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LETTER TO THE EDITOR

Cerebrovascular Complications and Polycythaemia Vera

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Introduction

Polycythaemia vera (PV) is a stem cell-derived myeloid haematologic malignancy. It is characterized by an expansion of one or more haematopoietic cell lineages, resulting in increased mature blood components in the peripheral blood. The disease features include erythrocytosis, leukocytosis and/or thrombocytosis, as a consequence of which PV may exhibit a unique prothrombic state [1, 2]. There is a possibility of progression into acute myeloid leukaemia or myelofibrosis, the 10-year risk ranging between 3% and 10%, but the life expectancy of patients with PV is commonly affected by thrombo-haemorrhagic events, with a reported incidence of 12–39% [1, 3]. The clinical manifestations of the thrombotic events in PV patients may vary from mild microvascular circulatory disturbances (e.g. erythromelalgia, tinnitus or vertigo) to more severe complications, such as migraine-like cerebral transient ischaemic attacks, transient ischaemic attacks, ischaemic stroke, myocardial infarction or venous thrombosis (e.g. cerebral sinus and venous thrombosis or deep venous thrombosis). Information relating to the association of PV and cerebrovascular complications such as stroke and transient ischaemic attacks from detailed clinical aspects are limited in the relevant literature [4–7].

The aim of our retrospective analysis was to assess the frequency and the main characteristics of the cerebrovascular complications of patients diagnosed with PV, with a view to describing typical neuroradiological lesions characteristic of PV.

Patients and Methods

Between 1999 and 2014, 108 patients (51 females and 57 males with a median age of 62.6 years, range: 25–82 years; and with a median 4.5 years follow-up) were diagnosed with PV and were selected from our institutional myeloproliferative neoplasm registry database, established for scientific research. All of the available medical data files and the haematological, radiological and neurological results on the enrolled patients were revised with the approval of the Regional and Institutional Human Medical Biological Research Ethics Committee. Informed patient consent was not required. Blood analysis was carried out routinely with automated blood count equipment within the diagnosis protocol. DNA isolated from EDTA-stabilized peripheral blood samples was screened for the *JAK2 V617F* mutation by means of an allele-specific PCR method [8]. The patients' haematological management strategy was based on risk-oriented recommendations: low-risk patients in certain cases received anti-platelet therapy, while cytoreductive drugs (e.g. hydroxyurea) in combination with anti-platelet medication were introduced for high-risk patients. Phlebotomy was recommended for patients at low-risk and in high-risk PV patients especially previously the cytoreductive treatment in order to reach the recommended target haematocrit level of 0.40–0.45 [9].

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Table 1 The main characteristics of the patients

Case No. Age /Gender/ Date of ET diagnosis	Cardiovascular risk factors	*Haematocrit* (%) at PV diagnosis	neurological complications		*Haematocrit* (%) at the time of cerebrovascular events	*Treatment*	
			neurological presentation	CT/MRI finding/s		*after the diagnosis of PV*	*after the first cerebrovascular event*
CASE 1 72/M/2005	hypertension, hyperlipidaemia, obesity	53	2011: VBI	CT: mild cerebral atrophy medium-sized chronic ischaemic white matter lesions	42	aspirin + phlebotomy	clopidogrel + phlebotomy
CASE 2 64/M/2010	hypertension, hyperlipidaemia, diabetes mellitus	57	2011: VBI	CT: no pathological lesion MR: mild chronic ischaemic white matter lesions	47	aspirin + phlebotomy	clopidogrel + hydroxyurea
CASE 3 70/M/2008	hypertension, hyperlipidaemia, MTHFR 677T homozygote polymorphism (with actually normal homocystein level)	64	2011: left ACM ischaemic stroke (mild) dementia (mixed) 2011: left hermispheric haemorrhagic stroke	CT (05/2011): mild cerebral atrophy, lacunes in the left basal ganglia, mild chronic left-sided ischaemic white matter lesions CT (11/2011): acute parenchymal haemorrhage (3x6 cm) in left parieto-temporal region (at that time the patient was on anticoagulant therapy because of AF); left ACM stenosis	45	aspirin+ phlebotomy+ *(warfarin because of AF)*	aspirin + hydroxyurea + *anticoagulant therapy (with a low-therapeutic INR value)*
CASE 4 79/M/2001	hypertension	62	2008: vertigo –VBI susp.	CT: mild cerebral atrophy, some lacunes in the basal ganglia, mild chronic ischaemic white matter lesions	57	aspirin + phlebotomy+ hydroxyurea	aspirin + phlebotomy+ hydroxyurea
CASE 5 53/M/2003	hypertension, hyperlipidaemia, obesity	59	2007: VBI 2010: VBI	CT: not available CT: mild cerebral atrophy	41	aspirin + phlebotomy	aspirin + phlebotomy + hydroxyurea +pentoxifylline
CASE 6 65/M/2011	hypertension, diabetes mellitus	53	2013: right ACM stroke (mild)	CT: acute infarct (2x2 cm) in white matter on the right side	41	phlebotomy	*(marfarin because of AF)*
CASE 7 76/M/2006	hypertension, obesity	56	2012: left ACM stroke (mild)	CT: medium sized cerebral atrophy. Chronic periventricular white matter lesions	42	aspirin + hydroxyurea + *(syncumar because of AF)*	clopidogrel + *(syncumar because of AF)*
CASE 8 57/M/2008	hypertension, hyperlipidaemia, diabetes mellitus, obesity	45	2008: right ACM stroke (mild), 2010: worsening of chronic neurological signs (dysarthria)	CT (2008, 2010): cerebral atrophy, lacunes in the basal ganglia, extensive chronic ischaemic white matter lesions	44	aspirin	clopidogrel
CASE 9 52/F/1998	hypertension, PAD	46	2004: TIA (VBI)	CT: negative	57	hydroxyurea+ aspirin+ *(syncumar)*	hydroxyurea +clopidogrel+ *(syncumar)*
CASE 10 77/M/2012	hypertension	66	2012: serious haemorrhagic right ACM stroke and death	CT: right-sided space-occupying haemorrhage in the basal ganglia with intraventricular extension Chronic white matter lesions.	42	aspirin	
CASE 11 54/F/2013	hypertension, hyperlipidaemia, obesity	47	2014: vertigo - VBI	CT: not available	41	aspirin	clopidogrel

Abbreviations: AF, Atrial fibrillation; *ACM*, Arteria cerebri media; *F*, female; *M*, male; *MCA*, middle cerebral artery; *PAD*, peripheral arterial disease; *PCA*, posterior cerebral artery; *PV*, polycythaemia vera TIA, transient ischemic attack; *VBI*, vertebrobasilar insufficiency

Results

One or more cerebrovascular events were observed and the documentation was sufficiently detailed for an adequate analysis in 11 of the 108 patients: 9 males and 2 females with a median age of 65 years [range: 52–79 years]. Ten (91%) of the 11 analysed cases were positive for the *JAK2 V617F* mutation. Most of the patients (8/11, 72%) presented at least two serious conventional vascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and obesity). At the time of the cerebrovascular events, almost all the patients were already on anti-platelet therapy, alone or in combination with cytoreductive therapy (e.g. hydroxyurea) or had undergone phlebotomy (Table 1).

The mean platelet count at the time of PV haematological diagnosis was 387 G/L [range: 111–843 G/L], whereas a lower platelet count was observed during the cerebrovascular complications: 270 G/L [range: 118–451 G/L]. Similarly to the platelet count changes, the mean haematocrit level was also decreased at the time of the cerebrovascular complication after the introduction of the haematological treatment (45% [range: 41–57%]) as compared with the mean haematocrit measured at the PV haematological diagnosis, 55% [range: 45–66%]. The mean haemoglobin count at haematological diagnosis was 176 g/L [range: 145–212 g/L], but was also decreased during the cerebrovascular thrombotic complications: 146 g/L [range: 125–172 g/L]. The mean leukocyte count at haematological diagnosis was 13 G/L [range: 5–24 G/L], which persisted (13 G/L [range: 5–25 G/L]) during the cerebrovascular thrombotic complications after the introduction of the haematological treatment.

In most of the cases (7/11 patients, 63%), chronic ischaemic white matter lesions were seen on brain CT at the time of the neurological complications. Mild cerebral atrophy was also frequent. The clinical presentation was predominated by lacunar syndromes or a vertebro-basilar insufficiency. There were 2 patients with apoplexia, one of whom was on anticoagulant therapy (with a low-therapeutic INR value) (Table 1). Overall, the above data allow the supposition that PV predisposes to small vessel cerebral disease, presenting in most cases with lacunar syndromes, even if most of the patients also had additional vascular risk factors.

Discussion

The presence of cerebrovascular complication in this cohort was 10.2% (11/108) which was markedly higher than the incidence of stroke reported earlier in the general population in Hungary (2/1000 in the age range 45–54, 3/1000 between 55 and 64, and 3–13/1000 above the age of 65 years in 2005) [10].

The relevant literature suggests that, besides the quantitave changes in the blood elements , that may have a role in blood hiperviscosity, the qualitative abnormalities (prothrombotic phenotype of red blood cells, thrombocytes and leukocytes) can together be responsible for the increased tendency to thrombosis in these patients [1]. However, as concerns PV-related cerebrovascular events, detailed laboratory studies are still limited. It has been reported that even haematocrit levels around the upper limit of the normal range could be an important factor in occlusive vascular diseases, and especially involving the cerebral circulation [1, 11]. An investigation of the cerebral blood flow in transgenic mouse models by means of two-photon excited fluorescence microscopy revealed that the fraction of capillaries with stalled flow increased when the haematocrit value exceeded 55% in PV mice, and interestingly the majority of the stalled vessels contained stationary red blood cells [12]. The current study revealed that PV patients have already undergone haematological treatment when they exhibited a stroke, transient ischaemic attacks and vertebrobasilar insufficiency at a mean 45% [range: 41–57%] haematocrit level. Among these patients, leukocytosis was observed at the time of the cerebrovascular complications despite the ongoing haematological treatment. Most of the current patients presented at least two serious conventional vascular risk factors such as hypertension, hyperlipidaemia, diabetes mellitus and obesity. Our findings lead us to suppose that, besides the previously reported quantitative changes and qualitative abnormalities in the blood elements in PV, other vascular risk factors could additionally contribute to the vascular complications in these patients.

Conclusions

Our results suggest that the best treatment to protect PV patients from thrombotic events is to give serious consideration to the overall vascular risk factors, which necessitates the close cooperation of the haematologist and other specialists in vascular medicine. The above data, permit the supposition that PV predisposes to small vessel cerebral disease, presenting in a majority of the cases with lacunar syndromes, even if most of the patients exhibit additional vascular risk factors.

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Compliance with Ethical Standards

Conflicts of Interest None declared.

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