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Polycythemia Vera Presenting with Generalized Chorea: A Case Report and Review of the Literature

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Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by erythrocytosis. Clinical symptoms can range in severity from headache and tinnitus to thrombohemorrhagic complications. Neurologic symptoms are common at the onset of polycythemia; however, chorea due to PV is a rare complication. We present the case of a 77-year-old female who was referred to our hospital because of choreic movement of the limbs, head and face. She was diagnosed with JAK2V617F mutation-positive PV. Her chorea was completely resolved by phlebotomy combined with hydroxyurea and aspirin. (Korean J Med 2014;87:619-624)

Keywords: Polycythemia vera; Chorea disorders

INTRODUCTION

Chorea is an abnormal involuntary movement disorder characterized by irregular, seemingly random, semi-directed movements. In most cases chorea is symmetrical and bilateral. Unlike ataxia or parkinsonism, the movements of chorea occur autonomously without conscious effort. Chorea can occur in a variety of hereditary or acquired conditions and disorders. Most inherited causes of chorea, such as Huntington's disease, are associated with gradual onset and progression. Rapid onset is more often associated with acquired causes such as pregnancy, drugs, stroke and rheumatic fever. Chorea is usually seen during general observation. A patient with mild chorea may not appear choreic during observation, so it is important to ask about fidgeting or restlessness.

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by clonal proliferation of myeloid cells. It is distinguished from other types of MPNs by the presence of

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an elevated red blood cell mass, and from idiopathic erythrocytosis by the JAK2 V617F mutation [1]. Neurologic symptoms such as headache, dizziness and blurred vision are attributed to the increased blood viscosity and reduced cerebral blood flow caused by erythrocytosis [2]. Headaches occur in 41% of untreated or poorly controlled PV patients, and dizziness or vertigo in 30%. The other frequent neurological manifestation is stroke, which causes significant morbidity and mortality. Chorea is a rare complication [3].

We present a case of PV in which chorea was the presenting symptom, and we review the literature on chorea associated with PV.

CASE REPORT

A 77-year-old female presented at our outpatient clinic because of progressive orolingual dyskinesia, generalized choreic movement and insomnia for a month. She complained of facial plethora for 2 months and weight loss of 10 kg over the previous 2 months. She had been diagnosed with hypertension 4 years previously and had suffered a vertebral compression fracture 1 year before. She has been taking antihypertensive medications and hypnotics for insomnia. She denied tobacco smoking and alcohol consumption. There was no family history of movement disorders or cerebral infarction. The patient denied dyspnea, blurred vision, headache, pruritus and burning pain. On physical examination, she appeared chronically ill but was alert and oriented with regard to time, place and person. Her face and palms looked flushed and her conjunctivae were injected. Her liver was not enlarged and her spleen was not palpated below the left costal margin. She revealed typical choreic movements of the orofaciolingual muscles, limbs and trunk. PV was confirmed based on the following laboratory data: leukocyte count 12.4 × 10^9/L, erythrocyte count 7.98 × 10^{12}/L, hemoglobin 221 g/L, hematocrit 0.661, mean corpuscular volume 82.8 fL, platelet count 451 × 10^9/L, JAK2 V617F mutation positive, serum erythropoietin 3.5 U/L (reference range 4.3-29.0 U/L) and a bone marrow biopsy showing hypercellularity for her age, with trilineage growth with prominent erythroid, granulocytic and megakaryocytic proliferation. Magnetic resonance imaging (MRI) of the brain showed a high signal intensity along the cortical vessels on FLAIR and T1WI. Electroencephalography (EEG) was normal when the patient was awake or sleeping, without epileptiform discharge.

The patient underwent phlebotomy of 400 mL of whole blood on two consecutive days, and then three times weekly, until her hematocrit was below 42%. The choreic movements noticeably improved after the third phlebotomy procedure, when her hematocrit decreased to 48.5%. Subsequently, the patient's chorea improved further with repeated phlebotomy, and her facial plethora also improved. In addition to phlebotomy, hydroxyurea (1,000 mg/day) and aspirin (100 mg/day) were administered to manage the high risk of thrombosis. At 6 months after diagnosis, the patient showed no further chorea but complained of occasional paresthesia in her hands and legs. Laboratory data were as follows: leukocyte count 6.93 × 10^9/L, erythrocyte count 4.21 × 10^{12}/L, hemoglobin 137 g/L, hematocrit 0.415, mean corpuscular volume 98.6 fL and platelet count 231 × 10^9/L.

DISCUSSION

Our case fulfilled the revised WHO criteria for PV [4]. We concluded that the chorea was caused by PV based on the fact that the chorea improved significantly when the hematocrit decreased below 42% and other diseases that cause chorea were not identified. The diagnostic criteria for PV proposed by the Polycythemia Vera Study Group (PVSG) [5] are no longer clinically useful and the revised WHO criteria are universally applied to establish the diagnosis of PV. However, owing to the limited number of cases, we reviewed cases of chorea associated with PV, diagnosed according to either the revised WHO criteria or the PVSG criteria.

We summarized a total of 24 cases reported since 1960, including our case [3,6] (Table 1). The median age was 71.5 years (range 45 to 82). The ratio of males to females was 8 to 16. Chorea was diagnosed prior to PV in 19 patients, with a median time to PV diagnosis of 3.5 months (range 0 to 432). Four patients were diagnosed with PV prior to chorea, with a

Table 1. Clinical cases of chorea due to polycythemia vera

Authors (Date)	Age (yr)/ Sex	Duration (PV to chorea, mon)	Duration (chorea to PV, mon)	Mental status	CSF	EEG	CT or MRI or SPECT	Hemo-globin (g/L)	Hemato-crit	Platelet count ($\times 10^9$/L)	Leukocyte count ($\times 10^9$/L)	Erythro-poietin (U/L)	JAK2 mutation	Organomegaly	Chorea status with PV treatment
Bakke (1963)	74/F		3	NR	NR	NR	NR	184	NR	250	18.4	NR	NR	Splenomegaly	Persisted
Friedemann (1965)	62/F	12		NL	NR	NR	NR	185	NR	NL	NL	NR	NR	NR	Improved
Gutier-Smith (1967)	74/F		5	Confusion	NR	Episodic bursts	NR	230	0.730	650	8.3	NR	NR	No	Improved
Gutier-Smith (1967)	57/F		48	NL	NR	NR	NR	222	0.770	450	18.1	NR	NR	Splenomegaly	Improved
Heathfield (1968)	77/F		6	NL	NR	NR	NR	185	0.660	320	8.8	NR	NR	No	Improved
Bietti (1968)	75/F	228		NL	NR	NR	NR	173	NR	360	14.5	NR	NR	NR	Worsened
Sangstaer (1970)	71/F		1.5	NL	NR	NR	NR	249	NR	120	15.6	NR	NR	Splenomegaly	Improved
Ashenhurst (1972)	68/M	84		NL	NR	NR	NR	212	0.655	NR	NR	NR	NR	NR	Improved
Edwards (1975)	45/M		432	NR	NL	Sharp wave focus in the left temporal region	NR	210	0.610	363	8.9	NR	NR	No	Improved
Voiculescu (1979)	53/F		12	NL	NR	NR	NR	196	0.650	220	12.0	NR	NR	Splenomegaly	Improved
Voiculescu (1979)	72/M		1.5	NL	NR	NR	NR	190	0.680	260	9.0	NR	NR	Splenomegaly	Improved
Borg-Costanzi (1981)	59/M		2	NL	NR	Theta activity	CT NL	218	0.686	183	19.1	NR	NR	No	Persisted
Mas (1985)	72/F		24	NL	NR	Theta activity in the left temporal region	CT NL	185	0.570	190	12.1	< 4 (normal = 5-20 U/L)	NR	No	Improved
Mas (1985)	73/F		5	NL	NR	Theta activity in the temporal region	CT NL	185	0.570	372	10.7	< 4 (normal = 5-20 U/L)	NR	No	Improved
Cohen (1989)	65/F		NR	NL	NR	NR	CT NL	182	0.580	450	11.6	NL	NR	Splenomegaly	Improved

Table 1. Continued.

Authors (Date)	Age (yr)/ Sex	Duration (PV to chorea, mon)	Duration (chorea to PV, mon)	Mental status	CSF	EEG	CT or MRI or SPECT	Hemo-globin (g/L)	Hemato-crit	Platelet count ($\times 10^9$/L)	Leukocyte count ($\times 10^9$/L)	Erythro-poietin (U/L)	JAK2 mutation	Organomegaly	Chorea status with PV treatment
Nazabal (2000)	74/F	120		NL	NL	NR	MRI NL	168	0.460	474	25.0	< 4 (normal = 5-20 U/L)	NR	No	Improved
Midi (2006)	66/M		0.03	NL	NL	NR	MRI NL	191	0.605	NL	NL	NR	NR	No	Improved
Kim (2008)	65/M		0.07	NL	NR	NR	SPECT NL	188	0.560	378	9.73	1.0 (normal = 3.7-31.5 U/L)	NR	Splenomegaly	Improved
Kumar (2009)	82/F		0.25	NL	NR	NR	MRI NL	181	0.560	492	9.6	3.2	Positive	No	Improved
Ahmad (2009)	60/M		1	NL	NR	NR	CT NL	192	0.658	NL	5.1	NR	NR	No	Improved
Huang (2011)	70/F		6	NL	NL	NR	MRI NL	168	0.517	769	NL	4.8 (normal = 3.7-31.5 U/L)	Positive	No	Improved
Ben Ghorbel (2011)	78/M		4	NL	NR	NR	CT NL	200	0.623	NL	NL	NR	Positive	No	Improved
Severs (2012)	73/F		6	NL	NR	NR	MRI: Mild ischemic white matter lesions	187	0.570	NL	NL	NR	Positive	No	Improved
Kim (2013)	77/F		1	NL	NR	NR	MRI: High-intensity signal along the cortical vessels	221	0.661	451	12.4	3.5 (normal = 4.3-29.0 U/L)	Positive	No	Improved

PV, polycythemia vera; CSF, cerebrospinal fluid; EEG, electroencephalography; CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; JAK2, Janus kinase 2; M, male; F, female; NL, normal; NR, not reported.

median time to chorea of 102 months (range 12 to 228). Only one patient presented with mental confusion. Cerebrospinal fluid (CSF) assay results were only available for four patients, all of whom demonstrated normal CSF findings. Results for computed tomography (CT), MRI or single-photon emission computed tomography (SPECT) of the brain were available in 13 patients: 1 had a nonspecific high-intensity signal along the cortical vessels, another had mild ischemic white matter lesions, and the others had normal findings. EEG showed theta activity in the temporal region in two patients; a nonspecific abnormality with irregular theta activity in one patient; a sharp wave focus in the left temporal region in one patient; episodic bursts of rhythmic 4-5 cycle per second waves on a background of a poorly formed 9 cycle per second alpha rhythm in one patient; and normal findings in one patient. The median hemoglobin value was 189 g/L (range 168 to 249); the median hemoglobin values for males and females were 196 g/L (range 188 to 218) and 185 g/L (range 168 to 249), respectively. JAK2 V617F mutation analysis results were available for five patients, all of whom were positive for the mutation. Serum erythropoietin level was measured in eight patients: it was below the normal range in six patients and within the normal range in two. None of the patients had a family history of chorea. Splenomegaly was documented in 7 out of 21 patients. Chorea improved significantly with the successful treatment of PV, mainly by repeated phlebotomy, in 21 patients; however, it persisted or worsened in 3 patients, in spite of phlebotomy.

The median age at diagnosis of PV was 60 years [5]. The incidence increased with age and the age-adjusted incidence was higher for males than for females (M:F = 2.8:1.3) [7]. Polycythemic chorea (PC) developed in older patients compared to PV and occurred predominantly in females (M:F = 1:2). The prevalence of PC in PV patients has not been clearly documented, owing to the small number of cases.

The pathophysiology of PC has not been clearly defined. Edwards et al. proposed that impaired oxygen transport in the basal ganglia due to blood hyperviscosity and an excess of dopamine in the basal ganglia resulting from increased numbers of dopamine-laden platelets play important roles in the pathogenesis of PC [6]. Bruyn and Padberg hypothesized that PC is due to dopaminergic hyperactivity, presuming that it is increased as a result of increases in neostriatal catecholestrogen levels [8]. Brain imaging studies of PC failed to demonstrate characteristic abnormalities, as we have described in our review cases. Autopsy of PC patients showed congestion of cerebral and meningeal veins, multiple small thrombi, scattered zones of perivenous demyelination, subdural and putaminal hemorrhage, and intense demyelination of the anterior pallidum on both sides [6].

The JAK2 V617F mutation is a molecular marker for the diagnosis of PV. Hemichorea has been reported in a patient with the JAK2 V617F mutation and a normal hematologic profile [9]. The hemichorea was completely resolved after therapeutic phlebotomy and hydroxyurea therapy. The mechanism underlying PC requires further study.

Other neurologic problems can occur in PV. Common neurologic complications are nonspecific and include headache, dizziness and paresthesia. Specific complications include motor or sensory deficit associated with ischemic or hemorrhagic stroke, blurred vision related to transient ischemic attacks in the occipital cortex and vaso-occlusive disease. Visual disturbances occur in 11% of untreated or poorly controlled patients [2]. Isolated monocular vision loss as an initial manifestation of PV that improved markedly after phlebotomy has been reported [10].

In summary, PV can cause a variety of neurologic abnormalities, especially in untreated or poorly controlled patients. PC is rare in PV patients, but its incidence is increased in elderly female patients. Choreic movement improves with the successful treatment of PV, mainly by repeated phlebotomy. It is important to maintain the hematocrit below 45% in males and 42% in females to prevent the recurrence of PC. In addition, cytoreductive therapy and low-dose aspirin are strongly recommended because they have been demonstrated to reduce the thrombosis rate.

중심 단어: 진성적혈구증가증; 무도병

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