

## Neurological disorders in essential thrombocythemia

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### ABSTRACT

Patients with essential thrombocythemia often complain of various subjective neurological symptoms. This prospective study aims to assess their incidence and response to therapy. Among 37 consecutive patients with essential thrombocythemia, 11 presented with neurological symptoms. Among them 4 had thrombotic events, 7 complained of transient or fluctuating subjective symptoms, and one had both. Brain magnetic resonance imagery failed to detect any substratum in patients with subjective symptoms. JAK2V617F mutation was found in 9 of 11 patients with neurological symptoms versus 14 of 26 patients without symptoms. Ten patients received low-dose aspirin for these symptoms: complete resolution was observed in 3, improvement with persisting episodes in 2, and resistance to aspirin in 2 patients, in whom addition of cytoreductive therapy became necessary to resolve those disabling symptoms.

In this prospective cohort, 30% of patients with essential thrombocythemia presented neurological symptoms. Aspirin was fully efficient in only 30% of cases. JAK2V617F mutation could be a risk factor for such symptoms.

Key words: essential thrombocythemia, stroke, cerebrovascular disease, magnetic resonance imaging, JAK2V617F

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### Introduction

Essential thrombocythemia (ET) is an acquired myeloproliferative neoplasm (MPN) characterized by an expansion of the megakaryocytic lineage, leading to an isolated elevation of platelets.<sup>1</sup> ET is often asymptomatic, but can also be revealed by vascular occlusive events or hemorrhagic manifestations.<sup>2,4</sup> The recently identified acquired JAK2V617F mutation in the Janus kinase 2 (JAK2) rapidly became the first molecular marker of Philadelphia-negative chronic MPN, found in about 60% of ET patients.<sup>5</sup> The presence of this mutation, especially in a homozygous state, seems to increase the risk of thrombosis.<sup>6-8</sup>

Transient ischemic attack (TIA),<sup>9</sup> stroke or cerebral venous thrombosis may complicate ET.<sup>10-12</sup> However, in patients with ET, the majority of neurological symptoms are transient and subjective, e.g. blurry vision, headache, tinnitus, dizziness.<sup>13,14</sup> Such manifestations have been frequently (20-55% of patients) reported in ET although these figures should be interpreted with caution since they have been only obtained in retrospective studies.<sup>14,15</sup> The etiology of these neurological symptoms and risks factors for their development are not known.<sup>1</sup> One could suspect a role for microvascular occlusion since anti-

aggregation is known to be efficient in treating these symptoms, but no magnetic resonance imaging (MRI) study has documented this hypothesis.<sup>12</sup> Finally, the impact of the JAK2V617F mutation on the frequency of neurological symptoms has not so far been assessed.

We describe the neurological symptoms that occurred in a series of 37 consecutive ET patients. We aimed to prospectively identify clinical and biological characteristics associated with neurological symptoms, and to detect possible abnormalities of cerebral perfusion with MRI. We also assessed the response of neurological symptoms to therapy.

### Design and Methods

From January 1<sup>st</sup> 2008 to June 30<sup>th</sup> 2009, all new patients managed in our center with a diagnosis of ET according to World Health Organization criteria were included in the study.<sup>16</sup> JAK2V617F mutation was detected by a single nucleotide polymorphism genotyping assay performed in DNA samples extracted from purified granulocytes using real-time PCR-based mutation detection (Taqman® ABI Prism 7700) as previously described.<sup>3</sup>

In all patients, the first known date of platelet elevation and date of onset of aspirin (ASA) and/or cytoreductive treatment during the

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study period were recorded. The status of vascular risk factors was assessed in all patients: smoking, alcoholism, diabetes mellitus (fasting plasma glucose level >7.0 mmol/L), hypertension (blood pressure >140/90 mmHg or antihypertensive treatment), serum cholesterol (LDL cholesterol >4.1 mmol/L), Body Mass Index over 30, history of cardiac or cerebral ischemic event.

All the patients with neurological symptoms were referred to the neurologist and had a complete neurological examination. Neurological thrombotic symptoms were defined as stroke, TIA or cerebral venous thrombosis. Other neurological symptoms were also recorded: headache, tinnitus and dizziness, visual disturbance, and others. A complete blood count (CBC) was recorded in all patients at time of ET diagnosis, and at time of onset of the neurological symptoms. Patients with neurological symptoms were investigated with brain MRI, including perfusion time-to-peak (TTP) weighted images when possible. Cardio-vascular exploration (trans-thoracic echocardiography and supra-aortic echosonography) was also performed in patients presenting true thrombotic symptoms.

This study was approved by the PV-Nord institutional review board, and patient informed consent was obtained in accordance with the Declaration of Helsinki.

### Statistical analysis

Non-parametrical variables were presented as median (with range). Qualitative variables were presented as absolute and relative frequencies. Comparisons between categorical variables were tested by  $\chi^2$  or Fisher's exact tests.

## Results and Discussion

From January 1<sup>st</sup> 2008 to June 30<sup>th</sup> 2009, 37 new patients with a diagnosis of ET were seen at the Hôpital Avicenne. Among them, 13 were subsequently referred to the neurologist for evaluation of neurological symptoms. Two patients had a long history of migraine-like manifestations before ET diagnosis. As characteristics of the headaches were not modified after ET diagnosis, these patients were excluded from this study. Symptoms found in the 11 remaining patients are presented in Table 1.

### Description of neurological symptoms

A cerebral thrombotic event (first disease manifestation leading to ET diagnosis) was recorded in 4 of the 11 patients (Table 1). One patient presented persistent headache during diagnostic workup of portal vein thrombosis, leading to the subsequent discovery of a cerebral venous thrombosis (CVT) by MRI. Three other patients had transient symptoms, lasting from a few seconds to 15 min, diagnosed as TIA:<sup>9</sup> aphasia, amaurosis fugax and left hemiparesis. Two of these 3 patients had associated cardiovascular risk factors.

Subjective symptoms were recorded in 8 patients, chronic cephalalgia being the most frequent (Table 1). Cephalalgia had no particular characteristics, and patients did not describe any "aura like" episode before headache. The second most frequent neurological manifestation was transitory dizziness. Episodes were very brief, lasting from a few seconds to a few minutes. Two patients described bilateral visual disturbances, and one patient reported transient brief loss of consciousness without evidence of a triggering factor. All the patients had normal neurological examination. In all the cases, semiology was atypical and could not be attributed to well defined syndromes.

### Imaging and laboratory investigations in patients

### presenting with neurological symptoms

Brain MRI was performed in 9 of 11 patients at time of neurological symptoms, including perfusion analyses in 7 of 11 (Table 1). Of note, all patients were already treated with ASA for a few days but still had neurological symptoms at time of MRI. In all but 2 patients, MRI was normal. In one patient described above, a left transverse sinus thrombosis was discovered. In the second patient, MRI showed a small sequela of a cerebellar infarct. This patient had complained of fluctuating dizziness one year before the MRI was carried out. This image was considered to be unrelated to the clinical symptoms, because the patient had experienced episodes of fluctuating dizziness over one year, and the infarct was small and located in the cerebellar hemisphere. In the 3 patients who had TIA, cardiac transthoracic and supra-aortic echography and ultrasonography were performed. No cardiovascular etiology was confirmed.

### Evolution of neurological symptoms during therapy

Among the 11 patients with neurological symptoms, 3 (including 2 with fluctuating dizziness and one with chronic cephalalgia) were already receiving an anti-aggregating agent at time of neurological symptoms. In the 8 remaining patients, one was excluded from assessment of the impact of low-dose aspirin (ASA) on neurological symptoms because she was already on anticoagulant treatment and did not receive ASA. ASA (100 mg/day) was started in the 7 other patients. In 3 of those 7, neurological symptoms rapidly resolved with ASA only. In 2 patients, symptoms significantly improved, but transient episodes persisted. In the remaining patients, ASA treatment had no efficacy on the neurological symptoms, which subsequently resolved when platelet count was normalized after the addition of a cytoreductive treatment. In these last 4 patients, in whom ASA alone was not fully efficient, combination of 2 anti-aggregating agents (aspirin plus clopidogrel) was prescribed in 3 patients without further improvement in their neurological symptoms.

Altogether, with respect to neurological symptoms, ASA treatment could be evaluated in 10 patients, and induced complete response in 3, partial response in 2, and failed in 5 patients, respectively. Combination therapy with ASA and a cytoreductive agent induced a complete response in both of 2 patients.

**Table 1.** Neurological symptoms in ET patients (some patients >1 symptom).

Neurological symptoms	N. patients	N. MRI performed and results	N. MRI with perfusion images and results
Thrombotic symptoms	4/11	4	3
Transient ischemic attack	3	Normal in 3	Normal in 2
Cerebral venous thrombosis	1	CVT in 1	CVT in 1
Others	8/11	6	5
Cephalalgia	5	Normal in 5	Normal in 5
Dizziness, instability, tinnitus	5	sequela of stroke in 1	
Visual disturbances	2		
Loss of consciousness	1		
Associated vascular events	2/11	NA	NA
Portal vein thrombosis	2		

CVT: cerebral venous thrombosis; NA: not applicable.

### Predictive risk factors for neurological symptoms

In the total cohort of 37 patients, we compared those presenting neurological symptoms (11 of 37) with those without neurological symptoms (26 of 37). The characteristics of both groups are shown in Table 2.

There was no significant difference between the two groups with respect to age, gender, associated cardiovascular risk factors, hemoglobin, platelet and leukocyte counts at time of ET diagnosis. The JAK2V617F mutation was found in 9 of 11 (82%) patients with neurological symptoms *versus* 14 of 26 (54%) in patients without symptoms ( $P=0.11$ ).

Overall, we found that 30% of the patients in this prospective unselected cohort who were referred to the hematologist for a diagnosis of ET presented neurological symptoms. This high proportion of neurological symptoms in ET patients is in agreement with previous retrospective studies, which reported such symptoms in 20-63% of ET patients.<sup>12-15,17</sup> A transient or fluctuating evolution, and an imprecise semiology characterized neurological symptoms in our ET patients. Except for 4 of 11 patients who had thrombotic events, which are classical complications of ET,<sup>10-12,18</sup> most of the patients presented with various functional symptoms, including headache, dizziness, and visual disturbances. Such atypical presentation raised the question of somatoform disorders. However, the high proportion of patients complaining of these symptoms, along with cases of improvement after treatment with anti-aggregating agents does not support this hypothesis. Such symptoms are now recognized and may even be quantified using a validated self-assessment form recently developed for MPN patients.<sup>19</sup>

It should be stressed that these ET-related symptoms differ from what is known as the hyperviscosity syndrome that is observed in polycythemia vera or hypergammaglobulinemia, and includes headaches, vertigo, and paresthesia.<sup>20</sup> The pathophysiological mechanisms underlying the neurological symptoms in ET are not fully understood. Platelet activation and aggregation in arterioles have been shown to be responsible for peripheral manifestations, such as erythromelalgia in ET.<sup>14,21</sup> Of note, systematic MRI studies have never been carried out in ET patients with neurological symptoms. Interestingly, we did not find any abnormalities in these patients using the imaging techniques currently available in clinical practice, including MRI with perfusion weighted images. This might be explained by the limited sensitivity of MRI to identify microthrombotic events, and suggests that routine imaging is of little value for the diagnosis of neurological symptoms in these patients.

Anti-aggregating agents, mainly aspirin, are known to improve symptoms related to microvascular disturbances in ET and are largely prescribed in that setting, sometimes even in asymptomatic patients as a primary vascular event prevention. With respect to the central nervous system, previously published studies led to conflicting results. Michiels reported no relapse of neurological events after introduction of ASA in a series of 17 patients,<sup>22</sup> while in Jabaily's cohort, 6 of the 29 neurological events occurred in ASA-treated patients.<sup>13</sup> Our study provides new data that may help refine treatment recommendations, as only 50% of the patients clearly benefited from ASA treatment. Furthermore, combination of 2 anti-aggregating agents (aspirin and clopidogrel) appeared to be of little benefit. In 2 patients, neurological symptoms only resolved when a

**Table 2.** Characteristics of patients with essential thrombocythemia at diagnosis (n=37).

	ET with neurological symptoms (n=11)	ET without neurological symptoms (n=26)
Median age at ET diagnosis	47	58
Vascular risk factors (diabetes mellitus, smoking, systemic hypertension, cholesterol)	3/11 (27%)	6/26 (23%)
Sex ratio	7F/4M (64%)	18F/7M (72%)
Platelet count ( $\times 10^9/L$ )		
Median at ET diagnosis	860	750
Median at onset of neurological symptoms	700	/
Hemoglobin (g/dL)		
Median at ET diagnosis	14.5	13.9
Median at onset of neurological symptom onset	15.7	/
Leukocytes ( $\times 10^9/L$ )		
Median at ET diagnosis	7.8	8.6
Median at onset of neurological symptoms	8.1	/
JAK2V617F mutation	9/11 (82%)	14/26 (54%)

F: female; M: male.

cytotoxic treatment for ET was added. These data suggest that cytoreductive therapy should be considered in ET patients already treated with aspirin and who develop disabling neurological disorders regardless of their risk category, a clinical indication that was overlooked in the recently published international MPN management guidelines.<sup>23</sup>

A trend for higher prevalence of the JAK2V617F mutation was found in patients with neurological symptoms than in patients with no symptoms, but the difference did not reach significance, possibly due to the relatively limited number of patients. This is in line with the fact that this mutation is a potential risk factor for thrombosis in ET,<sup>6-8</sup> but no study has focused specifically on neurological symptoms. In this study, no other risk factor for the development of neurological symptoms could be identified among demographic, clinical or biological data. In particular, a high platelet count was not associated with the occurrence of neurological symptoms, in agreement with studies assessing risk factors for vascular events in ET.<sup>24</sup> Of note, Kesler reported a significant predominance of females in patients with neurological symptoms,<sup>17</sup> but this observation was not confirmed in our series.

In conclusion, in this prospective study of 37 consecutive ET patients, the incidence of neurological symptoms was 30%. Brain MRI was always normal in patients with subjective symptoms suggesting that MRI is not useful in the baseline evaluation of ET patients with atypical neurological symptoms, after careful exclusion of focal neurological deficits. Response to ASA was heterogenous, only 30% of patients experiencing resolution of their symptoms. Addition of cytoreductive therapy should be considered in such patients. JAK2V617F mutation could be a risk factor for developing neurological symptoms in ET; an observation that needs to be confirmed in a larger cohort of patients.

## Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with

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