Case Presentation: Cerebral Venous Sinus Thrombosis in a patient with *JAK2* V617F Mutation Myeloproliferative Neoplasm

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Background: Cerebral venous sinus thrombosis (CVST, aka sinovenous thrombosis) is a rare neurovascular disorder affecting 5 in 1,000,000 per year (Capecchi, 2018) and about 1% of all strokes (Heiber et al. 2020). It arises as a result of thrombus formation in the dural venous sinus of the brain, impairing drainage, increasing pressure and potentially causing micro-haemorrhages from cell damage and subsequent leakage into cerebral tissue. The clinical presentation and course of CVST is highly variable (Devasagayam, 2016), thus often presenting a diagnostic conundrum. Not uncommonly, multiple sinuses are affected, and this has been correlated to the extent of parenchymal involvement (Zubkov et al., 2009) and severity of clinical signs and symptoms. Several risk factors have been identified, including haematological disorders such as JAK 2 positive myeloproliferative neoplasms.

Case presentation: A 35-year-old Caucasian man was admitted with a 5-day history of fronto-temporal headache, followed by episodic disorientation, vomiting and visual disturbances. He had presented to the emergency department 4 days earlier but discharged following a normal CT brain. A few months earlier, he had presented with unexplained thrombocytosis and basophilia, an 'ear infection' and flu-like symptoms which affected his sinuses and resulted in residual occipito-frontal headaches. **Past Medical History:** perianal abscess, nil else. **On examination**, he had no photophobia or rash, temp: 37.0), BP 154/62mmHg, other vital signs normal. He was delirious with a Glasgow Coma Score of 14/15. Erythema of the left external auditory canal and brisk patellar reflexes were present. Coordination and cranial nerves assessment was limited due to confusion, but impaired hand coordination reported. **Investigations:** Haemoglobin: 149g/L, **WCC 18.3 x10^9** , **Neutrophils 16.6x 10^9**, **Platelets 611 x 10^9**, INR 1.3, normal B12, autoimmune screen, renal and thyroid function; CRP: 20. Viral screens: negative. ***JAK2 V617F detected*** *percentage mutant: 21.54%.* Folate: 2.9 ng/mL. LDH: 442 IU/L. Fundoscopy and visual fields; normal. **ECG: sinus arrythmia**. Chest X-ray: unremarkable. CT Venogram revealed **a filling defect within the sagittal, left transverse and straight sinuses** consistent with cerebral venous sinus thrombosis CVST). This was further elucidated on MRI; also signal abnormalities within the deep white matter bilaterally, predominantly parieto-occipitally, with some high T2 signal changes on diffusion weighted imaging, **suggesting infarction.**

Management: Initial management plan included commencement of antimicrobials for possible meningitis with a plan to perform a lumbar puncture. Plan updated on detection of *JAK2 V617F somatic mutant with the* haematologist: Urgent **cytoreductive therapy** with hydroxycarbamide 1g daily (lifelong); **lifelong anticoagulation with Warfarin** to commence after 2 weeks of bridging with low molecular weight heparin. Simple analgesia initially and then Amitriptyline commenced for migraine prophylaxis. Gabapentin was also prescribed but for short term therapy. LP was no longer required to relieve pressure as headache improved. Antimicrobials were reviewed to treat otitis media.

The patient was transferred to the stroke unit where therapy needs were assed. There were no speech, language, or swallowing needs. He had a MoCA score of 25/30, with good executive function but lost 2 points for memory. No baseline cognitive or functional deficits. A slight change in personality (increased swearing) was reported. He was discharged home with outpatient haematology follow up.

Discussion: This case is a reminder that certain non-thunderclap headache syndromes are associated with significant morbidity and potential mortality**.** A wider consideration of differential diagnoses based on risk factors is important (see table below). CVST can be the first symptom of a myeloproliferative neoplasm (MPN, these include myelofibrosis, polycythaemia vera and essential thrombocythemia) and patients may carry the *Janus kinase 2* (JAK2 V617F) mutation, regardless of cell count (Passamonti et al. 2012), necessitating screening for proper management. MPNs predisposes to recurrent infections and thrombocytosis, features present in this case. The importance of not ignoring unexplained cell counts is also highlighted. Although uncommon, CVST is serious enough to be considered when faced with headache and confusion, with or without other symptoms of raised intra cranial pressure. The incidence of CVST is increasing; more so now that it has been associated with vaccine associated thrombotic thrombocytopaenia (VATT).(Greinacher et al. 2021).

Table: Risk factors for CVST (Filippidis et al. 2009)

Genetic Prothrombotic States	Hematology
antithrombin deficiency	polycythemia
protein C and S deficiency	thrombotic thrombocytopenic purpura
resistance to activated protein C	thrombocythemia
factor V Leiden mutation	severe anemia and autoimmune hemolytic
prothrombin mutation (A–G at position 20210)	anemia
methylenetetrahydrofolate reductase (MTHFR)	paroxysmal nocturnal hemoglobinuria
mutations leading to homocysteinemia	heparin-induced thrombocytopenia
Acquired Prothrombotic States	**Drugs**
pregnancy	oral contraceptives
puerperium	lithium, androgens
homocysteinemia	sumatriptan
antiphospholipid antibody	intravenous immunoglobulin
nephrotic syndrome	hormone replacement therapy
	asparaginase
	steroids
	illicit drugs (such as ecstasy)
Infection	**Mechanical Causes**
meningitis	head trauma
otitis	neurosurgical procedures
mastoiditis	jugular vein catheterization
sinusitis	lumbar puncture
neck, face, mouth infection	injury to cerebral sinuses
systemic infectious diseases	intravenous drug abuse
AIDS	
Inflammatory and Autoimmune Diseases	**Other Causes**
systemic lupus erythematosus	dehydration, especially in children
Adamantiades-Behçet disease	thyrotoxicosis
Wegener granulomatosis	arteriovenous malformations
sarcoidosis	dural fistulae
inflammatory bowel disease	congenital heart disease
thromboangiitis obliterans	postradiation
Malignancy	
CNS tumors	
systemic malignancies	
solid tumors outside CNS	

Take home Points

- Exclude CVST as a cause of persistent non-thunderclap headaches in patients with no prior history of migraines and a normal brain CT scan.
- A significant recent infection in the head and neck region in combination with persistent headaches should raise suspicion of CVST.
- *JAK2 V617F mutation screening should be done in* persistent thrombocytosis
- Young patients presenting with neurovascular (stroke) syndromes must have a comprehensive thrombophilia screen
- Multidisciplinary management is essential in the management of CVST; involve the stroke physician and haematologist.

References

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