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Neurologic Complications of Thrombocythemia: Six Cases and Review

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THROMBOCYTHEMIA (thrombocytosis) with platelet counts above 400,000/mm^3 may occur with exercise or parturition, or after injection of epinephrine. It is also seen after splenectomy or other splenic diseases, malignancy or systemic infections, inflammatory diseases or iron deficiency anemia. Qualitative as well as quantitative platelet abnormalities characterize thrombocythemia.[1] Thrombocythemia is also seen in primary myeloproliferative disorder characterized by persistent thrombocythemia, peak age of onset late middle-age and without predelineation for either sex.

The hematologic and systemic medical complications have been emphasized in the literature, but there has been little information about the neurologic effects of thrombocythemia. I therefore reviewed six cases of thrombocythemia presenting with acute cerebrovascular and other neurologic symptoms and findings. Clinical and hematologic data were correlated in these six cases and compared to 48 additional published case reports.

Patients and Methods

Six patients coming for medical evaluation with neurologic findings were studied at the Massachusetts General Hospital. Detailed history, physical examination and complete neurologic and hematologic evaluations were performed. Complete laboratory investigations were performed in all patients and in some, special platelet studies were also done. Where indicated appropriate neuroradiologic studies were performed.

This study was conducted in part while the author was a resident at Massachusetts General Hospital, Boston, and was reported in part at the 3rd Joint Meeting on Stroke and Cerebral Circulation in New Orleans on February 16-18, 1978. Dr. Bernad is now in private practice at 10721 Main Street, #3500, Fairfax VA 22030.
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Criteria for inclusion in the study were platelet counts exceeding 400,000/mm^3, with normal leucocyte count and hematocrit. None of the patients had a malignancy, but some had a myeloproliferative disorder.

Case Reports

Patient No. 1. A 79-year-old right-handed woman had transient right-sided weakness and slurred speech for 30 minutes. Past medical history, general physical and neurologic examination were unremarkable. Urinalysis, VDRL, chest x-ray, EKG, routine laboratory studies were normal. White blood count and hemoglobin were normal. Blood smear revealed numerous large platelets and a platelet count of 1.085×10^6/mm^3. Test of coagulation, including prothrombin time, partial thromboplastin time, bleeding time and platelet aggregation studies, were abnormal (Table 1).

The admission diagnosis was transient ischemic attack with thrombocythemia. Normal studies included dynamic palpation of facial pulses, thermography, ocular plethysmography, ultrasonography of periorbital vascular structures, computerized tomographic scan of the brain and electroencephalogram. Carotid angiogram revealed mild atherosclerosis involving the carotid bulb but without ulceration. During arteriography the patient experienced right-sided weakness and numbness for 15 minutes, and she had five other transient ischemic attacks involving her right side, face, tongue, arm and leg. A hematologist concurred with the diagnosis on the basis of normal physical exam, hematocrit, complete blood count, leucocyte alkaline phosphatase, B12 and consistently elevated platelet counts.

Complications included rectus sheath hematoma and retroperitoneal hemorrhage. Treatment included plasmaphoresis, fresh frozen plasma transfusion, and busulfan. After one month she was discharged asymptomatic and has remained asymptomatic for three years with platelet counts of 300,000, taking only aspirin and sulfinpyrazone. Platelet aggregation improved (Table 1).

Patient No. 2. A 70-year-old right-handed man suddenly had difficulty speaking and reading but could write. On the next day he had numbness and tingling in the right hand for eight minutes. Past medical history revealed that he had had Parkinson's disease for at least ten years, which was treated with right stereotactic thalamotomy. Examination showed features of Parkinson's with right hemiparesis, left Babinski (from thalamotomy) and right hemianopsia on confrontation. Normal studies

included urinalysis, VDRL, chest film, EKG, chemistries, bone marrow, white blood count and hemoglobin. Blood smear showed large platelets and a total platelet count of $1.5 \times 10^6/mm^3$. There was increased uptake in the left occiput on the technesium brain scan. Computerized tomographic scan of the brain showed low absorption lesion deep in the left hemisphere posteriorly.

He was treated with busulfan 2 mg daily. One month later the platelet count was 600,000 and the patient was asymptomatic.

Patient No. 3. A 71-year-old right-handed man presented with an enlarged prostate, urinary obstruction and Parkinson's disease. After perineal prostatectomy he became confused and lethargic with a hemiparesis. Routine chemistries were normal. Platelet count was 873,000. Computerized tomographic scan of the brain showed an infarction in the distribution of the left middle cerebral artery. In an angiogram there was evidence of multiple emboli in the middle cerebral artery. The patient was treated with aspirin and dipyridamole. The platelet count increased to $1.257 \times 10^6/mm^3$ in three weeks. He was then given busulfan 4 mg daily for four weeks. Three years later the platelet count remained at 325,000 and he has been asymptomatic except for his Parkinson's disease.

Patient No. 4. A 50-year-old woman was admitted because of transient ischemic attacks involving hands and face, scalp, eye and cheek as well as nose, chin and neck. She also had numbness in the left leg. Examination and laboratory studies were normal except for platelet count of $1.5 \times 10^6/mm^3$. After treatment with 32P (radioactive phosphorus), platelet count was normal and the patient has remained asymptomatic.

Patient No. 5. A 67-year-old right-handed woman developed global aphasia with dense right hemiparesis, left gaze preference, and right homonymous hemianopia. The patient also had a past history of transient ischemic attacks consisting of dizziness and diplopia. A platelet count was noted to be $1.1 \times 10^6/mm^3$. On blood smear the platelets were large. No other hematologic abnormalities were noted. The computerized tomographic scan of the brain showed increased density in the area of the left middle cerebral territory. Electroencephalogram showed runs of delta activity in the left temporal region. After stabilization, busulfan therapy was contemplated. However, the patient died suddenly and autopsy was denied.

Table 1. Platelet Aggregation Studies Before and After Treatment, Patient No. 1.

		Before	After
2 × λ epinephrine	=	0%	0%
4 × λ epinephrine	=	0%	7%*
8 × λ epinephrine	=	0%	
5 × λ collagen	=	100%	0%
2 × λ collagen	=	0%	100%
4 × λ ADP	=	100%	100%
2 × λ ADP	=	55%	100%
1 × λ ADP	=	0%	100%
0.1 × λ ADP	=	0%	0%

* Delay in second wave

Patient No. 6. A 51-year-old right-handed woman had menometrorrhagia and frequent nose bleeds for three months. She complained of severe throbbing and aching paresthesias in the fingertips and toes especially after exertion. The only abnormal laboratory test was an elevated platelet count of $1.7 \times 10^6/mm^3$ with many large platelets on blood smear. She was treated with busulfan. Neurologic symptoms abated when the platelet count was reduced to normal. She remains asymptomatic three years later.

Discussion

Neurologic manifestation of thrombocythemia have been poorly documented, but in the cases reported,[1-21] neurologic symptoms have ranged from unilateral weakness to hemiplegia and included transient monocular blindness as well as other visual disturbances, seizures, headache, dizziness, diplopia, nausea and vomiting, aphasia, dysarthria, facial pain and tingling and ischemia of the extremities. Platelet counts have ranged from approximately 450,000 to over 4,000,000. Ages have ranged from 30 to 81 years. The majority of patients improved with some form of antiplatelet therapy.[1-21]

Thrombocythemia may be defined as an increased platelet count greater than 400,000 of unknown etiology with normal hematocrit and normal white count and often associated with both thrombosis and bleeding. Gunz separated thrombocythemia from polycythemia vera and other myeloproliferative syndromes.[22]

The hematologic literature cites few neurologic complications. Silverstein[23] studied 15 patients; six had gastrointestinal hemorrhage, one had a subdural hematoma, and four of six deaths resulted from thrombotic complications.

Histologically, the platelets seem large and proliferative in primary thrombocythemia in contrast to the small platelets of reactive thrombocytosis.[24] Large platelets were found in all six of the patients reported here. In one study the bleeding time increased in 14 of 23 patients, while all of the standard clotting tests were normal.[4] The effective thromboplastin generation tests associated with a defect in

platelet formation has been seen but this was not true in the patients studied with thrombocythemia.

McClure founded bleeding time was significantly correlated with platelet number in thrombocythemia[25] and that platelets have decreased adhesiveness, decreased ability for seratonin uptake, and decreased Factor 3 availability.

Spaet et al reported no platelet aggregation with epinephrine, impaired aggregation with ADP, and normal aggregation with collagen[26] but availability of platelet Factor 3 was normal. Seratonin uptake was poor. One patient in the present series showed no aggregation with epinephrine.

Diffuse intravascular platelet aggregation may account for the microvascular symptoms.[19] Prostaglandin synthetic pathways are important both in platelet aggregation and antiplatelet therapy. Exposed collagen at the site of injury activates platelet membrane phospholipase leading to release of arachidonic acid from platelet membrane phospholipids. Arachidonic acid is the precursor of prostaglandins, which mediate synthesis of prostacyclin (by veins and arteries), an inhibitor of platelet aggregation, and thromboxane A2, a potent platelet aggregator that is released by platelets. Control of thrombogenesis depends on a delicate balance between the concentration of these two agents. Platelet suppressive agents are directed at this molecular level of platelet and vascular wall interaction.[30,31]

Some effective therapeutic modalities to decrease high platelet counts are available in the acute situation of thrombosis or bleeding. Rapid diminution of the platelet count can be achieved by thrombocytopheresis[32] for major thrombo-hemorrhagic phenomena in conjunction with administration of nitrogen mustard and busulfan. Seven to nine units of plasma had to be removed to adequately lower platelet counts, and it has been noted that platelet counts rose after each phlebotomy. After 10-14 days the alkalating agents gave adequate long-term control of platelet counts. The thrombocytopheresis promptly controlled the symptoms. Other agents include melphalan (alkalating agent) and 32P. Patients in the current series showed improvement in neurologic symptoms and findings when their platelet counts were decreased. Acetylsalicylic acid and sulfinpyrazone have been used once the platelet count was reduced but also were shown to be effective in controlling minor symptoms prior to reducing the platelet count.

How common are neurologic complications resulting from elevated platelets? There is no clear-cut answer to that question. Thirty-eight patients with platelet counts over 1,000,000 (ranging 1.1 to 5,000,000) were studied retrospectively for 1-24 years. No patient had received any specific therapy to reduce the platelet count. Documented thromotic events in three individual (7.9%) included transient ischemic attacks and stroke.[34] The later study was not a case control study and did not specifically address the issue of neurologic complications in thrombocythemia. A recent report documented a high frequency of neurologic complications occurring in a prospectively studied group of patients with rigidly defined essential thrombocythemia.[34] This was part of the Polycythemia Vera Study Group, which reported a single case with transient ischemic attack, and reviewed the neurologic findings in other cases described in the literature.[34] In the group's findings 21 patients had neurologic manifestations at some point during their course, including headaches (13 patients) paresthesiae (10), posterior cerebral circulatory ischemia (9), visual disturbance (6), and epileptic seizures (2). All patients with neurologic symptoms responded satisfactorily to treatment, although continuous or repeated treatment was often required. The symptoms and findings were very similar to those presented in this paper.

Summary

The patients presented in this study have all shown neurologic complications in association with elevated platelets. The platelets in these patients were abnormal in number and size and did not aggregate normally in vitro. These platelets may be viewed as inherently defective and possibly responsible for the neurologic complications.

All patients with neurologic symptoms and findings should have a platelet count on admission. The platelet function tests are more difficult and expensive to perform routinely. If the platelet count is very high and platelet function abnormal, reducing the absolute count may relieve some of the symptoms and avert a neurologic catastrophe. It is postulated that excessive elevation of platelet count in conjunction with qualitative platelet abnormality may play a key role in the diverse cerebrovascular dysfunction of the central nervous system and may be responsible for certain neurologic symptoms and findings which evade adequate explanation.

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