. *The Canadian Journal of Neurological Sciences* 50: 194–200, <https://doi.org/10.1017/cjn.2021.512>

© The Author(s), 2021. Published by Cambridge University Press on behalf of Canadian Neurological Sciences Federation

**Table 1:** Cases of dural venous sinus thrombosis seen in neuro-ophthalmology clinic

Case	Relevant clinical history	JAK2 mutation	Other mutation
28 F	Fertility treatment, medroxyprogesterone, letrozole	Negative	
36 F	Essential thrombocytosis	Positive	
22 M		ND	Factor V Leiden
41 F	Trauma, subsequently had pulmonary embolism	ND	
55 M	Subsequently developed dural arteriovenous fistula	Negative	
72 F		Negative	
55 F	Dural sinus compression by meningioma	ND	
19 F	Behcet's	ND	
40 F		Positive	
66 F	Polycythemia vera, styloidogenic jugular compression	Positive	
64 M	Polycythemia vera, subsequently developed dural A-V fistula	Positive	
28 F	Pregnancy	Negative	
43 M		Negative	
48 M	Mild lymphocytosis, elevated Hb	Negative	
49 F	Crohn's disease, mildly elevated homocysteine	Negative	

ND = not done.

wide range of signs and symptoms, including headache, altered sensorium, and seizures.<sup>4</sup> It can be associated with high morbidity and even mortality due to associated cerebral edema and venous infarction thus all patients with DVST require a thorough work-up in order to identify risk factors predisposing them to thrombotic events.<sup>5,6</sup>

We reviewed all cases of patients with papilledema seen over 3 years who were found to have DVST and identified four patients amongst this group who were found to have Janus Kinase 2 (*JAK2*) V617F mutation on subsequent genetic testing. This mutation is well known as a cause of myeloproliferative neoplasms (MPN)<sup>7</sup> and in two out of four patients described here it was the presenting event leading to diagnosis of polycythemia vera (PV). These cases illustrate the importance of including *JAK2* mutation in the work-up for hereditary causes of hypercoagulability as it has implications for treatment, future thrombotic risk, and long-term prognosis.

## Methods

A retrospective chart review was performed of all patients seen in a single tertiary neuro-ophthalmology practice between July 2017 and July 2021 with papilledema who were found to have DVST on MRI of the brain with venography. Clinical charts, results of neuroimaging and results of hypercoagulability work-up were reviewed, including genetic testing for *JAK2* mutation. The study protocol was reviewed and approved by the Health Sciences Research Ethics Board at the University of Toronto.

## Results

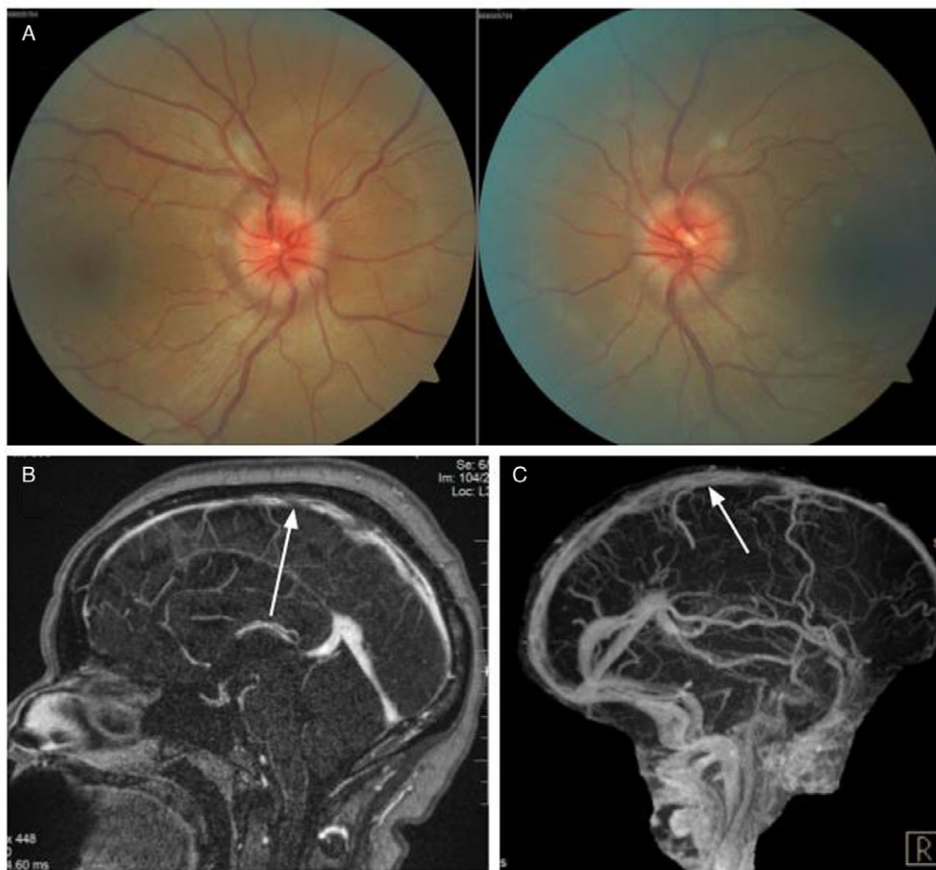
Fifteen patients with papilledema secondary to DVST were included in the study. Of these, 5 (33%) were male. The age of included patients ranged from 19 to 72. All underwent investigations for underlying prothrombotic factors and findings are presented in Table 1. One patient was positive for Factor V Leiden and 3 had systemic conditions that are linked to a

hypercoagulable state: pregnancy, Crohn's disease and Behcet's disease. In 1 case, a meningioma resulting in severe compression of the left transverse sinus was determined to be the cause of DVST. Four patients (27%) had positive *JAK2* V617F mutation on genetic testing. Only 2 out of 15 patients were deemed to have idiopathic DVST after extensive investigations.

### Case Descriptions of Patients with DVST Secondary to *JAK2* V617F

#### Case 1

A 40-year-old woman with a history of IIH diagnosed elsewhere 4 years ago presented with a 3-week history of binocular horizontal diplopia, intense headaches, pulsatile tinnitus, nausea, and vomiting. Visual acuity was 20/20 in each eye with no relative afferent pupillary defect (RAPD). She had normal ocular motility with a small esophoria at distance. Dilated fundus exam (DFE) revealed severe bilateral optic nerve edema (Figure 1A), which was corroborated on optical coherence tomography (OCT) of the peripapillary retinal nerve fiber layer (RNFL). 24-2 Humphrey visual field testing was normal in both eyes. MRI and MRV of the brain revealed a thin, nonocclusive linear filling defect in the superior sagittal sinus (Figure 1C, D). Her previous imaging from 4 years earlier was reviewed and no thrombosis was present at this time. A standardized hypercoagulability work-up was undertaken which included peripheral blood assays for antithrombin III, prothrombin mutation, Protein C and S, Factor V Leiden, homocysteine, antiphospholipid, and anticardiolipin antibodies, *JAK2*, and *CALR* (calreticulin) mutation. She was found to be positive for the *JAK2* V617F mutation. There was no evidence of PV and while she had a history of previously treated anemia, her hemoglobin was within normal limits at 133 g/L. She was started on preventative anticoagulation therapy with warfarin and remained well with no evidence of MPN.



**Figure 1:** Case 1. (A) Papilledema on fundus examination. (B) MRI and MR venogram (C) showing a nonocclusive thin, linear filling defect in the superior sagittal sinus (white arrows).

### Case 2

A 64-year-old man was seen for incidentally discovered bilateral optic disc edema which was not present on his annual optometry screening examination a year ago. A noncontrast computed tomography (CT) head in the emergency room followed by an MRI of the brain were interpreted as unremarkable. He did not have headaches, diplopia, pulsatile tinnitus, or transient visual obstructions. His vision was 20/20 in each eye without an RAPD. DFE revealed severely edematous optic nerves bilaterally (Figure 2A). 24–2 Humphrey visual fields were normal and OCT of the peripapillary RNFL confirmed severe elevation of the optic nerve head in each eye.

An urgent MRV of the brain revealed extensive thrombosis of the posterior superior sagittal sinus and left transverse sinus (Figure 2B). Numerous serpiginous flow voids along the left transverse sinus and a prominent occipital vessel were suspicious for dural arteriovenous fistula (dAVF). Left occipital-transverse sinus dAVF was confirmed on MR angiography and subsequent digital subtraction angiography (Figure 2C). His hypercoagulability work-up revealed a borderline high hemoglobin (170 g/L) with elevated hematocrit (0.51) and positive *JAK2* V617F mutation. Bone marrow biopsy was performed and demonstrated cellular marrow with trilineage hematopoiesis, consistent with the diagnosis of PV. His dAVF was successfully embolized, and he was started on anticoagulation therapy with rivaroxaban. Papilledema improved and he was maintained on cytoreductive treatment with hydroxyurea and repeat phlebotomies.

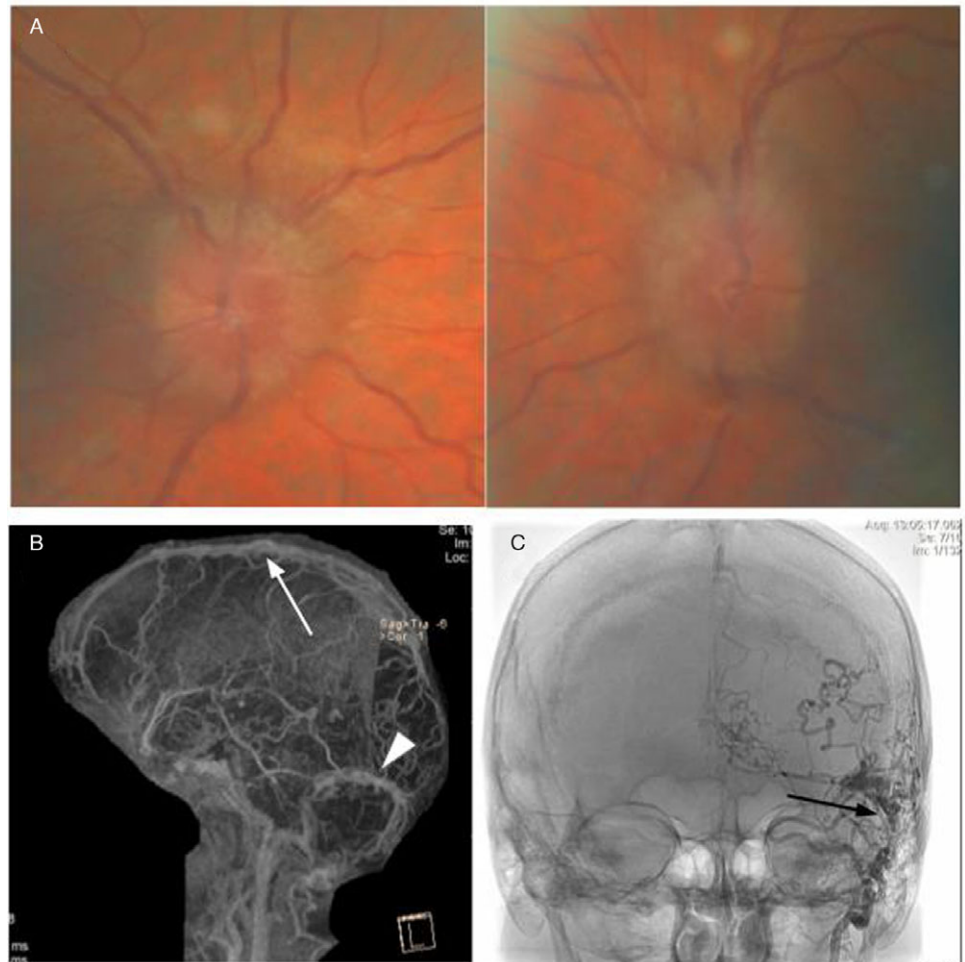
### Case 3

A 66-year-old woman noticed blurry vision in each eye, headache, and pulsatile tinnitus. After multiple visits to an emergency

department where she was repeatedly diagnosed with migranous headache, she was referred to an ophthalmologist who noticed bilateral optic disc edema (Figure 3A). CT of the head with CT venography was performed and revealed right transverse and sigmoid sinus thrombosis extending to the internal jugular vein as well as short segment nonocclusive thrombosis of the left distal sigmoid sinus. When assessed in our clinic, vision was 20/25 in each eye with no RAPD. DFE demonstrated bilateral severe optic disc edema with peripapillary choroidal folds. 24–2 Humphrey visual fields demonstrated enlarged blind spot in the right eye and non-specific changes in the left eye. MRV revealed complete opacification of the right transverse and sigmoid sinus extending through the jugular foramen just below the skull base within the internal jugular vein (Figure 3B, C), with venous stenosis confirmed on angiography (Figure 3D, E). A hypercoagulability work-up was positive for the *JAK2* V617F mutation. She also had elevated hematocrit (0.52) and hemoglobin of 168 g/L. Bone marrow biopsy showed atypical megakaryocytes and loose clusters, hypercellularity, and panmyelosis with minimal fibrosis interpreted as consistent with the diagnosis of PV. She was treated with acetylsalicylic acid and started on anticoagulation with apixaban and repeat phlebotomies but declined treatment with hydroxyurea. Clinically, she remained stable with no further thrombotic events.

### Case 4

A 36-year-old woman presented with a 1-year history of increasing headaches and recent onset of blurry vision in each eye. She had been diagnosed with essential thrombocythemia 11 years earlier after incidentally noted elevated platelet counts. Therapy with 81 mg of daily aspirin was recommended by a hematologist; however,



**Figure 2:** Case 2. (A) Papilledema on fundus examination. (B) MR venogram showing large thrombotic segments of the posterior superior sagittal sinus (white arrow) and left transverse dural venous sinus (white arrowhead). (C) Digital subtraction angiography revealed a left occipital transverse sinus dural arteriovenous fistula (black arrow).

she did not adhere to treatment. Her optometrist noted bilateral optic disc edema and referred her to an ophthalmologist, who ordered a CT of the brain with contrast. While awaiting this appointment, she developed nausea and vomiting and went to an emergency department where a noncontrast CT head was normal. Her vision was 20/20 in each eye without an RAPD. DFE revealed severe optic nerve head edema. 24–2 Humphrey visual fields were normal in each eye. Urgent MRI of the brain with venography demonstrated extensive right-sided DVST (Figure 4). Genetic testing was positive for *JAK2* V617F mutation. Treatment with warfarin resulted in complete resolution of optic nerve head edema after 2 months.

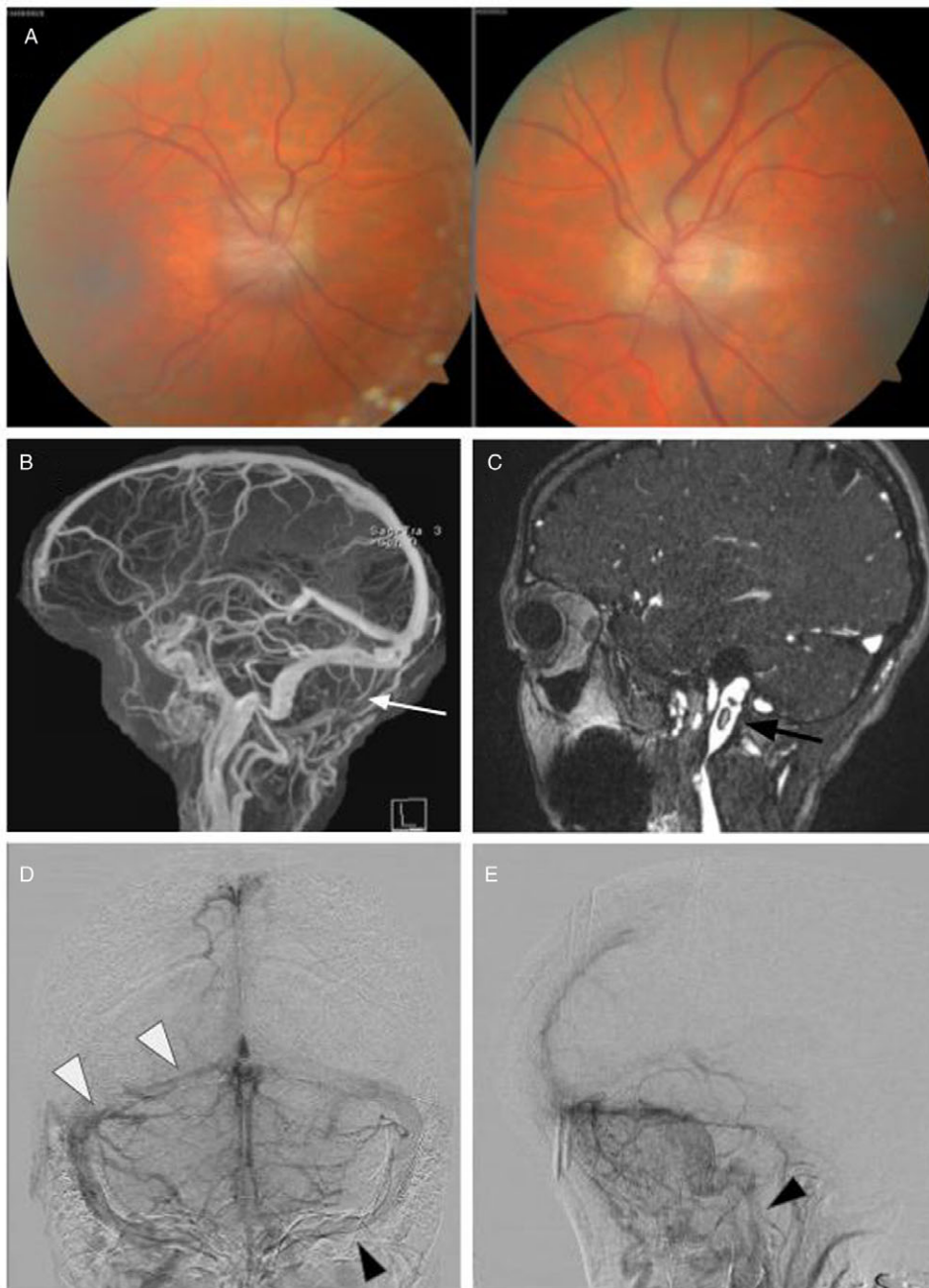
## Discussion

DVST produces papilledema in the majority of symptomatic cases. In addition to symptoms of increased ICP, patients may present with focal neurologic signs, seizures, or altered level of consciousness. DVST should be suspected in all patients with papilledema as it can present in a very similar manner to IIH as was seen in Case 1.<sup>3,8</sup> All cases of DVST should be investigated for an underlying hypercoagulable state, which is likely to be present in most patients. We found that only 2 out of 15 patients in our series (13%) had no identifiable prothrombotic factors. Increased risk for DVST can be seen with any systemic cause of hypercoagulable state such as pregnancy, hyperhomocysteinemia, antiphospholipid antibodies, myeloproliferative disorders, or other malignancy.<sup>9</sup>

There were two patients with DVST in our study who had an underlying systemic inflammatory condition: 1 had a history of Behcet's disease and 1 had known inflammatory bowel disease, with DVST having been previously reported as a rare complication of both.<sup>10,11</sup> The mechanism of DVST in Behcet's disease is thought to relate to vasculitis involving dural veins causing phlebitis, while in Crohn's disease indirect effects on platelets and fibrinolysis are hypothesized to be the causative prothrombotic factors.<sup>12</sup>

In the absence of an identifiable prothrombotic cause, genetic predisposition to thrombotic events should be explored. Hereditary causes have been reported in up to 41% of patients with DVST and include Protein C and S deficiency, antithrombin III deficiency, prothrombin mutation, and Factor V Leiden.<sup>13,14</sup> The importance of *JAK2* mutation as a cause of DVST has only been recognized recently thus we wanted to investigate its prevalence in our cohort of patients with papilledema who were discovered to have DVST and found that it accounted for a full quarter of all DVST cases. While one of the patients with *JAK2* V617F mutation had a known diagnosis of MPN, in two patients detection of this mutation led to the diagnosis of MPN.

The *JAK2* substitution mutation of phenylalanine (F) for valine (V) at the 617 position was first described in 2005 as a driver mutation in MPN.<sup>7</sup> *JAK2* V617F mutations and PV are important contributors to venous thrombosis throughout the body, including portal vein thrombosis, deep vein thrombosis, and DVST.<sup>15,16</sup> In reported series of patients with DVST, this mutation is found in 6.6%–11% of cases and 60% of these had a myeloproliferative



**Figure 3:** Case 3. (A) Papilledema on fundus examination. (B, C) MRI with venography revealed complete lack of opacification of the right transverse and sigmoid sinus (B, white arrow) extending through the jugular foramen with multiple visible thrombi including within the left jugular vein (C, black arrow). A-P (D) and lateral (E) digital subtraction angiography images showing stenosis of the right transverse and sigmoid sinuses (D, white arrowhead) and the left jugular bulb (D, E, black arrowhead).

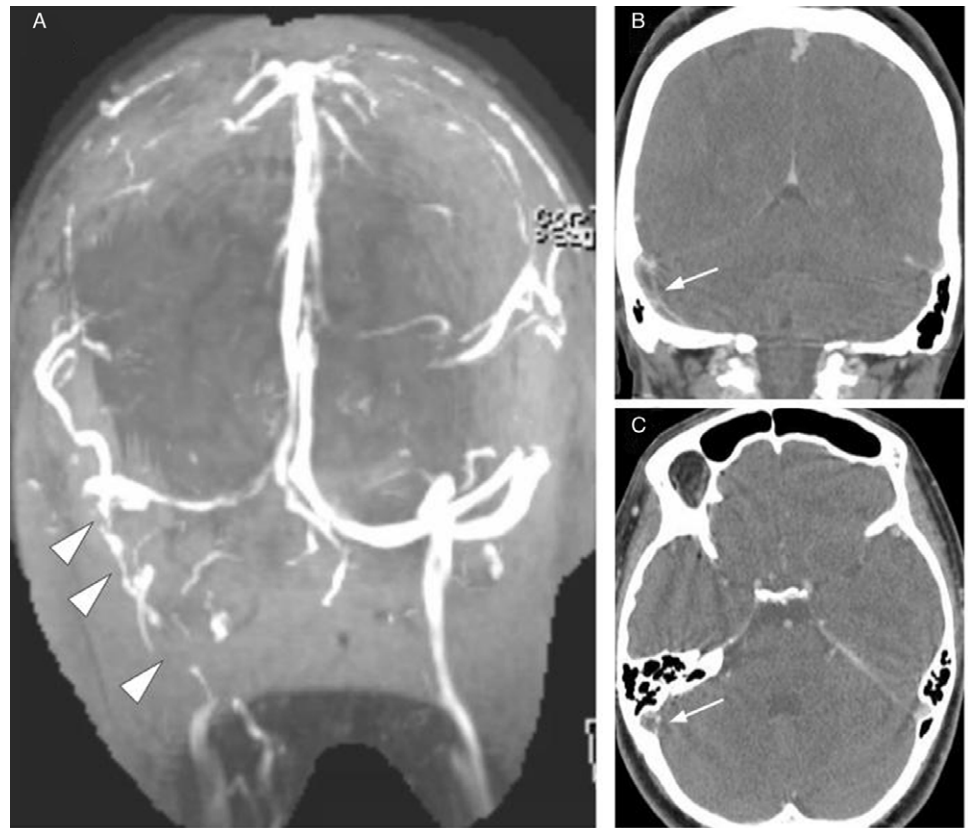
disorder.<sup>15,17</sup> When only patients without myeloproliferative disorder were studied, *JAK2* V617F was present in around 3%–6% of DVST cases; these patients tended to be older and have higher, though still normal, hemoglobin and platelet counts.<sup>16,18,19</sup> Importantly, a higher risk of recurrent thrombosis has been identified in patients with *JAK2* V617F mutation, regardless of the presence of overt myeloproliferative disorder.<sup>19,20</sup>

In our series, the prevalence of *JAK2* V617F was 26%, which is higher than previously reported, however our sample size is quite small. Our study also included only a subset of all cases of DVST, specifically ambulatory patients with papilledema and though it is unclear why this mutation could be more common in these cases, we speculate that thrombosis in these patients could be more chronic or low grade. Papilledema takes time to develop, and onset is often observed well after the

diagnosis of DVST.<sup>21</sup> Patients with acute, severe thrombosis would be more likely to present with seizure, altered level of consciousness, and other neurologic symptoms and thus would not be included in our cohort.

DVST is treated with anticoagulation, which may be in the form of heparin, vitamin K antagonists, or novel oral anticoagulants. If there is incomplete recanalization of the thrombus, fibrinolytic agents, mechanical thrombolysis, or thrombectomy may be required.<sup>22,23</sup> There is no clear consensus as to the optimal duration of anticoagulation in DVST, with or without *JAK2* V617F.<sup>24</sup>

In DVST with *JAK2* V617F mutation and no identified MPN, CBC must be monitored on a regular basis. Patients with PV and venous thrombotic events require anticoagulation in addition to specific therapy for their myeloproliferative disease, the mainstay of which consists of cytoreductive therapy with phlebotomy and



**Figure 4:** Case 4. (A) MRI brain with time-of-flight venography showed signal loss in the right sigmoid sinus extending into the jugular vein (white arrowheads). CT venogram coronal (B) and axial (C) confirmed extensive filling defects within transverse and sigmoid sinuses, extending to the jugular vein (white arrows).

antineoplastic agents such as hydroxyurea.<sup>25,26</sup> Timely administration of hydroxyurea in patients with PV can reduce the number of thrombotic events and greatly increases median survival time in symptomatic disease.<sup>27,28</sup>

## Conclusion

DVST is an important secondary cause of papilledema seen in the ophthalmology clinic. We propose that genetic testing including *JAK2* mutation analysis should be performed in all patients with DVST with an abnormal CBC, absence of risk factors for thrombosis or when hypercoagulable work-up is unrevealing. Testing for this allele is readily available in tertiary centers as it is widely performed in the evaluation of myeloproliferative disorders. Ophthalmologists should be aware of the *JAK2* V617F mutation due to this increased risk of myeloproliferative disease and risk of recurrent thrombosis and these patients should be comanaged with hematologists. Early diagnosis and treatment in these patients can dramatically improve outcomes.

**Conflicts of Interest.** The authors have no conflict of interest to report.

**Statement of Authorship.** LD and EM designed the study, LD and AD collected data and wrote the manuscript, EM revised the manuscript for intellectual content, all authors approved the final draft.

## References

1. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE. Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. *J Neurol Sci.* 1993;116:18–28. doi: [10.1016/0022-510X\(93\)90084-C](https://doi.org/10.1016/0022-510X(93)90084-C)
2. Bidot S, Saindane AM, Peragallo JH, Bruce BB, Newman NJ, Biousse V. Brain imaging in idiopathic intracranial hypertension. *J Neuro-Ophthalmol.* 2015;35:400–11. doi: [10.1097/WNO.0000000000000303](https://doi.org/10.1097/WNO.0000000000000303)
3. Agarwal P, Kumar M, Arora V. Clinical profile of cerebral venous sinus thrombosis and the role of imaging in its diagnosis in patients with presumed idiopathic intracranial hypertension. *Indian J Ophthalmol.* 2010;58:153–55. doi: [10.4103/0301-4738.60092](https://doi.org/10.4103/0301-4738.60092)
4. Ferro JM, Correia M, Pontes C, Baptista MV, Pita F. Cerebral vein and dural sinus thrombosis in Portugal: 1980–1998. *Cerebrovasc Dis.* 2001;11:177–82. doi: [10.1159/000047635](https://doi.org/10.1159/000047635)
5. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. *Lancet Neurol.* 2007;6:162–70. doi: [10.1016/S1474-4422\(07\)70029-7](https://doi.org/10.1016/S1474-4422(07)70029-7)
6. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med.* 2005;352:1791–98.
7. James C, Ugo V, le Couédic JP, et al. A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera. *Nature.* 2005;434:1144–48. doi: [10.1038/nature03546](https://doi.org/10.1038/nature03546)
8. Eliseeva N, Serova N, Yakovlev S, Mikeladze K, Arkhangel'skaya Y, Gasparyan S. Neuro-ophthalmological features of cerebral venous sinus thrombosis. *Neuro-Ophthalmol.* 2015;39:69–76. doi: [10.3109/01658107.2014.953697](https://doi.org/10.3109/01658107.2014.953697)
9. Green M, Styles T, Russell T, et al. Non-genetic and genetic risk factors for adult cerebral venous thrombosis. *Thromb Res.* 2018;169:15–22. doi: [10.1016/j.thromres.2018.07.005](https://doi.org/10.1016/j.thromres.2018.07.005)
10. Uluduz D, Midi I, Duman T, et al. Behçet's disease as a causative factor of cerebral venous sinus thrombosis: subgroup analysis of data from the VENOST study. *Rheumatology (United Kingdom).* 2019;58:600–8. doi: [10.1093/rheumatology/key153](https://doi.org/10.1093/rheumatology/key153)
11. Cognat E, Crassard I, Denier C, Vahedi K, Bousser MG. Cerebral venous thrombosis in inflammatory bowel diseases: eight cases and literature review. *Int J Stroke.* 2011;6:487–92. doi: [10.1111/j.1747-4949.2011.00620.x](https://doi.org/10.1111/j.1747-4949.2011.00620.x)

12. Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammation and coagulation in inflammatory bowel disease: the clot thickens - CME. *Am J Gastroenterol.* 2007;102:174–86. doi: [10.1111/j.1572-0241.2006.00943.x](https://doi.org/10.1111/j.1572-0241.2006.00943.x)
13. Silvis SM, Middeldorp S, Zuurbier SM, Cannegieter SC, Coutinho JM. Risk factors for cerebral venous thrombosis. *Semin Thromb Hemost.* 2016;42:622–31. doi: [10.1055/s-0036-1584132](https://doi.org/10.1055/s-0036-1584132)
14. Komro J, Findakly D. Cerebral venous sinus thrombosis in adults with prothrombotic conditions: a systematic review and a case from our institution. *Cureus.* 2020;12:e7654. doi: [10.7759/cureus.7654](https://doi.org/10.7759/cureus.7654)
15. de Stefano V, Fiorini A, Rossi E, et al. Incidence of the *JAK2* V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. *J Thromb Haemost.* 2007;5:708–14. doi: [10.1111/j.1538-7836.2007.02424.x](https://doi.org/10.1111/j.1538-7836.2007.02424.x)
16. Shetty S, Kulkarni B, Pai N, Mukundan P, Kasatkar P, Ghosh K. *JAK2* mutations across a spectrum of venous thrombosis cases. *Am J Clin Pathol.* 2010;134:82–85. doi: [10.1309/AJCP7VO4HAIZYATP](https://doi.org/10.1309/AJCP7VO4HAIZYATP)
17. Passamonti SM, Biguzzi E, Cazzola M, et al. The *JAK2* V617F mutation in patients with cerebral venous thrombosis. *J Thromb Haemost.* 2012;10:998–1003. doi: [10.1111/j.1538-7836.2012.04719.x](https://doi.org/10.1111/j.1538-7836.2012.04719.x)
18. Mahe E, Pedersen KM, Çolak Y, et al. *JAK2*-tree: a simple CBC-based decision rule to guide appropriate *JAK2* V617F mutation testing. *J Clin Pathol.* 2019;72:172–76. doi: [10.1136/jclinpath-2018-205527](https://doi.org/10.1136/jclinpath-2018-205527)
19. Lamy M, Palazzo P, Agius P, et al. Should we screen for Janus Kinase 2 V617F mutation in cerebral venous thrombosis? *Cerebrovasc Dis.* 2017;44:97–104. doi: [10.1159/000471891](https://doi.org/10.1159/000471891)
20. Martinelli I, de Stefano V, Carobbio A, et al. Cerebral vein thrombosis in patients with Philadelphia-negative myeloproliferative neoplasms. An European Leukemia Net study. *Am J Hematol.* 2014;89:E200–5. doi: [10.1002/ajh.23809](https://doi.org/10.1002/ajh.23809)
21. Liu KC, Bhatti MT, John J Chen JJ et al. Presentation and progression of papilledema in cerebral venous sinus thrombosis. *Am J Ophthalmol.* 2020;213:1–8. doi: [10.1016/j.ajo.2019.12.022](https://doi.org/10.1016/j.ajo.2019.12.022).
22. Bose G, Graveline J, Yogendrakumar V, Fergusson D, Dowlatsahi D. Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review protocol. *Syst Rev.* 2019;8:99. doi: [10.1186/s13643-019-1022-8](https://doi.org/10.1186/s13643-019-1022-8)
23. Saposnik G, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42:1158–92. doi: [10.1161/STR.0b013e31820a8364](https://doi.org/10.1161/STR.0b013e31820a8364)
24. Ferro JM, Bousser MG, Canhão P et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. *Eur J Neurol.* 2017; 24:1203–13.
25. de Stefano V, Za T, Rossi E, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica.* 2008;93:372–80. doi: [10.3324/haematol.12053](https://doi.org/10.3324/haematol.12053)
26. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med.* 2013;368:22–33. doi: [10.1056/nejmoa1208500](https://doi.org/10.1056/nejmoa1208500)
27. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood.* 2014;124:2507–13. doi: [10.1182/blood-2014-05-579136](https://doi.org/10.1182/blood-2014-05-579136)
28. Chievitz E, Thiede T. Complications and causes of death in polycythaemia vera. *Acta Med Scand.* 1962;172:513–23. doi: [10.1111/j.0954-6820.1962.tb07186.x](https://doi.org/10.1111/j.0954-6820.1962.tb07186.x)