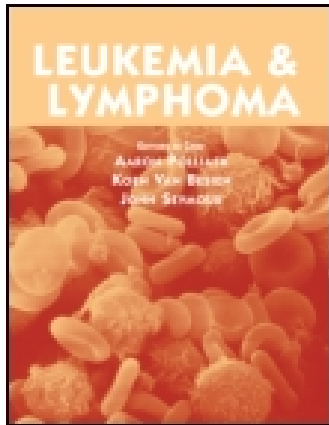


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Atypical Transient Ischemic Attacks in Thrombocythemia of Various Myeloproliferative Disorders

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Neurological symptoms of transient unsteadiness, dysarthria, dysphasia, dysbasia, transient mono- or hemiparesis, hemiparesis, scintillating scotomas, amaurosis fugax, vertigo, dizziness, migraine accompaniments, syncope and seizures were the presenting manifestations of thrombocythemia in various myeloproliferative disorders. Erythromelalgia preceded or followed the neurologic ischemic attacks. The neurologic and ocular attacks usually had a sudden onset, lasted for a few seconds to several minutes and occurred independently or sequentially rather than simultaneously. This clinical syndrome is caused by platelet-mediated ischemic and thrombotic processes in the end-arterial microvasculature and reflects the existence of a platelet dependent and aspirin responsive arterial thrombophilia in thrombocythemia as novel disease entity, which confirms and elucidates Mitchell's hypothesis

KEY WORDS: Erythromelalgia migraine amaurosis fugax transient ischemic
attacks aspirin thrombocythemia

INTRODUCTION

Mitchell first described erythromelalgia (erythros=red, melos = extremity and algos = pain) as burning painful and red congested extremities, which should not be confounded with red and painful extremities in rheumatoid arthritis.¹ Typical cases suffered from episodes of burning distress and red congestion in one or more toes and fore foot sole, which progressed to unbearable burning pain and acrocyanotic ischemia or even gangrene. Longterm clinical courses in Mitchell's cases were complicated by attacks of vertigo, amnesia, dysarthria, transient hemiparesis, stroke and seizures.¹ Based on this broad spectrum of clinical manifestations Mitchell stated that: "Whether or not I am correct in suspecting that they

may represent stages of one malady can only be determined by future research: but with this word in caution and reserve there can be no harm in calling attention to them as members of one genus".¹

Smith and Allen discovered that in their patients with erythromelalgia complete relief of burning pain for several days was obtained by a single dose of aspirin.² The aspirin responsive erythromelalgia appeared to be tightly linked to chronic myeloproliferative disorders, where due to thrombocythemia platelet-mediated inflammation, vascular changes and thrombotic occlusions occur in the acral end-arterial microvasculature leading to erythromelalgia and acrocyanotic ischemia.^{3,4,5} The diagnostic longlasting effect of a single low dose of aspirin is explained by its irreversible effect on platelet cyclo-oxygenase activity.⁴ Accumulating clinical and experimental evidence indicate that thrombocythemia is the causative underlying disorder not only for erythromelalgia, a microvascular thrombotic disease of the extremities, but also for arterial vas-

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cular disease involving the cerebral and coronary arterial circulation.⁶⁻¹⁵

In the present neurological study evidence is produced in favor of Mitchell's hypothesis that the spectrum of erythromelalgia, its microvascular ischemic complications and the association with migraine accompaniments and cerebral ischemic manifestations are the consequence of one common pathogenetic pathway of platelet-mediated sludging and ischemic, thrombotic processes in the end-arterial circulation in patients with thrombocytopenia as the causative denominator.

METHODS

Clinical, hematological and hemostatic data were obtained routinely. According to the criteria of the Polycythemia Vera Study Group, the diagnosis of essential thrombocythemia is one of exclusion.¹⁶ The Rotterdam diagnostic criteria of thrombocythemia as determined by careful documentation of peripheral blood and bone marrow specimens are a persistent increase of platelet count in excess of $400 \times 10^9/L$ and an increase of clustered mature megakaryocytes in bone marrow biopsy material in the absence of any sign or cause for reactive thrombocytosis. Confirmative criteria for thrombocythemia were an elevated score for the leukocyte alkaline phosphatase stain, the presence of fine or coarse reticulin fibers in bone marrow biopsy material, and slight hematopoietic splenomegaly on scan.

The neurological manifestations were reviewed by an experienced neurologist (PJK).

CASE REPORTS

Case 1

A 40-year-old man suffered in 1982 since 3 years from burning acroparesthesias and episodes of flickering scotomas, blurred vision and/or amourosis fugax lasting for about half an hour, usually followed by severe migraine and frequently complicated by unstable gait, which compelled the patient to sit or to lay down for a few hours rest. Essential thrombocythemia was diagnosed. Because of a documented aspirin allergy¹⁷ the patient was treated with busulfan to reduce the increased platelet counts to normal values. Maintained remission of thrombocythemia for 4 years was associated with no recurrence of symptoms. A symptomatic relapse of essential thrombocythemia in 1987 was again effectively treated with busulfan and the patient retired from further follow up. Since 1990 the patient again suffered from episodes of

flickering scotomas and blurred vision for about 15 minutes, followed by severe migrainous headache up to a frequency of 5 times a week at platelet counts of $700 \times 10^9/L$. In July 1994 a sudden attack of transient hemiparesis of the right arm for a few minutes was followed by unstable gait and an attack of typical migraine with flickering scotomas, blurred vision and aching headache. Two weeks later, transient paresis of both arms and unstable gait was not followed by migraine.

Case 2

A 64-year-old woman suffered since 10 years from essential myelofibrosis of the bone marrow and progressive splenomegaly. Splenectomy of a large spleen, 4.000 gram showing extramedullary hematopoiesis, was complicated by deep venous thrombosis of the left leg. Two to three months after splenectomy while on adequate oral anticoagulation she first suffered from severe progressive and disabling asymmetric burning pain in both feet, most severe in the right fore foot sole and toes. The sole of the right fore foot and toes were red, swollen, warm and extremely painful and interpreted as of unknown origin. At this time postsplenectomy thrombocythemia had developed. Treatment with paracetamol was unsuccessful. However low dose aspirin completely relieved the burning distress and inflammatory symptoms consistent with erythromelalgia. After correction of platelet count to normal by busulfan treatment and subsequent discontinuation of aspirin the erythromelalgic distress did not recur.

Case 3

A 66-year-old woman presented with a single episode of transient paresis of the left arm lasting for a few hours associated with dysarthria, which did not recover completely. Duplex scanning of the carotid arteries revealed a small plaque in the right carotid bulb without stenosis. Computer tomography of the brain showed left occipital and right parietal small diffuse hypodensity. However, these CT findings were not consistent with the clinical symptoms. Laboratory investigations of peripheral blood and bone marrow were compatible with essential thrombocythemia. While on low dose aspirin 30 mg per day for 4 years no recurrences of ischemic attacks did occur.

Case 4

A 66-year-old healthy man complained since one year of blurred vision for a few minutes, painful finger tips of the left hand, and two attacks of poorly localized cerebral symptoms of unstable gait and sudden falling without loss of consciousness or weakness. In addition he

recently suffered from red burning painful and swollen soles of the fore feet, the left middle toe and the right middle and little toe. As all painful symptoms in the extremities completely disappeared by one low dose aspirin for two days classical erythromelalgia was diagnosed as the presenting symptom of thrombocythemia in polycythemia vera (PV) (hemoglobin 11.9 mmol/l, hematocrit 0.57 and platelets $681 \times 10^9/l$). Polycythemia vera was treated with regular bloodletting keeping the hematocrit below 0.45, but the persistent painful distress in the extremities only resolved by treatment with low dose aspirin once a day.

Case 5

A 38-year-old man suffered since 1992 from migraine associated with blurred vision, blind spots in the visual fields followed by pulsatile headache. Recurrent attacks of hemiparesis of the right arm for several minutes and attacks of dysarthria for a few minutes did occur independently.

In 1993 he first suffered from episodic burning acroparesthesias in the soles of the fore feet in particular after a long walk. In 1994 and early 1995 burning pain in fore feet and toes progressed to a disabling distress complicated by acrocyanosis. The burning and disabling distress completely relieved by low dose aspirin 100 mg per day.

Case 6

A 44-year-old healthy women presented with an acute attack of aphasia and right hemiparesis. The hemiparesis recovered after 3 days and the aphasia ameliorated after 10 days. CT scanning of the skull revealed a left frontoparietal infarction of the left medial cerebral artery. A slight right facialis paresis, minor motoric disturbances of the right extremities and dysarthria persisted. While on aspirin for 3 years no recurrences of ischemic events did occur.

RESULTS

The clinical and hematological findings in the presented patients with thrombocythemia of various myeloproliferative disorders are summarized in table 1. The clinical manifestations were acroparesthesiae, erythromelalgia, migraine accompaniments, followed by focal transient cerebral ischemic attacks (TIA) in one, erythromelalgia in one, erythromelalgia followed by atypical TIA's in one, atypical TIA's in one, aphasia and hemiparesis in one and migraine accompaniments followed by atypical TIA's subsequently by erythromelalgia in a sixth case.

Platelet counts were between 477 and $960 \times 10^9/L$ (mean $677 \times 10^9/L$) at time of symptoms.

Paracetamol in 3 cases, adequate oral anticoagulation in case 2 and bloodletting in case 4 were ineffective. Acroparesthesias and erythromelalgia disappeared after daily intake of low dose aspirin in 4 cases. While on continuous low dose aspirin no recurrences of ischemic events were observed. Indomethacin 25 mg 3dd in case 1 with aspirin allergy abolished the symptoms of erythromelalgia, migraine accompaniments and prevented the recurrence of ocular symptoms and TIA's. Busulfan induced and maintained remissions of thrombocythemia with platelet counts below $400 \times 10^9/L$ and discontinuation of indomethacin and aspirin in case 1 and 2 were not associated with recurrence of symptoms. Thrombotic risk factors of smoking hypertension, diabetes, hypercholesterolemia and a family history of arterial thrombosis were absent. Antigen concentration and functional values for antithrombin, proteine C and S, APC-cofactor, lupus anticoagulant and anticardiolipine titers were normal.

Case reports from the literature

The specific clinical manifestations of essential thrombocythemia in 12 reported case histories from the literature are summarized in table 2.¹⁸⁻²⁵ The neurologic symptoms were poorly localized cerebral symptoms of unsteadiness, unstable gait or attacks of sudden falling down without loss of consciousness in 4, dysarthria in 4 and aphasia or organic psychosyndrome in 2. Focal cerebral symptoms of TIA or hemiparesis was recorded in 3. Focal transient visual symptoms were amaurosis fugax of one or two eyes in 4. Global visual symptoms of scintillating scotomas or blurred vision occurred in 5 patients. Syncope in one and seizures in another case were observed. Painful acroparesthesias in fingers feet and toes suspicious for erythromelalgia preceded the neurologic symptoms in 3 cases. (Table 2)^{20,21}

Platelet counts at time of symptoms were between 615 to $1000 \times 10^9/L$ in 6 and between 1000 to $2361 \times 10^9/L$ in another 6 patients. (Table 2)

Coumadin was ineffective in one case, who became asymptomatic after reduction of platelet counts to $206 \times 10^9/l$ by treatment with busulfan. Longterm low dose aspirin treatment was effective in two cases.^{18,24} No data on treatment and outcome was available in other 9 cases.

DISCUSSION

The differential diagnosis of burning feet includes the various hyperalgesic neuropathies (diabetes, alcoholism,

Table 1 Presenting symptoms, hematological findings and outcome of treatment in 6 patients with thrombocytopenia of various chronic myeloproliferative Disorder

Case	M/F	Age	Presenting Symptoms	Hematological Diagnosis	Platelets $\times 10^9/L$	Bone Marrow			Outcome of treatment
						Cell.	Mega.	Retic.	
1	M	40	Erythromelalgia Scotomas, amourosis fugax, migraine accompaniments	Essential Thrombocytopenia	890	N	↑	↑	Paracetamol – Busulfan* +
		52	TIA + Migraine scotomas	Relapse of Essential Thrombocytopenia	710	N	↑	↑	Indomethacin +
2	F	64	Erythromelalgia	Essential Myelofibrosis Postsplenectomy Thrombocytopenia	960	↑	↑↑	↑↑↑	OAC* – Paracetamol – Aspirin 100mg + Busulfan +
3	F	66	Monoparesis left arm Dysarthria	Essential Thrombocytopenia	484	N	↑↑	↑↑	Aspirin 30 mg +
4	M	66	Erythromelalgia Blurred vision Unsteadiness	Polycythemia vera Thrombocytopenia	681	↑	↑↑	↑	Bloodletting – Paracetamol – Aspirin 100 mg + Aspirin 100 mg +
5	M	38	Attacks of migraine scotomas followed by pulsatile headache. Attacks of transient paresis of the right arm for about 5 minutes. Attacks of dysarthria. Erythromelalgia	Essential Thrombocytopenia	477	N	↑	N	Aspirin 100 mg +
6	F	44	Acute attack of aphasia and right hemiparesis, which slowly recovered after 3 days. On CT-scan infarction of the left medial cerebral artery	Essential Thrombocytopenia	541	N	↑↑	↑	Aspirin 100 mg +

Busulfan* = busulfan induced remission of thrombocytopenia with platelet counts of less than $400 \times 10^9/L$; OAC = Oral anticoagulation with acenocoumarol; Cell. = cellularity; Mega. = megakaryocytes; Retic. = reticulins fibers; – = ineffective; + = complete relief of erythromelalgia and no recurrences of ischemic events.

Fabry's disease), reflex sympathetic dystrophy, the ischemic blue toe syndrome, erythromelalgia and erythromelalgia.^{26–30} Recognition of erythromelalgia is particularly relevant in the evaluation of peripheral neuropathies, which it may mimic.^{27–30}

Acroparesthesias, migraine-accompaniments and atypical transient ischemic attacks frequently remain unrecognized to be causally related to thrombocytopenia as the underlying disorder because of unfamiliarity with this relationship. The presented case reports (table 1 and 2) show that in essential thrombocytopenia erythromelalgia may precede or follow atypical focal or diffuse cerebral ischemic events and ocular manifestations at rather low platelet counts in excess of $500 \times 10^9/L$. In an elegant study of 33 patients with unequivocal primary thrombocytopenia and platelet counts in excess of $1000 \times 10^9/L$,

21 had neurologic symptoms that included transient ischemic attacks, stroke, headache, dizziness, visual disturbances and seizures.¹¹ Aspirin and reduction of platelet count to below $600 \times 10^9/L$ were reported to be effective. However, acroparesthesias, headache, dizziness, vertigo, scotomata, syncope and seizures did recur already at relapse of thrombocytopenia with platelet count between 494 to $792 \times 10^9/L$ in 6 patients.¹¹ In a recent study, 22 patients with essential thrombocytopenia presented with focal symptoms of transient monocular blindness, transient mono- or hemiparesis, and migraine-accompaniments in 11 and non-focal symptoms of transient postural instability, dysarthria and scintillating scotomas in 14.¹³ The transient ischemic attacks and visual symptoms in essential thrombocytopenia all had a sudden onset, lasted for a few seconds to several minutes

Table 2 Presenting symptoms and specific findings in 12 cases with essential thrombocythemia from the literature

<i>Author</i>	<i>Age/year</i>	<i>F/M</i>	<i>Clinical manifestations</i>	<i>Platelets × 10⁹/L</i>	<i>Comments</i>
1. Olivarius 1959	58	M	Several attacks of a few minutes with sudden weakness and lack of control of the right arm Sudden attacks of right hemianesthesia for 5 minutes Complete blindness of the left eye for 5 minutes	1.332–2.361	Cerebral attacks possible being the result of emboli of agglutinated platelets
2. Levine 1968	40	F	Attacks of monocular blindness Sudden flickering lights associated with decreased vision in the right eye for 15 minutes Sudden attacks of diplopia, clouding vision (3 minutes) followed by persistent headache, which was relieved by aspirin Scintillating scotoma	615–683	Slight splenomegaly Coumadin ineffective Myleran → platelets 206 and symptom free
3. Singer 1969	37	M	A slight and a serious attack of aphasia Repeated attacks of temporary blindness in the right eye, occurring on an average of 3 to 4 times a week, lasting for 2 to 3 minutes	1.144	Non-occlusive emboli in the retinal arteries migrating to the periphery on funduscopy during an attack of amaurosis fugax
4. Koreman 1969	40	F	Pain and cyanosis in feet and hands Episodes of syncope and extreme weakness of the right arm Dysarthria, aphasia and right hemianopsia	1.500 750	
5. *	69	M	Painful soles of both feet Organic mental syndrome and no evidence of focal neurological findings	1.178–1.200	
6. *	56	M	Left hemiparesis. 2 episodes of twitching left arm	980–1.086	
7. *	81	M	Falling down apathia, drowsy and mild right leg paresis. Right homozygous hemianopsia	1.700–2.044	
8. *	76	M	Daily intermittant right facial pain	996	Palpable spleen
9. Mundall 1972	63	F	Numbness of the right hand and 4 episodes of transient left monocular blindness Several very brief episodes of sparking lights Numerous episodes of bright white flashes of light “like fireworks” in the left eye Episodes of left monocular blindness for about 1 minute up to 15 times a day	625	Longterm Aspirin effective
10. Bousser 1980	63	M	Three attacks of transient paresis of the left arm for 5 minutes followed by pulsatile frontal headache Bilateral blurred vision, unstable gait and dysarthria, preceded or followed by bilateral frontal headache	797	
11. Delangre 1985			Painful hand and feet Paresthesias—Headache Impairment of gait Scotoma	839–1.105	CT Right superior Cerebellar Ischemia Heparine ineffective Aspirine effective Hydroxyurea → platelets Normal for 2 years and Asymptomatic
12. Benassi 1989	30	M	Dysarthria, headache and seizure Several episodes of transient visual disturbances consisting of a moving shimmering light over the entire visual field Brief episodes with interruption of ongoing activity, immobility and loss of contact	1.100	CT Ischemia left temporoparietal regio Angiography showed absence of terminal branches of the left MCA

and were usually associated with or followed by a dull pulsatile headache. This clinical picture and the absence of vascular risk factor is very atypical for and differs from the transient ischemic attacks and stroke as occurs in arteriosclerotic vascular disease. The striking similarity of poorly localized atypical transient ischemic attacks with migraine-accompaniments support the crucial role of blood-platelets in the pathogenesis of ischemic circulation disturbances in essential thrombocythemia. The pivotal role of platelets is further substantiated by the consistent observations that low-dose aspirin and reduction of platelet-count to normal ($<350 \times 10^9/l$) not only relieved the erythromelalgic distress quickly and completely but also prevented the recurrence of the cerebral ischemic circulatory disturbances.^{11,13,18,21,23,(table 1 and 2)} The presented observations and data from the literature confirm the hypothesis of Mitchell that the broad spectrum of acroparesthesias, erythromelalgia and acrocyanotic ischemia or gangrene together with the episodic neurologic symptoms of vertigo, migraine, attacks of amnesia, dysphasia, dysbasia, TIA, hemiparesis and seizures all are the consequence of that only one underlying disorder called thrombocythemia vera, in which platelet-mediated inflammatory and thrombotic processes in the endarterial microvasculature reflect the existence of a new disease entity of a platelet dependent arterial thrombophilia in thrombocythemia vera.^{31,32}

REFERENCES

- Mitchell, S. W. (1978) On a rare vasomotor neurosis of extremities and on the maladies with which it may be confounded. *Am. J. Med. Sci.*, **117**, 1–14.
- Smith, L. A. and Allen, F. V. (1938) Erythromelalgia (erythromelalgia) of the extremities. A syndrome characterized by redness heat and pain. *Am. Heart J.*, **16**, 175–188.
- Michiels, J. J., Ten Kate, F. W. J., Vuzevski, V. D. and Abels, J. (1984) Histopathology of erythromelalgia in thrombocythemia. *Histopathology*, **8**, 669–678.
- Michiels, J. J., Abels, J., Steketee, J., van Vliet, H. H. D. M. and Vuzevski, V. D. (1985) Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia. *Ann. Int. Med.*, **102**, 466–471.
- Michiels, J. and Van Joost, Th. (1990) Erythromelalgia and thrombocythemia, a causal relation. *J. Am. Acad. Dermatol.*, **22**, 107–111.
- Vreeken, J. and van Aken, W. G. (1971) Spontaneous aggregation of blood platelets as a cause of idiopathic thrombosis and recurrent painful toes and fingers. *Lancet*, **2**, 1394–1397.
- Preston, F. E., Emmanuel, I. G., Winfield, D. A. and Malia, R. G. (1974) Essential thrombocythaemia and peripheral gangrene. *Br. J. Med.*, **3**, 548–552.
- Redding, K. G. (1977) Thrombocythemia as a cause of erythromelalgia. *Arch. Dermatol.*, **1**, 2383–2388.
- Singh, A. K. and Wetherley-Mein, G. (1977) Microvascular occlusive lesions in primary thrombocythemia. *Br. J. Haematol.*, **36**, 553–564.
- Vera, J. C. (1979) Antiplatelet agents in the treatment of thrombotic complications of primary thrombocythemia. *Can. Med. Assoc. J.*, **120**, 60–61.
- Jabaily, J., Iland, H. J., Laszlo, J., Massey, E. W., Faguet, G. B., Briere, J., Landaw, A. and Pisciotto, A. V. (1983) Neurologic manifestations of essential thrombocythemia. *Ann. Int. Med.*, **99**, 513–518.
- Scheffer, M. G., Michiels, J. J., Simoons, M. L. and Roelandt, J. R. T. C. (1991) Thrombocythemia and coronary artery disease. *Am. Heart J.*, **122**, 573–576.
- Michiels, J. J., Koudstaal, P. J., Mulder, A. H. and van Vliet, H. H. D. M. (1993) Transient neurologic and ocular manifestations in primary thrombocythemia. *Neurology*, **43**, 1107–1110.
- Michiels, J. J. and ten Kate, F. W. J. (1992) Erythromelalgia in thrombocythemia of various myeloproliferative disorders. *Am. J. Hematol.*, **39**, 131–136.
- Van Genderen, P. J. J. and Michiels, J. J. (1993) Primary thrombocythemia; diagnosis, clinical manifestations and management. *Ann. Hematol.*, **67**, 57–62.
- Murphy, S., Iland, H., Rosenthal, D. and Laszlo, J. (1986) Essential thrombocythemia: an interim report from the Polycythemia Vera study Group. *Semin. Hematol.*, **23**, 177–182.
- Speer, F., Denison, T. R. and Baptist, J. E. (1981) Aspirin allergy. *Ann. Allergy*, **46**, 123–126.
- Olivarius, B. F. (1957) Cerebral manifestations in thrombocythemia. *Acta. Psychiatr. Neurol. Scand.*, **32**, 77–82.
- Levine, J. and Swanson, P. D. (1968) Idiopathic thrombocytosis. *Neurology*, **18**, 711–714.
- Singer, G. (1969) Migrating emboli of retinal arteries in thrombocythemia. *Br. J. Ophthalmol.*, **53**, 279–281.
- Korenman, G. (1969) Neurologic syndromes associated with primary thrombocythemia. *J. Mount. Sinai. Hosp.*, **36**, 317–323.
- Mundall, J., Quintero, P., Von Kaulla, K. N., Harmon, R. and Austin, J. (1972) Transient monocular blindness and increased platelet aggregability treated with aspirin. *Neurology*, **22**, 280–285.
- Bousser, M. G., Conard, J., Lecrubier, C. and Bousser, J. (1980) Migraine ou accidents ischémiques transitoires au cours d'une thrombocytémie essentielle. *Ann. Med. Interne.*, **131**, 87–90.
- Delangre, T., Mihout, B., Borth, J.-Y. and Samsom, M. (1985) Primary thrombocythemia in a patient with cerebellar infarction. *Stroke*, **16**, 524–526.
- Benassi, G., Ricci, P., Calbucci, F., Cacciato, F. M. and D'Alessandro, R. (1989) Slowly progressive ischemic stroke as first manifestation of essential thrombocythemia. *Stroke*, **20**, 1771–1772.
- Herskovitz, S., Loh, F., Berger, A. R. and Kucherov, M. (1993) Erythromelalgia: Association with hereditary sensory neuropathy and response to amitriptyline. *Neurology*, **43**, 621–622.
- Michiels, J. J. (1990) Erythromelalgia versus erythromelalgia. *Lancet*, **336**, 454–455.
- Drenth, J. P. H. and Michiels, J. J. (1994) Erythromelalgia and Erythromelalgia: Diagnostic Differentiation. *Int. J. Dermatol.*, **33**, 393–397.
- Michiels, J. J. and Drenth, J. P. H. (1994) Erythromelalgia and Erythromelalgia. Lumpers and Splitters. *Int. J. Dermatol.*, **33**, 412–413.
- Michiels, J. J. and Drenth, J. P. H. (1995) Classification and diagnosis of Erythromelalgia and Erythromelalgia. *Int. J. Dermatol.*, **34**, 97–100.
- Michiels, J. J. and Zijlstra, F. J. (1993) Prostaglandin cyclooxygenase products but not thromboxane A₂ are involved in the pathogenesis of erythromelalgia in thrombocythemia. *Mediators of Inflammation*, **2**, 385–389.
- Van Genderen, P. J. J., Michiels, J. J., Lindemans, J., Van strik, R. and van Vliet, H. H. D. M. (1995) Platelet consumption in thrombocythemia, complicated by erythromelalgia. reversal by aspirin. *Thromb. Haemostas.*, **73**, 210–214.