Vision loss secondary to cerebral venous sinus thrombosis as the first presenting symptom of a JAK2 positive myeloproliferative neoplasm

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Myeloproliferative neoplasms (MPNs) are a group of acquired haematopoetic stem cell disorders that include essential thrombocytosis (ET), polycythaemia vera (PCV) and primary myelofibrosis (PMF). The majority of patients with MPNs share a mutation in *JAK2* that affects haematopoetic signal-transduction pathways (95–98% of patients with PCV and 50–60% of those with ET/PMF), resulting in haematologic disruption that increases thrombotic risk across all organ systems, including the central nervous system and the eye.[3]

Vision loss due to MPN is uncommon but may occur in the setting of cerebral venous sinus thrombosis (CVST) secondary to severe papilloedema. Less than 1% of patients with known MPN develop CVST, and fewer still present with vision-threatening papilloedema as a consequence.[4–6] We report a case of progressive bilateral vision loss secondary to CVST as the initial presentation of an underlying *JAK2*-associated MPN.

Case report

A 56-year-old man presented to the acute ophthalmology clinic with a 3-month history of progressive generalised visual blurring in both eyes and an associated generalised dull headache for 2 months. He denied any diplopia, transient loss of vision, nausea or focal neurological symptoms. His past ocular and medical history were unremarkable other than previous appendicectomy 6 years prior. There was no known personal or family history of thrombophilia.

Visual acuity at presentation was 6/60 on the right and 6/120 on the left, improving with pinhole to 6/24 and 6/30 respectively. Intraocular pressures were normal and there was a full range of eye movements with no relative afferent pupillary defect noted. The patient was unable to read any numbers on Ishihara testing in either eye. Slit lamp examination demonstrated bilaterally swollen optic nerves consistent with papilloedema (Figure 1). Formal visual field testing showed gross visual field defects in both eyes. The patient was also noted to be hypertensive at 145/89mmHg.

An urgent computed tomography (CT) head and CT venogram (CTV) were arranged but did not reveal any obvious pathology to account for the patient's symptoms. Following consultation with neurology a lumbar puncture (LP) was performed, showing a cerebrospinal fluid (CSF) opening pressure of 46cm of water (reference range: 6–25cm H_2O) and resulting in a provisional diagnosis of idiopathic intracranial hypertension (IIH). The patient was started on oral acetazolamide 500mg three times daily.

Review of the medical records subsequently revealed that the patient had a documented raised haemoglobin between 175–185g/L (reference range: 130–175g/L) for 2 years prior to presentation. This was associated with thrombocytosis ranging from 455–525 x 109/L (reference range: 150–400 x 109/L) over the same 2-year period, and a raised haematocrit (>0.54) for the last 12 months. Given the patient's high haemoglobin, thrombocytosis and newly diagnosed CVST, haematology input was sought. A subsequent diagnosis of MPN with a phenotype of polycythaemia was made, with confirmatory genetic testing revealing a mutation in *JAK2* (pVal617Phe genetic variant).

Due to the fundus appearance and aforementioned laboratory findings, a magnetic resonance venogram (MRV) was obtained, revealing thrombosis of the left transverse and sigmoid sinuses (Figure 2). The patient was anticoagulated using subcutaneous 1mg/kg low molecular weight heparin (Enoxaparin sodium) twice daily and continued on acetazolamide 500mg three times daily for intracranial hypertension. Serial LPs were performed on days 3, 10 and 12 of admission and revealed persistently raised opening pressures

Figure 1: Pseudo-colour images of the left and right optic discs (right and left respectively). A/B—appearance of discs at presentation. C/D—appearance of discs after ventriculo-peritoneal (VP) shunt placement.

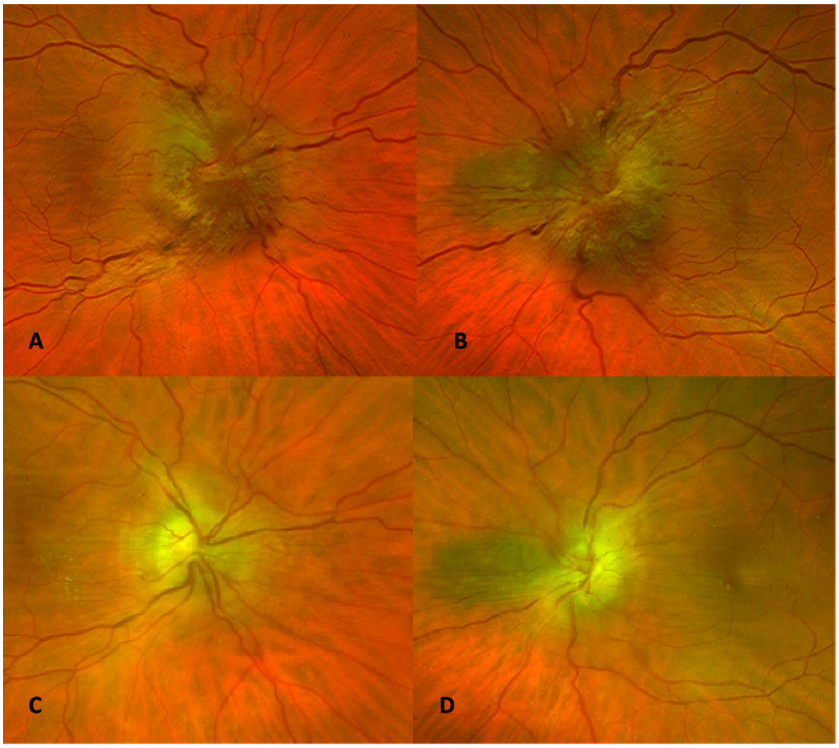
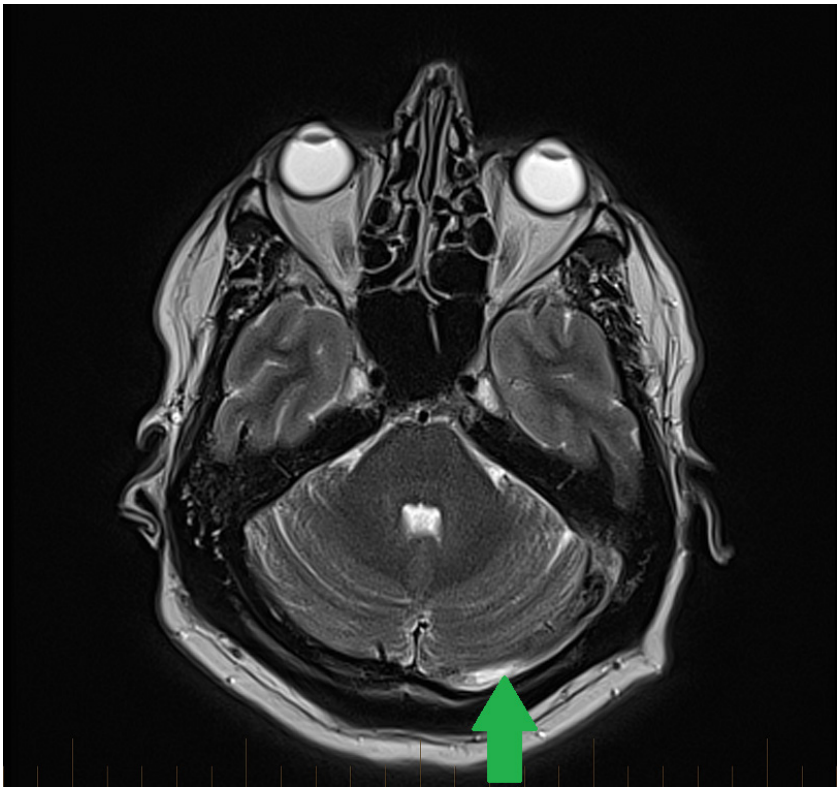


Figure 2: T2-weighted magnetic resonance venogram (MRV) of the brain with Gadolinium contrast demonstrating thrombus in the left transverse sinus, denoted by the green arrow.



above 25cm of water (26cm, 33cm and 29cm respectively). Due to concern regarding persistently raised intracranial pressure (ICP) despite serial therapeutic LPs, the patient was referred for neurosurgical intervention and a ventriculo-peritoneal shunt (VP shunt) was placed. This resulted in gradual resolution of the patient's papilloedema over the course of 3 months, with development of optic disc pallor noted post-operatively (Figure 1).

Gradual clinical improvement was noted following VP shunting, with vision improving to 6/9.5 and 6/7.5 on the right and left respectively, and visual fields improving to above the minimum driving standard by 12 months post-operatively. Colour vision did not recover, indicating chronic optic neuropathy. Initial venesection combined with Hydroxycarbamide was effective in reducing the patient's haematocrit, however he subsequently developed pyrexia (>39.0°) secondary to this medication and it was consequently ceased. He then developed thrombocytosis despite good control of his haematocrit, and therefore he commenced intermittent pulsed oral Busulphan at an initial dose of 4mg per day tapered over 8 weeks (maintaining a platelet count <400 x 109/L) after counselling for leukaemia risk associated with the medication. He remains anticoagulated on Dabigatran 150mg twice daily and has monthly venesection alongside regular haematology follow-up to ensure his thrombotic risk remains well managed, and he does not presently require ongoing cytoreductive treatment.

Discussion

MPNs are a group of haematopoetic stem cell disorders including polycythaemia vera, essential thrombocythaemia and primary myelofibrosis. Approximately 60% of cases are associated with a mutation in the *JAK2* gene.[7] These haematopoetic disorders confer increased thrombotic risk and may result in vision-threatening CVST. Prior research has shown that MPN is present in approximately 3.8% of patients with CVST, and a mutation in *JAK2* is present in 6.6% of cases of CVST without a known MPN at presentation.[1]

CVST may present with non-specific neurological and ocular symptoms, including headache (present in 88% of cases), visual disturbances (present in 78%), nausea, vomiting and seizure activity.[1,8,9] Papilloedema is a frequent finding at presentation (present in 30–50% of patients) and may result in permanent visual loss.[10,11] In a series of 131 patients presenting with papilloedema and clinical suspicion for IIH, 10% had previously undiagnosed CVST on subsequent MRI—this diagnostic overlap highlights the importance of excluding CVST in patients presenting with symptoms of raised ICP.[12]

For cases of CVST in the context of MPN, raised ICP usually occurs as a result of occlusion of the superior sagittal sinus and typically results in bilateral symmetric papilloedema.[2] Up to 20% of patients experience progressive papilloedema despite treatment, and 40% of patients have resultant permanent visual field loss. Longstanding optic neuropathy due to papilloedema may occur and can permanently affect colour vision (as was the case with our patient). VP shunting in the setting of CVST occurs in less than 10% of patients.[10]

As demonstrated by our case, non-contrast CT scanning alone may not be sufficiently sensitive to make a definitive diagnosis of CVST. Non-contrast CT is a rapid and easily accessible initial imaging choice; however, it has been shown to be normal in up to two-thirds of patients with CVST at presentation. This is thought to be due to heterogenous radiographic appearances of thrombus depending on time of presentation, which may result in subacute or chronic cases being missed, particularly in subacute cases where density of the thrombus is similar to that of the surrounding brain parenchyma and vasculature.[13] In the current case, isodensity of the thrombus on both CT and CTV due to this phenomenon was the likely cause for the diagnosis initially being missed. Current literature suggests that MRV has a high sensitivity and negative predictive value irrespective of acuity of presentation (93% and 91% respectively); however, T2-weighted MRI sequences may be more specific, with a superior positive predictive value (95% and 93% respectively).[14–16] Furthermore, MRI is more useful than CT in discriminating features of IIH (e.g., posterior globe flattening, optic nerve tortuosity and emptiness of the sella turcica), making combined MRV/MRI the imaging modality of choice in suspected CVST.[17]

Multi-specialty input was vital for this patient, with involvement of ophthalmology, neurology, neurosurgery and haematology at different stages along the patient journey—a reflection of the multisystem impact of *JAK2*-associated myeloproliferative neoplasm. CVST is a rare cerebrovascular disease that makes up only 1–2% of all cases of stroke and frequently suffers from diagnostic delay (a mean 7 days from time of presentation

to diagnosis).[9,11] Exclusion of CVST is essential in cases of suspected IIH due to their similar presenting features, and therefore a blood count should be performed in the setting of vision loss due to papilloedema, irrespective of the presence of a headache. If polycythaemia or thrombocytosis is present, genetic testing for a mutation in *JAK2* should be strongly considered.[10,18]

COMPETING INTERESTS
Nil.

ACKNOWLEDGEMENTS
We would like to gratefully acknowledge the patient for providing written consent for publication of anonymised medical information in this manuscript.

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URL
https://nzmj.org.nz/journal/vol-137-no-1605/vision-loss-secondary-to-cerebral-venous-sinus-thrombosis-as-the-first-presenting-symptom-of-a-jak2-positive-myeloproliferative-

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