The Importance of the Full Blood Count in Cerebral Ischemia: A Review of 609 Consecutive Young Patients with Stroke and Transient Ischemic Attacks

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Background: Almost half of ischemic strokes in young individuals are cryptogenic. Thrombophilia testing is routinely sent despite limited evidence linking to arterial cerebrovascular events. A full blood count may identify underlying hematological disorder. *Methods:* We retrospectively reviewed all patients younger than 60 years with stroke and transient ischemic attack (TIA) presenting to a regional hyperacute stroke unit and daily TIA clinic from January 2015 to August 2016. We examined hematocrit level and platelet count, and whether abnormalities were further investigated. We examined if primary hematological disorders associated with stroke were considered, specifically myeloproliferative diseases (MPDs) and thrombotic thrombocytopenic purpura (TTP). *Results:* Of 609 patients who presented with stroke or TIA, there were 161 abnormalities in hematocrit level or platelet count in 153 patients (25.1%). One hundred sixteen patients had high hematocrit levels (19%), 19 had thrombocytosis (3.1%), 26 had thrombocytopenia (4.3%), and 8 had abnormalities in both lineages (1.3%). A total of 119 patients had repeat testing (74%). Molecular investigations for MPD were warranted in 19 patients (3.1%), performed in 3 patients (.5%) with 2 patients subsequently diagnosed. ADAMTS13 analysis was indicated in 10 patients with thrombocytopenia, performed in 2 patients with 1 diagnosed with TTP thereafter. *Conclusions:* One quarter of our cohort (n = 153) had abnormalities in hematocrit and/or platelets. MPD or TTP was present in 3 of the 5 patients specifically investigated. At least 22 patients (14%) merited further investigation. Although primary hematological disorders are rare in stroke aetiology, the full blood count is important to exclude known causes of arterial cerebrovascular events in young patients. **Key Words:** Stroke literacy—risk factors.

Background

The etiology of stroke in younger patients is diverse including cardiac anomalies, autoimmune disorders, thrombophilia, and traditional vascular risk factors. Despite extensive investigations, there is no clear cause for around 25%-40% of all stroke events.[1-4] Complex and costly thrombophilia testing is routinely sent despite controversy regarding evidence linking to stroke caused by arterial disease.[5-7] The panel will often include protein C, protein S, and antithrombin activity levels, factor II mutation (prothrombin G20210A mutation), factor V Leiden, homocysteine, and antiphospholipid antibody testing. Whereas there is some evidence for the role of

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antiphospholipid syndrome in the etiology of stroke in young patients,[8-10] data linking other potential thrombophilia markers with arterial thrombosis is less robust.[5,7,11] Thrombophilia testing protocols are also often poorly applied and followed up.

In contrast, analysis of the basic full blood count may be more helpful in signifying the presence of diseases, such as myeloproliferative diseases (MPDs) or thrombotic thrombocytopenic purpura (TTP), which could be causative. MPDs typically demonstrate an elevated hematocrit level, thrombocytosis and/or leukocytosis. TTP is characterized by a marked thrombocytopenia and microangiopathic hemolytic anemia.

MPDs are heterogeneous but linked by a shared abnormality of hematopoiesis with overproduction of 1 or more myeloid-derived cell lines. Polycythemia vera (PV), essential thrombocythemia (ET), and primary idiopathic myelofibrosis are included within this diagnostic group.[12] There is a clear link with arterial thrombosis,[13-16] with an incidence of 9% in an international ET cohort followed up over 6 years.[17]

The JAK II V617F mutation is seen in 95% of PV, thus the diagnosis is unlikely in the absence of this molecular marker, particularly combined with a normal or increased serum erythropoietin. Overall, molecular markers in ET include JAK II (55% incidence), CALR (25%), and MPL (3%), with "triple negative" disease seen in approximately 17% as described in a recent review.[13]

TTP is due to a deficiency of ADAMTS13, the vWF cleaving protein that controls the ultra large multimers of vWF released from the endothelium.[18] Although a rare disorder with a reported incidence of 6 cases per million in the UK,[19] the untreated mortality of TTP is 90%. TTP can present as an ischemic stroke—albeit usually with a markedly reduced platelet count—and is a crucial diagnosis to make to institute potential life-saving plasma therapy to remove autoantibody and replace ADAMTS13.

We retrospectively reviewed full blood counts, specifically hematocrit level and platelet count, and whether these were documented and further investigated if outside of the normal laboratory range. We examined whether less common primary hematological disorders known to cause stroke were considered and investigated, for example, molecular diagnosis for MPDs such as PV and ET and ADAMTS13 analysis for TTP.

Methods

In a regional hyperacute stroke unit (HASU), we retrospectively reviewed consecutive clinical and laboratory records for all patients younger than 60 years presenting to the service and discharged with a final diagnosis of stroke or transient ischemic attack (TIA). Because this was review of practice rather than instituting change, there was no institutional review board approval. Patients were either ward inpatients or daily attendees of the TIA clinic, inclusive from January 1, 2015 to August 7, 2016. Abnormal test results were followed up to see if they were repeated and whether there was resolution. Case notes were reviewed to confirm whether there was a secondary cause in all patients with thrombocytosis (defined as platelet count >400 $\times$ 10^9/L) and/or higher hematocrit levels (defined as Hct >.45), and whether further genetic testing such as JAK II was considered if there was none. Case notes were similarly examined in patients presenting with thrombocytopenia (defined as platelet count <150 $\times$ 10^9/L), and whether ADAMTS13 testing was conducted if no cause was determined.

Results

A total of 609 patients were included in the study: 379 had ischemic stroke (62.2%), 193 had TIA (31.7%), and 38 had hemorrhagic stroke (6.2%).

A total of 161 abnormal results with respect to hematocrit level or platelet count were found in 153 patients (26.4%): 116 had high hematocrit levels (19%, >.45), 19 had thrombocytosis (3.1%, with platelet count >400), and 26 had thrombocytopenia (4.2%, platelet count <150). Eight patients demonstrated abnormalities of both cell lines.

Of these initial 161 abnormal results, 118 were repeated in a total of 111 patients (73.3%). There was no further follow-up in 43 (26.7%) of the abnormal results seen in 42 patients. One patient was not included because he died shortly after initial presentation (Figure 1).

In those repeated tests, there was resolution of the discrepancy in 70 tests (59.3%). In the repeated tests showing no resolution, other etiologies were taken into account (Figures 2 and 3). However, even with repeated testing, there were a number of patients with a persistent or progressive abnormality, which was not further investigated (n = 22, 14.4% of patients with abnormal results).

Overall, JAK II testing was deemed warranted in 19 patients (2.8%), a persistently high or progressively high hematocrit level or great platelet count respectively, with normal liver and renal function and no other explicable cause. JAK II mutational analysis was only performed in 3 patients (.5%). One was proven positive for the V617F mutation, and hence was diagnosed with PV. Of the 2 negative JAK II results, 1 patient was subsequently diagnosed with chronic myeloid leukemia. Fourteen patients had no further testing or monitoring (see Figure 2)

Twenty-six patients (4.3%) had thrombocytopenia. ADAMTS13 testing was not warranted in 16 of these patients because there was either resolution of thrombocytopenia on repeat testing, or a clear alternative etiology (subsequent resolution of platelet count n = 6, human immunodeficiency virus n = 2, liver derangement n = 7, known immune thrombocytopenic purpura with no microangiopathic haemolytic anaemia n = 1). ADAMTS13 testing was indicated in 10 of these patients (38.5% of thrombocytopenic patients), defined as