Transient Ischaemic Attack as First Presentation of Polycythaemia Vera

Dear Editor,

Cerebrovascular disease (CVD) consists of an age-dependent spectrum of transient ischaemic attack (TIA), cerebral infarction and haemorrhage. It is the second leading cause of death globally, and fourth in Singapore, accounting for 10% to 12% of all deaths.[1] TIA is defined by the American Heart Association and American Stroke Association as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction.[2] We reported an interesting but rare case of TIA secondary to polycythaemia vera (PV). We also reviewed the literature and discuss management guidelines of PV in the emergency department (ED).

Case Report

A 65-year-old Chinese male, ex-smoker and hypertensive, presented to the ED after a transient episode of right-sided limb numbness and weakness, facial droop, dizziness and dysphasia. His symptoms resolved spontaneously within 15 minutes.

He was hypertensive with blood pressure of 177/91 mmHg. Physical examination and electrocardiogram were unremarkable. His ABCD2 score was 3. Initial investigations revealed a normochromic, normocytic erythrocytosis with haemoglobin (Hb) of 20.4 g/dL, red blood cell count of 6.56 x10^{12}/L and haematocrit (Hct) of 61.6%. His white cell, platelet counts, renal and liver function tests were normal. Magnetic resonance imaging (MRI) of the brain showed no acute infarct or intracranial haemorrhage. He was admitted to our observation ward and reviewed by a haematologist who diagnosed PV based on the World Health Organization (WHO) criteria (Hb >18.5 g/dL and/or Hct >60%). His erythropoietin level was normal. The diagnosis of PV was further corroborated by the *Janus Kinase 2* (*JAK 2*) mutation test which proved him to be a heterozygous mutant. This test affirmed our diagnosis according to the Polycythemia Vera Study Group (PVSG) criteria. He was started on aspirin 100 mg once daily, simvastatin 20 mg once at night and hydroxyurea 500 mg twice daily. He underwent 2 consecutive venesections and currently attends regular outpatient haematological follow-up.

Discussion

ED patients with a history suggestive of TIA undergo a standardised protocol of investigations, which include basic laboratory studies, electrocardiogram and brain imaging.[3] The main management aims for ED patients with suspected TIA are stratification of stroke risk, identification of treatable causes or conditions that can mimic symptoms of TIA. Laboratory testing is essential to exclude any reversible metabolic abnormalities and haematological disorders e.g. thrombocytosis.

PV is a rare but treatable cause of cerebral ischaemia in the Asian context. Thus far, only 1 Asian case had been reported.[4] PV is suspected as a potential source of cerebral ischaemia in TIA patients aged 45 or below with a history of clotting dysfunction, multiple venous and arterial occlusions, suspected or confirmed cancer, or family history of thrombotic events.[2] The diagnosis of our patient, however, is made more challenging. There were no symptoms or signs, and no family history to suggest or increase the suspicion of PV. Hence, all emergency physicians (EPs) should maintain a high level of suspicion for the rarer causes of CVD including PV, especially when there is erythocytosis or an elevated Hct level. EPs play a vital role in diagnosing and initiate early treatment in PV. Urgent therapeutic and preventative treatment including venesection should be commenced to prevent the development of organ infarction.

Patients with TIA in the ED are risk stratified for stroke development using the ABCD2 scoring system. Low risk patients receive aspirin and an urgent outpatient neurological referral. The National Stroke Association recommends admission for those with conditions which predispose them to a higher risk of stroke like atrial fibrillation, hypercoaguable state, crescendo TIAs, and high risk of early stroke after TIA stratified using the ABCD2 i.e. score 6 to 7.2. Our patient's ABCD2 score of 3 did not satisfy the admission criteria but he was admitted because of the suspicion of PV; a hypercoagulable state. This again emphasised the importance of careful interpretation of the Hb and Hct levels in our patient who would otherwise be discharged from the ED.

PV is a chronic myeloproliferative disorder with an annual incidence of 2.3/10,000 cases. The mean age of presentation

is around 60 years with a slight male predominance. It is associated with panmyelosis.[5-10]

The 2 main diagnostic criteria for PV are the WHO and the PVSG criteria; the latter are listed in Table 1. However, in patients with *JAK2* mutation, like our index case, a diagnosis of PV becomes valid in the presence of high Hct (>50% in men and >48% in women) or an increased red cell mass of >25% above the predicted value.[8] In *JAK2* gene mutants, production of blood cells is multiplied and their survival is prolonged. Approximately 96% of PV patients have *V617F* mutation.[11,12] Peripheral blood screening for *JAK2* mutation is now the first-line test for evaluation of suspected PV. Concomitant measurement of serum erythropoietin levels (which is known to be decreased in more than 90% of newly diagnosed PV) is also recommended.[13]

Erythrocytosis leads to a hyperviscous state; predisposing patients with PV to an increased risk of thromboembolic events with an annual risk of thrombosis at 3%. The risk of thromboembolism rises in a linear relationship with the Hct level and stroke/TIA, myocardial infarction, deep venous thrombosis/pulmonary embolism are the most common thromboembolic events. Management of PV is based on risk stratification of developing thrombotic events[8] as detailed in Table 2.

Cerebral blood flow is significantly reduced in PV patients. Venesection reduces blood viscosity by lowering the venous Hct to <45%; at which cerebral perfusion improves by 73%.[6,7] Low dose aspirin is also recommended unless contraindicated. Other treatment options such as cytoreduction have shown benefits in the management of patients with thrombocytosis. Hydroxyurea has shown effectiveness in myelosuppression as well as risk reduction of thrombosis compared to venesection alone for patients above the age of 40.[6-10,13]

Table 1. Polycythaemia Vera Study Group Criteria

A1: Raised red cell mass; male >36 mL/kg, female >32 mL/kg
A2: Normal arterial oxygen saturation >92%
A3: Splenomegaly
B1: Platelet count >400 x 10^9/L
B2: White blood cell count >12 x 10^9/L
B3: Leucocyte alkaline phosphatase >100
B4: Serum B12 >900 pg/mL or unbound B12 binding capacity >220 pg/mL
Diagnosis
A1 + A2 + A3 establishes PV
A1 + A2 + 2 of category B establishes PV

In *JAK2* mutants, the diagnosis of PV becomes valid with a high haematocrit (>50% in men and >48% in women) or an increased red cell mass of >25% above the predicted value.
PV: Polycythaemia vera

Table 2. Risk Stratification and Treatment Algorithm of Polycythaemia Vera According to Thrombotic Risk

Risk	Risk Factors	Treatment
High	Age ≥60 or previous thrombosis	Venesection + low dose aspirin + cytoreductive treatment (hydroxyurea)
Intermediate	Age <60 and no previous thrombosis, but with a. Thrombocytosis (<1500 x 10^9/L) b. Cardiovascular risk factors • Cigarette smoking • Diabetes • Hypercholesterolaemia c. Hypertension	Venesection + low dose aspirin
Low	None of the above	Venesection + low dose aspirin

Conclusion

EPs need to be aware of PV as a rare but treatable cause of TIA with an excellent outcome. The clinical clues to PV may be minimal and careful interpretation of the Hb and Hct levels is decisive.

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