

## Neurologic Manifestations of Essential Thrombocythemia

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**Essential thrombocythemia is a clonal myeloproliferative disorder, characterized predominantly by a markedly elevated platelet count without known cause. We report a case that was recognized during investigation of a transient ischemic attack, and review the neurologic findings in 33 patients with unequivocal essential thrombocythemia under prospective study by the Polycythemia Vera Study Group. Twenty-one patients had neurologic manifestations at some point during their course, including headache (13 patients), paresthesiae (10), posterior cerebral circulatory ischemia (9), anterior cerebral circulatory ischemia (6), visual disturbances (6) and epileptic seizures (2). All patients with neurologic symptoms responded satisfactorily to treatment, although continuous or repeated treatment was often required. Therapeutic recommendations include plateletpheresis for major thrombo-hemorrhagic phenomena, or megakaryocyte suppression with radioactive phosphorus, alkylating agents (such as melphalan), or hydroxyurea; minor symptoms may respond to platelet antiaggregating agents.**

**E**SSENTIAL THROMBOCYTHEMIA is a primary myeloproliferative disorder characterized by persistent thrombocytosis, the peripheral platelet count generally being in excess of  $1\,000\,000/\mu\text{L}$ . The peak age of onset occurs in late middle age, and there is no predilection for either sex (1-4). Synonyms for essential thrombocythemia include hemorrhagic, idiopathic, or primary thrombocythemia, and primary thrombocytosis.

The Polycythemia Vera Study Group has conducted a series of prospective therapeutic trials dealing with thrombocytosis occurring in the setting of myeloproliferative disorders. For these studies, the Polycythemia Vera Study Group has defined essential thrombocythemia as that subgroup of patients having persistent thrombocytosis (platelet count greater than or equal to  $1\,000\,000/\mu\text{L}$ ), megakaryocytic hyperplasia in the bone marrow, absence of other identifiable cause, absence of Philadelphia chromosome, absence of prominent marrow fibrosis or myeloid metaplasia or both, and absence of increased erythrocyte mass in the presence of normal iron stores (4). This definition distinguishes essential thrombocythemia from various infectious, inflammatory, neoplastic, and asplenic states in which there may be a secondarily elevated platelet count. This definition also excludes chronic granulocytic leukemia, iron deficiency anemia,

polycythemia vera (whether overt or masked), myelofibrosis, and other myeloproliferative disorders characterized by marked myeloid metaplasia.

Essential thrombocythemia is associated with both spontaneous hemorrhages and thrombotic phenomena involving the arterial and venous circulations (4-10). Pulmonary emboli may also occur. A small degree of splenomegaly is found in approximately one third of the cases of essential thrombocythemia (4); however, there need not be any clinical evidence of coagulopathy or splenomegaly.

Descriptions of neurologic complications have appeared in general treatises on thrombocythemia. The neurologic literature also contains case reports of amaurosis fugax (11, 12), transient ischemic attacks (13, 14), stroke (14) and other syndromes (15). We report a case of essential thrombocythemia recognized during investigation of a transient ischemic attack, and review 33 unequivocal cases, 21 with neurologic manifestations. These findings are compared with the literature on the neurologic sequelae of essential thrombocythemia and recommendations are made for treatment in this relatively uncommon but easily recognizable and treatable condition.

### Case Report

A neurosurgeon examined a 41-year-old right-handed black woman who had a 1-year history of right temporal headaches. The most recent headache had been accompanied by right facial numbness, hoarseness, and dimming of vision in the right eye for 10 to 15 seconds. She also had a 1-week history of intermittent right upper extremity numbness that was unrelated to the headaches, and she had occasional presyncopal, nonvertiginous dizziness.

General physical examination showed a tender right carotid artery whose upstroke was smaller than that of the left. There was no hepatosplenomegaly or evidence of bleeding. The neurologic examination showed only decreased pin appreciation in the right fingertips. The platelet count was  $916\,000/\mu\text{L}$ . The hematocrit was 40.9%; erythrocyte count,  $4.72 \times 10^6/\mu\text{L}$ ; and leukocyte count,  $15\,300/\mu\text{L}$ .

The patient declined admission to the neurology service and went home and took aspirin, which gave relief of her symptoms. After a second platelet count of  $924\,000/\mu\text{L}$  was obtained, the patient agreed to be hospitalized.

Results of a bone marrow biopsy showed hypercellularity with a marked increase in megakaryocytes, including morphologically atypical forms. Stainable iron was found. The patient was diagnosed as having essential thrombocythemia, and plateletpheresis was done to a count of  $393\,000/\mu\text{L}$  with an immediate improvement in her sense of well being. She was then treated with oral hydroxyurea,  $15\text{ mg/kg}$  body weight · d, and has maintained a platelet count in the  $400\,000$  to  $500\,000/\mu\text{L}$  range with no recurrence of symptoms during 4 months of follow-up.

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Table 1. Patients with Neurologic Manifestations (Group 1)

Patient	Platelet Count at Presentation	Neurologic Manifestations at Presentation	Initial Therapy	Platelet Count at Relapse	Neurologic Manifestations at Relapse	Relapse Therapy
20	1 450 000	Headache	Melphalan	207 000	Right-sided headache; spontaneously remitted after 1 week	None
26	2 650 000	Stroke with recovery 18 months earlier; subsequent headaches and paresthesiae	<sup>32</sup> P	128 000	Left hemiplegia	None
32	1 300 000	None	<sup>32</sup> P	1 250 000	Paresthesiae in feet	<sup>32</sup> P
39	1 310 000	Headache, scintillating scotomata, paresthesiae, tinnitus and syncope	<sup>32</sup> P	1 393 000	Same as at presentation	<sup>32</sup> P
				591 000	Same as at presentation	<sup>32</sup> P
				1 055 000	Headaches	Aspirin
52	1 535 000	Blurred vision and occipital headaches	Melphalan			
53	1 327 000	Epileptic seizures	Melphalan			
59	1 300 000	Posterior circulation transient ischemic attacks and paresthesiae	<sup>32</sup> P	...	...	...
72	1 600 000	None	<sup>32</sup> P	670 000	Headache, dizziness, and paresthesiae	Aspirin and dipyridamole
93	1 314 000	Paresthesiae in feet	<sup>32</sup> P	...	...	...
97	1 300 000	Paresthesiae in feet	<sup>32</sup> P	...	...	...
115	1 085 000	Headache	<sup>32</sup> P	...	...	...
133	1 490 000	Syncope, episodic visual dimming, paresthesiae and retinal hemorrhages	<sup>32</sup> P	...	...	...
191	2 300 000	Dizziness and headaches	<sup>32</sup> P	...	...	...
197	1 260 000	None	<sup>32</sup> P, aspirin and dipyridamole	792 000	Vertigo	<sup>32</sup> P and aspirin
235	1 282 000	None	<sup>32</sup> P	609 000	Anterior circulation transient ischemic attacks, headaches, scotomata, and paresthesiae	<sup>32</sup> P
295	1 455 000	Dizziness and headaches	Melphalan	...	...	...
398	1 000 000	Left facial transient ischemic attack	Melphalan	...	...	...
414	1 110 000	Headache, vertigo, paresthesiae, and amaurosis fugax	<sup>32</sup> P	591 000	Paresthesiae	None
436	2 139 000	Epileptic seizure and headaches	Melphalan	348 000	Anterior circulation stroke	Aspirin, dipyridamole and melphalan
509	1 700 000	Hemiplegic migraine and amaurosis fugax	<sup>32</sup> P	494 000	Seizure	As above
510	1 907 000	Posterior circulation transient ischemic attack and headache; subsequent left hemiplegia	Aspirin and dipyridamole; then melphalan	...	...	...

## Methods

We examined the files of 115 patients who were originally registered with the Polycythemia Vera Study Group for therapeutic trials for thrombocytosis associated with a myeloproliferative disorder other than polycythemia vera or chronic granulocytic leukemia. The major therapeutic portion of these studies involved randomization to radioactive phosphorus (<sup>32</sup>P) or melphalan, with the aim of maintaining the platelet count at less than 600 000/ $\mu$ L. Before randomization some patients had been treated by their physicians with platelet antiaggregating agents, but none had received myelosuppressive therapy. Thirty-seven cases were unequivocally considered essential thrombocythemia using the criteria listed above. Of these, 33 patients have had a minimum of 6-months follow-up (median, 36 months), and these constitute the study group reviewed here. Many of the other patients may well have had essential thrombocythemia but the diagnosis could not be confirmed because of

inadequacies in the documentation of the chromosomal studies, erythrocyte mass, or the extent to which iron deficiency contributed to the thrombocytosis.

The records of these 33 patients were examined for evidence of neurologic disorders. The original study required physicians to inquire into the presence and nature of headache, paresthesia, weakness, dizziness, and visual changes. The findings were noted and quantified both in the patient's personal file and, subsequently, in the Polycythemia Vera Study Group's computerized database. The details of treatment were also noted, together with sequential clinical and hematologic information obtained at regular follow-up assessments.

The patient presented above was not entered into the <sup>32</sup>P and melphalan study because her platelet count never exceeded 1 000 000/ $\mu$ L as required by the protocol, and patient accrual had already been terminated. However, because of the serious nature of her symptoms and her young age, active intervention

was initiated with plateletpheresis and hydroxyurea.

## Results

Twenty-one of the 33 patients who met the strict Polycythemia Vera Study Group criteria for essential thrombocythemia had neurologically symptomatic episodes at some time during their course (Group 1). These patients are shown in Table 1. Twelve patients had no neurologic complaints either at the time of presentation or during their follow-up period (Group 2), and are shown in Table 2. The presenting characteristics in both groups of patients are shown in Table 3. There were no significant differences between the two groups with respect to age, sex, median platelet count, hematocrit, or leukocyte count. The patients in Group 1 have been followed longer than those in Group 2 ( $p < 0.01$ ; Table 3). It is possible that as the patients in Group 2 reach a median follow-up period comparable to that of Group 1 patients, some of them may also have neurologic manifestations. Thus the frequency of neurologic episodes may be higher than our results show.

The 21 patients in Group 1 have had a total of 29 neurologically symptomatic periods. Twelve patients presented with neurologic symptoms but have had no further episodes after the platelet count was lowered. Patient 510 presented with posterior circulatory transient ischemic attacks and headache, and developed a left hemiplegia within 2 weeks of beginning melphalan therapy while the platelet count was still falling; because of the proximity of this episode to the commencement of myelosuppressive therapy, it has been regarded as having occurred at presentation rather than as a neurologically symptomatic relapse. Five patients had neurologic symptoms before lowering of the platelet count and have also had a total of eight further episodes. Four patients had no neurologic symptoms at presentation but have had one episode each after the platelet count was initially lowered.

Of the 29 neurologically symptomatic episodes, 17 occurred before initial myelosuppressive therapy (platelet count  $1\,000\,000/\mu\text{L}$  or greater), and 6 occurred during periods of hematologic relapse (platelet count  $600\,000/\mu\text{L}$  or greater). The remaining 6 episodes occurred with platelet counts less than  $600\,000/\mu\text{L}$  although in 2 of these the platelet count was  $591\,000/\mu\text{L}$  (Patients 39 and 414). Patient 20 reported a right-sided headache when the platelet count was  $207\,000/\mu\text{L}$ ; the headache resolved spontaneously in 1 week. Patient 26 developed myelofibrosis associated with progressive thrombocytopenia and had a left hemiplegia when the platelet count was  $128\,000/\mu\text{L}$ . This patient subsequently became severely thrombocytopenic and died of an acute subdural hematoma. Patient 436 had two neurologically symptomatic relapses at platelet counts of  $348\,000/\mu\text{L}$  and  $494\,000/\mu\text{L}$  respectively.

The patients in Group 1 were initially treated with  $^{32}\text{P}$  (14 patients) or melphalan (7 patients). All of these patients had a reduction in platelet count to less than  $600\,000/\mu\text{L}$ , and all original neurologic manifestations (17 patients) were relieved. The frequency of neurologically symptomatic relapses (neurologic episodes occurring after the platelet count was initially lowered to less

**Table 2. Patients Without Neurologic Complaints (Group 2)**

Patient	Platelet Count At Presentation $\mu\text{L}$	Initial Therapy
6	1 000 000	$^{32}\text{P}$
7	1 120 000	Melphalan
70	1 260 000	Melphalan
91	1 065 000	Melphalan
95	2 600 000	Melphalan
111	1 134 000	$^{32}\text{P}$
139	1 035 000	Melphalan
238	1 300 000	Melphalan
404	1 500 000	$^{32}\text{P}$
467	1 200 000	$^{32}\text{P}$
490	1 180 000	Melphalan
524	1 653 000	$^{32}\text{P}$

than  $600\,000/\mu\text{L}$ ) was greater in those patients initially treated with  $^{32}\text{P}$  than in those treated with melphalan. Six of the 19 patients who were randomized to  $^{32}\text{P}$  had neurologic relapses, compared with only 2 of 14 patients randomized to melphalan, but the difference is not statistically significant (Fisher's exact test,  $p > 0.1$ ). When these neurologic relapses were treated with additional myelosuppressive therapy or platelet antiaggregating agents, all symptoms were successfully controlled.

An analysis of the differing neurologic symptoms is shown in Table 4. Of 33 patients with essential thrombocythemia, headache occurred in 13 patients, paresthesiae in 10, symptoms of posterior cerebral circulatory ischemia in 9, anterior cerebral circulatory ischemia (excluding amaurosis fugax) in 6, visual disturbances (including amaurosis fugax) in 6, and epileptic seizures in 2.

Patient 26 developed myelofibrosis complicated by thrombocytopenia, and died of a subdural hematoma. This has not been included in our analysis of neurologic manifestations as the patient was severely thrombocytopenic at the time. There were no instances of extradural, subdural, intracerebral or subarachnoid hemorrhage in any patients during the thrombocytotic phase of their illness as described by Ozer and associates (7), in which a patient died of an acute cerebral hemorrhage.

Two patients developed iatrogenic complications as a direct result of melphalan. One young woman (Patient 52) developed early menopause, and an elderly woman (Patient 139) developed severe pancytopenia and died.

## Discussion

Essential thrombocythemia is a relatively uncommon disorder. However, the Polycythemia Vera Study Group has been able to collect the largest existing prospective database of patients with rigidly defined essential thrombocythemia through the cooperation of institutions in the United States, France, Sweden, Canada, and Israel. The standardized data have made it possible to realistically assess the incidence of various presenting characteristics. Similarly, the use of consistent therapeutic protocols and regular recording of data allow valid comparisons of clinical progress despite the widespread geographic locations of these patients.

Much of the literature on thrombocytosis barely men-

**Table 3. Presenting Characteristics and Duration of Follow-up in Groups 1 and 2**

	Group 1	Group 2	p Value
Patients, n	21	12	...
Age, yrs			
Range	27-84	25-80	NS*†
Median	62	68	
Sex, n			
Male	12	5	NS*‡
Female	9	7	
Platelet count, $\mu$ L			
Range	1 000 000-2 650 000	1 000 000-2 600 000	NS*†
Median	1 327 000	1 190 000	
Hematocrit, %			
Range	32-57	33-47	NS*†
Median	42	40	
Leukocyte count, $\mu$ L			
Range	7 400-41 100	6 000-35 600	NS*†
Median	11 700	11 500	
Duration of follow-up, mos			
Range	23-92	6-77	<0.01†
Median	44	22	

\* NS =  $p > 0.05$ .

† Mann-Whitney two-tailed U-test.

‡ Fisher's exact test.

tions neurologic complications, yet most of the patients in this study had neurologic sequelae either at presentation or during the course of their treatment. Neurologic manifestations that have been previously described include those of our patients. Most notably, in a study by Ozer and associates (7), 3 of 6 patients had clear neurologic complaints, although this occurred in 1 patient after a splenectomy. Two of the 14 patients with essential thrombocythemia described by Wu (16) had transient ischemic episodes that responded to aspirin and dipyridamole.

The neurologic literature confirms the existence of neurologic complications in essential thrombocythemia; Korenman (15) described five patients whose symptoms included brainstem and hemispheric strokes, radiculomyopathy, seizure, and trigeminal neuralgia. Olivarius (14) presented one case and reviewed two others with anterior cerebral circulatory ischemia. Levine and Swanson (13) presented a case of essential thrombocythemia with recurrent amaurosis fugax and contralateral hemiparesis that responded to therapy. Two other case reports (of amaurosis fugax) have been published (11, 12); both patients responded definitively to cytotoxic therapy.

Although a high incidence of neurologic manifestations was found in this series of patients, a comparison

was not made with an age-matched control group who did not have thrombocytosis. Therefore we cannot quantitate the "excessive" incidence of these problems in patients with essential thrombocythemia. Nevertheless, the clinician should be alerted to check the platelet count not only in patients with transient ischemic attacks but also in patients with headaches, visual changes, or paresthesiae.

Headaches were the commonest neurologic manifestation and paresthesiae the next. The precise pathogenetic mechanisms for these symptoms (in essential thrombocythemia) are unknown, but obstruction of the microvasculature may play an important role in view of the frequent relief afforded by either platelet antiaggregating agents or myelosuppressive therapy.

The present study, which is unselected for neurologic problems, also shows a high incidence of transient ischemic attacks of both the anterior and posterior cerebral circulation in patients with essential thrombocythemia. Such a finding is consistent with the widely accepted platelet emboli theory of transient ischemic attacks (17). Indeed, aspirin and dipyridamole, currently the mainstays of medical therapy for transient ischemic attacks, appeared to be quite efficacious in controlling symptoms even when platelet counts remained markedly elevated. However, in view of the lack of a definitive study that specifically addresses this question, it would be premature to conclude that platelet antiaggregating agents alone constitute adequate therapy for the neurologic manifestations of essential thrombocythemia.

An analysis of the general clinical and laboratory characteristics of this group of patients has been presented elsewhere (4). The pattern of bleeding seen in these patients, predominantly epistaxis and bruising, confirms the traditional view that hemorrhage related to quantitative or qualitative platelet abnormalities is usually mucocutaneous rather than in the deep tissues. Thus the absence of

**Table 4. Frequency of Neurologic Complaints Associated with Essential Thrombocythemia**

Manifestation	Patients (n = 33)
Headache	13
Paresthesiae	10
Posterior cerebral circulatory ischemia	9
Anterior cerebral circulatory ischemia	6
Visual disturbances	6
Epileptic seizures	2

intracranial bleeding is not surprising. The low incidence of severe thrombo-hemorrhagic phenomena would not have been expected from the classical essential thrombocythemia case reports, and highlights the value of a prospectively acquired database. It is possible, however, that patients with severe thrombo-hemorrhagic phenomena were less likely to be entered into a study that required an extensive medical and laboratory evaluation, and such patients may therefore have been underrepresented in the present series.

Several aspects of the pathophysiology of essential thrombocythemia remain poorly understood. Many studies of platelet function have been done and various abnormalities have been described, including evidence of both hyperaggregability (16, 18, 19) and hypoaggregability (10, 20-22). Similar abnormalities were seen in our patients (4). However, it is still not clear whether the hemostatic disorders, manifested at times by thromboembolism and at other times by hemorrhage, are due to these qualitative platelet abnormalities, or whether the thrombocytosis is primarily responsible. Nevertheless, a number of observations from the present study seem pertinent to this question. First, most neurologic episodes occurred either at presentation or during periods of hematologic relapse, whereas the platelet function abnormalities found in essential thrombocythemia may persist despite successful reduction in the platelet count (23). Although this finding suggests that the absolute number of platelets may be more important than qualitative abnormalities, platelet antiaggregating agents were also successful in controlling neurologic symptoms in some of our patients despite significant thrombocytosis. Furthermore, reactive thrombocytosis is rarely associated with thrombo-hemorrhagic phenomena in the absence of other related factors, such as postoperative immobilization or disseminated intravascular coagulation accompanying malignancy (24). Thus it is likely that both thrombocytosis and platelet dysfunction are prerequisites for most hemostatic abnormalities occurring in essential thrombocythemia.

Control of neurologic symptoms was achieved in most patients. Several therapeutic options are currently available. Hoagland and Silverstein (25) reviewed the Mayo Clinic experience with nine patients under 30 years of age who had asymptomatic thrombocythemia; they recommended conservative therapy with, at most, aspirin and dipyridamole for this subgroup of patients. A trial of platelet antiaggregating agents (aspirin, 300 mg/d, with or without dipyridamole, 50 mg three times daily) may also be indicated in symptomatic patients, because aspirin alone can produce rapid reversal of acute peripheral vascular disease (19). If, however, serious thrombo-hemorrhagic manifestations are present, urgent plateletpheresis (26, 27) with or without transfusion of normal platelets is indicated. This treatment should be combined with myelosuppression because of the rapidity with which the thrombocytosis usually recurs. It is essential that splenectomy should be avoided because of the extreme thrombocytosis and potentially fatal complications that often follow this procedure (28, 29).

Chronic megakaryocyte suppression can be achieved either with alkylating agents such as oral melphalan, or with intravenous  $^{32}\text{P}$  (30). The initial dose of melphalan is 6 to 10 mg/d for 1 week, followed by 4 to 6 mg/d until the platelet count is in the normal range; maintenance with 2 to 6 mg/wk is then continued indefinitely. Cytopenia is the commonest side effect. Treatment with  $^{32}\text{P}$  is initiated with 2.9 mCi/m<sup>2</sup> and may be repeated in not less than 3 months at the same or increased dose (3.6 mCi/m<sup>2</sup>), depending on response. One, two, or three courses are generally sufficient, but further doses may be given if the patient relapses at a later time. Pancytopenia is again the most frequent complication.

There is concern that these cytotoxic agents may increase the incidence of acute leukemia and other malignancies in essential thrombocythemia, and there is evidence of this in polycythemia vera (31). A third myelosuppressant, hydroxyurea, appears to have less mutagenic and carcinogenic potential (32). The use of this drug in essential thrombocythemia is currently under study by the Polycythemia Vera Study Group (HOLCOMB GL, MURPHY S, LASZLO J, et al. Unpublished data), but was not evaluated in this series of patients.

This report documents a high frequency of neurologic manifestations occurring in a prospectively studied group of patients with rigidly defined essential thrombocythemia, and recommends that a platelet count be included in the investigation of neurologic complaints. In addition, the importance of maintaining the platelet count below 600 000/ $\mu\text{L}$  has been shown in this population of patients with essential thrombocythemia by the observation that most neurologic manifestations occurred either at the time of presentation or during periods of hematologic relapse.

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