

Erythromelalgia: Clinical aspects, pathology and therapy

**Dissertation for the degree of philosophiae doctor
(Ph.D) at the University of Oslo, Norway 2012**

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Oslo 2012

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*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1293*

ISBN 978-82-8264-317-7

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Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

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**To my wife Ligia
and our children
Christian and Filipe**

"With ordinary talents and extraordinary perseverance, all things are attainable."

Sir Thomas Fowell Buxton

"Many of life's failures are people who did not realize how close they were to success when they gave up."

Thomas Edison

"One of the secrets of getting more done is to make a TO DO List every day, keep it visible, and use it as a guide to action as you go through the day."

Jean Fontaine

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ACKNOWLEDGEMENTS

I wish to thank all the people who have contributed to this thesis, in particular:

- Professor Knut Kvernebo, Department of Thoracic Surgery, Oslo University Hospital, my supervisor and mentor. His never ending optimism, enthusiasm, patience and great knowledge of the field of circulation physiology and a great many other aspects of medicine have been decisive for this thesis. His great expertise in medical research that I have observed in the laboratory setting and while drafting scientific papers together, as well as in clinical practice at a patient's bedside has impressed me profoundly. I want to express my deepest gratitude for his never failing support throughout the long period it has taken me to complete this thesis.
- My co-author professor Cato Mørk, Institute of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim for his co-work, friendship and support throughout this work.
- My co-authors professor Ole Petter F. Clausen, Department of Pathology, professor emeritus Thorstein Hovig, Department of Pathology, consultant in immunology and transfusion medicine Ove Johan Mellbye, Institute of Immunology, consultant thoracic surgeon Egil Seem, Department of Thoracic Surgery, all Oslo University Hospital.
- Professor emeritus Georg Rajka, former Chairman of the Department of Dermatology, Oslo University Hospital, Rikshospitalet for introducing me to the field of dermatology, giving me working facilities and for his encouragement and support.
- Professor emeritus Per Thune, former Chairman of the Department of Dermatology, Oslo University Hospital, Ullevål for generously lending us the laser Doppler flowmetry equipment used in the studies.
- The colleagues and other staff from the Department of Dermatology, Oslo University Hospital, Rikshospitalet during my time there.
- University of Oslo, Faculty of Medicine, for research facilities.
- Randi Kvernebo who has received me with great hospitality and encouragement in the Kvernebo family home for innumerable research meetings with her husband.
- My mother and my late father, Eldrid and Ole Kalgaard for their love, support and encouragement throughout my life.
- Last, but not least my wife Ligia and our children Christian and Filipe for their love, enduring patience, support and encouragement throughout this long project.

Nesøya, July 2011

Ole Magne Kalgaard

ABBREVIATIONS

AV	arterio-venous
AVA	arterio-venous anastomosis
EM	erythromelalgia
EPPA	erythromelalgic phenomenon primary acute
EPPC	erythromelalgic phenomenon primary chronic
EPSA	erythromelalgic phenomenon secondary acute
EPSC	erythromelalgic phenomenon secondary chronic
ES	erythromelalgic syndrome
ESG	erythromelalgia study group
LDF	laser Doppler flowmetry
AU	arbitrary units
FD	fibrin deposits
CD	complement deposits
IF	immunofluorescence
CRPS	complex regional pain syndrome
RSDS	reflex sympathetic dystrophy syndrome

LIST OF PAPERS

This thesis is based on the following papers referred to in the text by their Roman numerals:

- I Kalgaard OM, Seem E, Kvernebo K: Erythromelalgia: a clinical study of 87 cases. *J Int Med* 242: 191-7, 1997

- II Kalgaard OM, Clausen OP, Mellbye OJ, Hovig T, Kvernebo K: Nonspecific capillary proliferation and vasculopathy indicate skin hypoxia in erythromelalgia. *Arch Dermatol* 147(3):309-14, 2011

- III Mørk C, Kalgaard OM, Kvernebo K: Impaired Neurogenic Control of Skin Perfusion in Erythromelalgia. *J Invest Dermatol* 118:699-703, 2002

- IV Kalgaard OM, Mørk C, Kvernebo K: Prostacyclin Reduces Symptoms and Sympathetic Dysfunction in Erythromelalgia in a Double-blind Randomized Pilot Study. *Acta Derm Venereol* 83:442-4, 2003

INTRODUCTION

Definition

Erythromelalgia (EM) (*erythro* = red, *melos* = limb, *algos* = pain) is a term used to describe: "A rare disorder of unknown aetiology characterised by intense burning extremity pain associated with erythema and increased skin temperature. Warmth intensifies the discomfort while cold provides relief" (Thompson et al, 1979). This definition was used to include EM-patients in this work. The symptoms and findings are most often intermittent and often absent during physical examination. EM is commonly divided into primary and secondary cases (Smith and Allen, 1938), depending on whether or not there is an underlying disease. A rare subgroup, erythromelalgic syndrome (ES), (Kvernebo, 1998), has a strong hereditary component with affection of the feet and the leg skin. Some authors consider EM to be a symptom complex rather than a disease entity (Kvernebo, 1998).

History

The first case of what became later known as EM was reported by the famous Irish physician Robert James Graves in 1834 also known for describing Graves` disease of the thyroid gland (Graves, 1834). Dr. Silas Weir Mitchell, a prominent US neurologist and author of prose, verse and juvenile stories from Pennsylvania, in 1878 published a report of 16 patients and was the first to introduce the term EM (Mitchell, 1878). The condition is also known as "Weir Mitchell`s disease" or just "Mitchell`s disease". Weir Mitchell is also credited for the first description of the condition which is now known as "complex regional pain syndrome" (CRPS) (Mitchell, 1872).

By 26.6.2011 there are 546 publications indexed in the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) when searching with the term erythromelalgia, the first paper appearing in 1903.

Erythromelalgia research at the Mayo Clinic:

Smith and Allen in 1938 proposed a subdivision of EM into a primary and a secondary group. They also introduced the term erythermalgia, emphasising the temperature increase found in affected skin during symptomatic periods, leaving out the reference to extremity location (Smith and Allen, 1938). The term erythermalgia is still being used in the literature

until this day mostly in reference to primary, hereditary EM, but still by many authors synonymously with EM.

The more inclusive term erythrothermomalgia is probably considered too much of a mouthful by most authors, although it would be the most covering. Babb et al from the Mayo Clinic, USA in 1964 published a retrospective study of 51 cases, the largest material published at that time in the western world, with a detailed description of clinical and epidemiological characteristics of the patient material. Temperature provocation studies were carried out, and in 28 of 31 patients (19 primary and 12 secondary EM) a positive result, considered diagnostic for EM, was found with painful distress in affected skin of the patients at 31-33 °C (Babb et al, 1964). Davis and co-workers have contributed to numerous papers covering a great variety of aspects regarding EM, including epidemiology, clinical manifestations, pathophysiology and therapy (Sandroni et al, 1999; Davis et al, 2000; Davis et al, 2003; Davis et al, 2005; Davis et al, 2006; Sandroni and Davis, 2006; Reed and Davis, 2009). They have collected one of the largest EM patient cohorts in the world, publishing results from their database of 168 patients seen in their clinic from 1970-1994 (Davis et al, 2000).

Erythromelalgia research in Norway:

Einar Hval (1901-1958) from Department of Dermatology, Rikshospitalet reported the first EM patient in Norway (Hval, 1928).

EM research in Norway started in 1983 when a female patient with severe EM (cooled her feet in cold water up to 20 hours per day) was referred to my thesis advisor and co-author Knut Kvernebo at the Department of Vascular Surgery, Aker Hospital, Oslo. He published a preliminary report of the results of physiological examinations of this patient together with Egil Seem (Kvernebo and Seem, 1987). A radio report in NRK (National broadcasting corporation) of the condition lead to a number of self-referrals and physician referrals to the clinic. A monograph reporting on 40 patients, with a clinical classification system, detailed patient case histories, microvascular studies, histopathology examinations of skin biopsies and as well as results of a prostaglandin E1 intravenous therapeutic trial was published (Kvernebo, 1998). For this work Kvernebo was awarded His Majesty King Olav's Gold Medal in 1990.

Cato Mørk continued the EM studies at the Department of Dermatology, Rikshospitalet, Oslo and expanded the database to 160 patients. Today the patient cohort is probably one of the world's largest with 201 patients followed for up to 27 years. Mørk focused on studies of microvascular pathophysiology using laser Doppler perfusion imaging, capillary assisted video microscopy and laser Doppler flowmetry, as well as study of misoprostol therapy and presented his Ph.D dissertation in 2004 (Mørk, 2004b).

My EM-research at Department of Dermatology, Rikshospitalet with focus on clinical aspects, pathology and therapy was initiated in 1991 and completed in 2010. An EM Study Group (ESG) has been established under the leadership of professor Kvernebo. ESG has for many years worked in close collaboration with the group of professor Göran Salerud, Department of Biomedical Engineering, University Hospital, Linköpings University, Sweden. A collaboration with Laboratory of Clinical Neurophysiology, Department of Neurology, Rikshospitalet, Oslo University Hospital (Ørstavik K & Jørum E) has also resulted in publications studying autonomous neurological dysfunction (Ørstavik and Jørum 2003; Ørstavik et al, 2004; Ørstavik and Jørum, 2010).

Mari Skylstad Kvernebo is now updating the EM registry and continuing the EM studies at the Department of Dermatology, Oslo University Hospital, Rikshospitalet.

Epidemic erythromelalgia in China

Epidemic outbreaks of EM from China, probably induced by poxviruses have been reported (Zheng et al, 1988). The outbreaks has primarily affected young females and occurred with a few years interval. Reports from other parts of the world regarding epidemic EM and the suspected role of viruses in the pathogenesis have not been published.

The Erythromelalgia Association

The Erythromelalgia Association (TEA) founded in 1999, has as its mission "to identify, educate, and support those suffering EM's painful symptoms; to help fund research leading to a cure for this rare disorder; to raise public awareness of EM; and to educate healthcare practitioners to recognize and diagnose EM. TEA places a special emphasis on helping identify, educate, support and assist those individuals who do not have access to the Internet. Because most physicians are NOT familiar with EM symptoms and/or treatment

there is a great need to educate the medical community as well.” TEA has currently over 750 members residing in 17 countries. TEA was created, and is still operated by volunteers. (TEA website: <http://www.erythromelalgia.org>)

Clinical presentation

EM is a clinical diagnosis. No laboratory test exists that can verify the diagnosis.

The following inclusion criteria (symptoms and signs) has been applied (Thompson et al, 1979; Mørk and Kvernebo, 2000c):

Symptoms:

- Burning extremity pain
- Pain aggravated by warming
- Pain relieved by cooling

Signs:

- Erythema of affected skin
- Increased temperature of affected skin

Each criterion is dependent on the individual clinical judgement.

Fig. 1 illustrates typical clinical presentations of EM.



Fig.1. Foot affected by erythromelalgia.

Factors such as exercise, warm socks or shoes, bed covering, limbs in a depending position, alcohol intake may precipitate or aggravate symptoms. EM symptoms are most frequently intermittent, and one has to rely on the medical history to establish the diagnosis.

Transitional erythema can be documented by easily available digital cameras.

Babb found EM to be more common in lower limbs, and claimed that primary EM was restricted to the lower extremities (Babb et al, 1964).

Kvernebo observed primary EM also in the upper extremities, and found the involvement to be symmetrical in 38 cases, and asymmetrical in two secondary EM-cases (Kvernebo, 1998).

EM occurs in all age groups. Primary EM starts earlier than secondary EM. Babb found secondary EM only in >40-year old subjects, while Kvernebo also observed secondary EM in the <40 age group. Primary EM appears to be more common in women, while the ratio is more even for secondary EM, tab.1

Author	Primary EM	Secondary EM	Total
Babb	10 ♀ 20♂	11 ♀ 10♂	21 ♀ 30♂
Kvernebo	25 ♀ 3♂	6 ♀ 6♂	31 ♀ 9♂
Davis			122 ♀ 46♂

Tab.1. Female/male ratios found in previous studies (Babb et al, 1964; Kvernebo, 1998; Davis et al, 2000).

Differential diagnosis

A detailed medical history and a physical examination, keeping in mind that signs of EM are usually intermittent should usually distinguish EM from other conditions that may manifest with similar symptoms and signs. Laboratory investigations to rule out other conditions may be valuable.

Acrocyanosis is a persistent blue or cyanotic discoloration of the extremities with cold skin that is often clammy and typically made worse on cooling and improves with warming. Pain is not typical for the condition.

Acrodermatitis chronica atrophicans is rare disorder caused by the *Borrelia* spirochete species *B. burgdorferi*, *B. garinii*, *B. afzelli* and *B. valaisiana*. It is more often unilateral, and burning pain is usually absent. *Borrelia* serology may aid the diagnosis, although it is not reliable in many cases.

Angiodyskinesia is condition described in only four PubMed indexed reports from 1968-1974 with clinical features of lower extremity pain and patchy erythema and increased skin temperature of the affected leg skin on standing. Ryan describes it in a 14 year old boy with osteochondritis dissecans, and suspected that an axon reflex vasodilatation from a painful knee contributed the condition in his patient (Ryan and Wilkinson, 1974).

Burning feet syndrome is a relatively common disorder characterised by a burning sensation and heaviness in the feet and lower extremities. There is no specific etiology. Warming may aggravate symptoms.

Chronic venous insufficiency. In this condition classified according to the CEAP clinical classification of lower extremity venous disease, stage C4a with pigmentation and eczema (Porter and Moneta, 1995) erythema and increased skin temperature with painful discomfort may be present, but the patients do not generally experience relief from cooling.

Complex regional pain syndrome (CRPS) Type I (formerly known as reflex sympathetic dystrophy syndrome (RSDS), does not have demonstrable nerve lesions), Type II (formerly known as causalgia) has evidence of obvious nerve damage (Stanton-Hicks et al, 1995).

Diagnostic criteria of CRPS I (IASP: <http://www.iasp-pain.org>) are as follows:

1. The presence of an initiating noxious event or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia disproportionate to the inciting event.
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the area of pain.
4. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction (i.e. EM).

CRPS II (IASP: <http://www.iasp-pain.org>) is diagnosed as follows:

1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.

2. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
3. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction (i.e. EM).

Deep vein thrombosis may be diagnosed by ultrasound or venography, and may present with a positive Homan's sign on clinical examination.

Eosinophilic fasciitis is an idiopathic, fibrotic disorder with the histopathologic hallmark of fascial fibrosis. The presentation of eosinophilic fasciitis is acute with painful, swollen extremities progressing to disabling cutaneous fibrosis. Joint contractures, arthritis, neuropathy, and myositis may be associated with eosinophilic fasciitis. Many authors consider eosinophilic fasciitis to be a variant of morphea, others consider it a distinct entity.

Erysipelas is most frequently unilateral, which is less common in EM. Rapid onset fever, malaise, increased C-reacting protein and leucocytosis are common findings. The condition is rapidly cured by antibiotics.

Fabry's disease is a rare genetic disorder caused by a deficiency in the enzyme alpha galactosidase which results in accumulation of a glycolipid in the blood vessels and other tissues usually observed in early childhood may give acral pain or paresthesia. It can be ruled out with a blood test to measure alpha galactosidase activity or even more accurately with chromosomal analysis of the GLA (galactosidase, alpha) gene.

EM like processes in the face and the scrotum have been published (Gaur and Korosil, 2007; Prevost and English, 2007).

Many types of skin cooling has been observed in EM patients: low room temperature, cold air fans, putting feet outside quilt at night, standing on cold floors, putting feet in a cold water bucket, walking bare feet in snow. Cooling with water directly on the skin produces skin maceration, and should be discouraged. It is common to get relief from elevation. EM symptoms are usually worse at night. Some patients with EM at times also experience Raynaud's phenomenon, which may be considered the antithesis to EM (Slutsker, 1990; Lazareth and Priollet, 1990). A continuous spectrum from Raynauds through normal to EM therefore exists in some patients, illustrated in fig. 2.

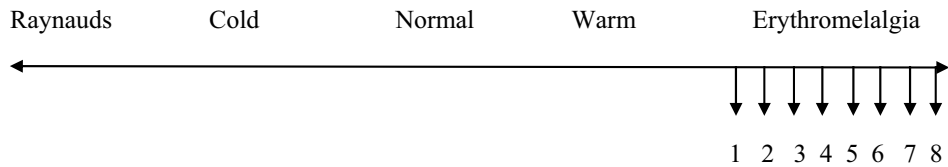


Fig. 2. The continuous spectrum of Raynaud's phenomenon-normal-EM (severity groups 1-8, described in Kalgaard et al,1997). Modified after Kvernebo (Kvernebo, 1998).

Impact on quality of life.

Pain associated with EM is difficult to relieve, even with opiate analgesics.

Cooling efforts may lead to behaviour that appears bizarre to the general public; carrying around buckets of iced water (Fig. 3), showering the feet with cold water, walking barefoot, even in the winter.



Fig. 3. Water cooling in erythromelalgia.

Studies have shown that many patients suffer inability to walk long distances (50%) and inability to drive (12, 5%) (Davis et al, 2000).

The morbidity and mortality of EM is high. Davis et al found impaired health status scores (SF-36), and concluded that “EM is a syndrome with significantly increased mortality and morbidity compared with the US general population” (Davis et al, 2000). Three of the patients in the Mayo clinic material committed suicide because of their disease. Additionally, an affected relative of one patient committed suicide. In this material six out of 33 deaths were attributed to myeloproliferative diseases. Mean life span from diagnosis of EM until death was $6, 3 \pm 4, 8$ years (range 0, 44-18, 84 years). Littleford found that over a third of their EM patients reported depression or depressed states (Littleford, 1997). A case report describes a female of 14 years that died as a result of exhaustion due to severe refractory EM symptoms (Drenth et al, 2008).

Epidemiology

Reed and Davis found a mean incidence of EM of 1, 3 per 100,000 persons living in Olmsted County MN, USA (Reed and Davis, 2009). This is approximately five times greater than the incidence rate reported in Norway in 1998 (0, 25 per 100,000 persons per year), (Kvernebo, 1998). Davis points out that EM is getting a more common since the incidence and has been increasing each decade according to their studies. The number of EM patients in Kvernebos' monograph was 40. Mørk reported an incidence of 0, 33 per 100 000 of moderate to severe EM in a clinical study on 102 EM-patients (Mørk, 1997). Later the Norwegian database grew to 201 by April 2009, the number of patients alive and residing in Norway at that time was 193. This would imply that the difference in the incidence between Olmsted County and Norway is much smaller. The true incidence may be much higher since some potential referring physicians may lack of knowledge about this rare condition. In particular patients in lower severity groups may not present their symptoms to their doctor, or their doctor may not see the need for referral to a specialised centre for further evaluation. Differences in diagnostic criteria of EM may also contribute to the variations in incidence between Olmsted County and Norway. In the Norwegian material we have stuck to the criteria defined in the clinical presentation chapter of this thesis. In the Mayo Clinic material EM was defined as a convincing history of unexplained redness, heat, and painful extremities. The subjective elements of redness, heat and pain were required to fulfil the diagnosis. (Davis et al, 2000).

EM is described mostly in Caucasians, in addition to the epidemic reports from China (Zheng et al, 1988). Whether this reflects a true difference in incidence and prevalence, or under-reporting of the condition from African and Indian continents is uncertain. To observe erythema in very dark skin is difficult, so consequently the diagnosis of EM would be more difficult.

An extensive list of diseases related to secondary EM has been published (Mørk, 2004b). The most common conditions are metabolic conditions, blood dyscrasias, autoimmune disease, neurological disease, pharmacological substances, musculoskeletal disorders, infections, cancer as well as cardiovascular disease. EM secondary to colon cancer and AIDS have been reported by our group (Appendix I and II).

In the last few years, a case report on a 10 year old girl with EM secondary to mercury intoxication associated with hypertension should be noted (Chang et al, 2007).

Pathogenesis

The clinical picture of EM is heterogenous regarding age, sex, underlying primary diseases, symptom location, duration of disease and disease severity. In most textbooks EM is considered to be a separate disease entity. Our group has argued that EM represents a symptom complex, a condition rather than a well-defined disease (Kvernebo, 2003).

Hypothesis: Microvascular shunting as **the final common pathway of pathogenesis**

The hypothesis that symptoms are caused by skin microvascular arteriovenous (AV) shunting with corresponding tissue hypoxia and hyperaemia independent of the aetiology, has been proposed by our group (Kvernebo, 1998). This is analogous to the view that inflammation is not one single disease, but a physiologic response to stimuli such as infection, trauma, or tumour. Further we believe that the microvascular AV shunting may be induced by a number of mechanisms and diseases (Kvernebo, 1998; Mørk, 2004b).

Skin microvessels are arranged into subpapillary capillaries predominantly serving a nutritional function (epithelial proliferation), as well as a superficial and a deep horizontal plexus mainly serving thermoregulatory functions, fig.4. Nutritional perfusion is controlled

mainly through local metabolites (e.g. oxygen metabolism) and sensory stimuli. The blood flow to the deeper plexa and thus thermoregulation is under sympathetic neural control (Boron and Boulpaep, 2005).

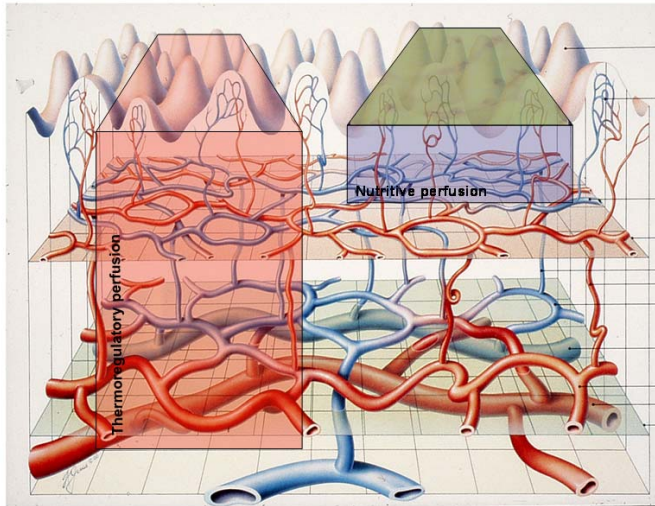


Fig. 4. The localisation of thermoregulatory- and nutritive perfusion within the skin.

Mescon et al stated that “The arteriovenous anastomoses (AVA) of the skin are specialized vascular structures which shunt the blood directly from arterioles to venules parallel to the capillaries. An AVA together with related vessels and nerves constitutes a unit called a "glomus". The AVA are most abundant in the pads and nailbeds of the fingers and toes but also occur in the palms and soles, ears, nose, eyelids, lips, cheeks and forehead. The AVA apparently constricts and dilates under nervous control and the resulting great changes in blood flow through the skin are related to the temperature regulation of the body. During exposure to cold the AVA may cyclically constrict and dilate (Lewis' "hunting reaction") which presumably helps preserve the viability of the surface tissues” (Mescon et al, 1956).

Clinical observations and pathophysiological findings indicate coexistence of hyperaemia and hypoxia in affected EM skin areas. Based on these observations Kvernebo proposed the

shunt hypothesis for the pathogenesis of erythromelalgia (Kvernebo, 1998):

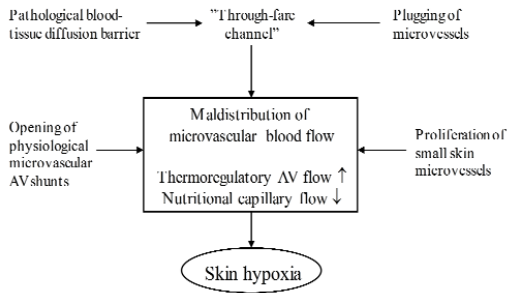


Fig 5. Suggested pathogenesis of erythromelalgia modified after Kvernebo. The hypoxia is caused by maldistribution of skin blood flow with insufficient nutritive perfusion and increased thermoregulatory perfusion. Maldistributed skin perfusion may be a consequence of opening of anatomical arteriovenous shunts and closure of precapillary sphincters (primary erythromelalgia), “through-fare channels” (disturbed blood-tissue diffusion barrier or plugging of vessels) serving as physiological shunts (secondary erythromelalgia) and shunting through proliferating vessels (erythromelalgia syndrome). (Copied with permission from Mørk, 2004b)

Skin hypoxia is in this hypothesis postulated to be a key to the initiation of EM symptoms. Oxygen tension in affected skin varies considerably, and with normal levels next to perfused vessels, if the blood-tissue barrier is not disturbed, and with lower levels between the vessels. As the oxygen diffusion capacity is poor, areas relatively far from the nearest perfused vessels may be hypoxic. If there is a maldistribution, there will be a great variation in the oxygen tension offered to different skin cells. Some cells may have adequate supply, while others may be severely hypoxic, fig. 5. This hypothesis gives an explanation for why cooling

universally reduces pain. The cooling reduces metabolism and thereby the hypoxia; the improvement of tissue oxygenation reduces the arteriolar dilatation; and hyperemia is less pronounced: the vicious cycle (fig. 6) is reversed.

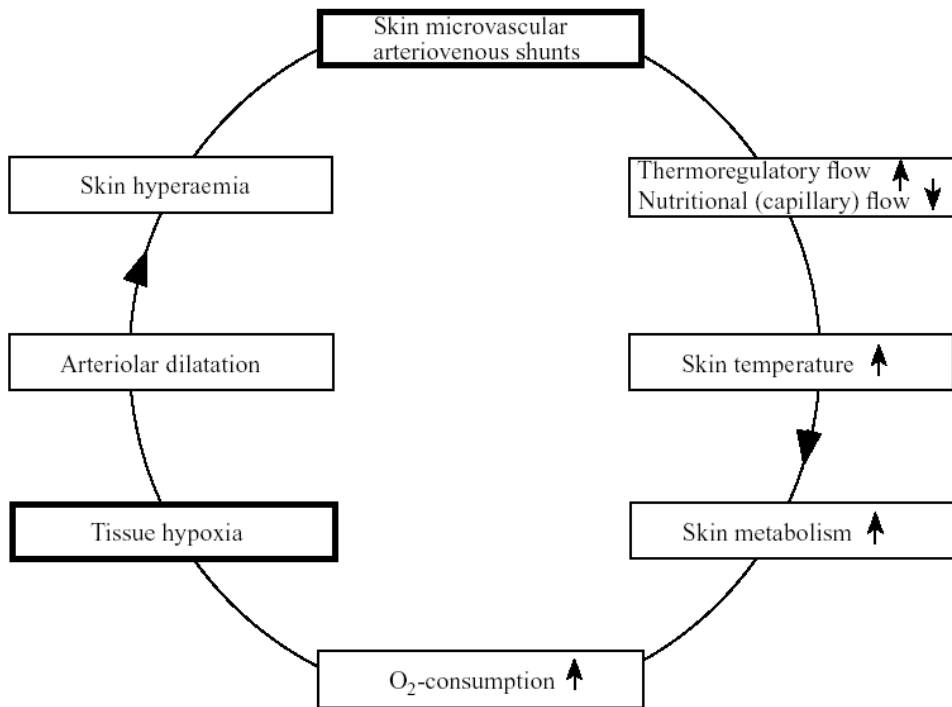


Fig.6. The vicious cycle of erythromelalgia (copied with permission from Mørk, 2004b).

Our group has published results in favour of the shunting hypothesis: This hypothesis gives an explanation for why cooling universally reduces pain, although pain relief by cooling may also be a direct desensitization on sensory nerve endings. Distribution of blood flow is regulated by smooth muscle cell tone in arterioles and pre-capillary vessels. Smooth muscle cell tone is again influenced by the metabolic state of the tissue, neurogenic, and endothelial activity, as well as the trans-mural hydrostatic pressure.

At present the debate in the literature has focused on two different mechanisms triggering the skin microvascular shunting: the vascular and the neurogenic pathway.

Studies supporting the vascular pathogenesis

Using laser Doppler flowmetry (LDF), Kvernebo found increased blood flow values in the toe pulp microcirculation during EM attacks. After post occlusive 3 min. hyperaemia testing an “on-off response” with maximal hyperaemia before occlusive period was found in

approximately 50% of the patients tested. This finding indicates that the skin volume measured was maximally circulated prior to the vasodilatory stimulus.

Transcutaneous oxygen tensiometry (TCpO₂) measurements in the skin with the equipment currently commercially available have several limitations. Measurements are not possible on thick skin such as on the plantar aspect of the foot where EM symptoms are most common. Kvernebo measured TCpO₂ values in the ES patient on leg skin and between the toes in one other severely affected EM patient and found severe hypoxia.

Littleford et al did microvascular studies on 61 EM patients with LDF measuring basal skin erythrocyte flux and hyperaemic response to local heating and found a vasoconstrictor tendency in patients with EM, thought to be related to functional or structural changes in skin microvessels. They believed that, in EM, vasoconstriction precedes reactive hyperaemia, similar to that seen in Raynaud's phenomenon. Toe temperature was significantly reduced in both EM groups compared with control subjects in their study (Littleford et al, 1999a).

Littleford et al also concluded in another study that patients with EM have diminished vasoconstrictor ability to cold challenge and inspiratory gasp using laser Doppler flowmetry (Littleford et al, 1999b).

Mørk found, using laser Doppler perfusion imaging and skin temperature at rest and after central body heating, that attacks of EM were induced in eight out of fourteen patients after heat provocation. In the plantar region of the foot, the location of numerous anatomical AV shunts, these patients had significantly increased skin perfusion as compared with asymptomatic patients with EM and controls. In the dorsal region, with few AV shunts, no significant differences between the groups were demonstrated. The results showed a relation between clinical symptoms and increased perfusion in the region of numerous anatomical AV shunts, and supported the hypothesis of increased thermoregulatory AV shunt flow during attacks in primary EM (Mørk et al, 2000a).

In another study, using an enhanced technique of computer-assisted capillary microscopy with temperature measurements before and after central body heating, Mørk found in fourteen patients and ten healthy control subjects that the number of visible capillaries decreased significantly in EM patients after warming in areas with numerous AV anastomoses (nail bed region). In symptomatic patients an even more significant reduction was observed. The capillary size was also significantly reduced in symptomatic patients. The

change in capillary density in the nail bed area was significantly larger in EM patients compared to controls, and in symptomatic patients compared to asymptomatic patients and controls. The reduced skin capillary density after heating is compatible with increased microvascular AV shunting of blood and a corresponding relative deficit in nutritive perfusion (steal phenomenon) with skin hypoxia, causing the symptoms in EM (Mørk et al, 2002a). Another study demonstrated that the prostaglandin E1-analog misoprostol reduces symptoms and microvascular AV shunting in EM (Mørk et al, 2004a). This drug acts by vasodilatation and inhibition of platelet activation, and our assumption is that the vasodilatory effect on precapillary sphincters increases nutritive skin perfusion. According to the vascular hypothesis, affected skin is hypoxic during attacks. Since hypoxia is known to be a strong stimulus for angiogenesis (Ryan, 1976), findings of microvascular proliferation in affected skin in EM patients would support the hypothesis of a vascular pathogenetic mechanism.

Studies supporting the neurogenic pathogenesis

A primary neurogenic dysfunction of peripheral autonomous nerves could induce a secondary maldistribution of perfusion with a microvascular shunt mechanism. Sandroni et al have shown in extensive studies, using LDF, TCpO₂, neurophysiologic testing, autonomic reflex screening and recordings of peripheral autonomic surface potentials, that during symptoms, an increase in flow and temperature is accompanied by a paradoxical decrease in oxygenation of the affected area. They conclude that a high proportion of patients have a distal small fibre neuropathy with selective involvement of cutaneous sympathetic fibres. In addition, large fibre neuropathy is often present (Sandroni et al, 1999). Davis et al have tested nerve and vascular function in asymptomatic patients and in symptomatic EM patients following exercise or by increasing ambient temperature. During symptoms, the skin temperature increased approximately 8 °C, and blood flow increased 10x, but with unchanged TCpO₂. Most patients had abnormal autonomic reflex screening. They concluded that most patients with EM had small-fibre neuropathy in addition to other forms of neuropathy, (Davis et al, 2003). Ørstavik et al examined patients with primary EM (n=25) by neurological testing, neurography and quantitative sensory testing. EM patients threshold for heat, cold, heat-

pain and cold-pain detection were compared with those of a group of 29 healthy controls. The patients had significantly higher heat and cold detection thresholds at the dorsal aspects of their feet compared to the controls. These findings show an impaired small fibre function inside or close to the symptomatic EM area. Brush-evoked allodynia (n=7), and punctate hyperalgesia (n=14) inside or close to the symptomatic areas in their feet were demonstrated. The patients could be clustered into two groups; reduced small-fibre input/no hyperalgesia and normal thermal thresholds/hyperalgesia. They concluded that the affection of afferent small nerve fibres together with the nature of the symptoms, may imply a neuropathic component in EM patients (Ørstavik et al, 2004).

Knowledge of histopathological findings in diseased skin of EM patients is limited. Davis found capillary alterations with hyperplasia, ectasia, endothelial swelling or dermal fibrosis in a high proportion of biopsies (n=29) using light microscopy and immunohistochemistry. These findings were considered to be non-specific. A decrease in nerve ending density associated with dilated capillary loops was also observed, but no vascular thrombi (n=16) (Davis et al, 2006).

Inheritance and genetics

Several authors have reported familial EM (Thompson et al 1977; Finley et al, 1992; Kvernebo, 1998). In the Norwegian material of 87 patients presented later in this thesis there were two cases, mother and daughter, classified as erythromelalgic syndromes (ES). Nine other patients had mostly female relatives with a possible history of EM. Drenth et al found that the primary erythromelalgia-susceptibility gene is located on chromosome 2q31-32. They investigated DNA from five families with hereditary EM and located the gene responsible to chromosome 2q31-32, but did not identify the gene (Drenth et al, 2001). Yang later concluded that mutations in the gene SCN9A cause primary erythromelalgia based on the previous study by Drenth et al (Yang et al, 2004). Cummings et al have shown that familial EM is a channelopathy caused by mutations in the gene encoding the Nav 1.7 sodium channel which leads to altered channel function (Cummings et al, 2004). In 2005 Waxman and Dib-Hajj states: "EM is the first human disorder in which it has been possible to associate an ion channel mutation with chronic neuropathic pain. Identification of mutations within a peripheral neuron-specific sodium channel suggests the possibility of rational therapies that target the affected channel. Moreover, because some other pain

syndromes, including acquired disorders, involve altered sodium channel function, EM may emerge as a model disease that holds more general lessons about the molecular neurobiology of chronic pain" (Waxman and Dib-Hajj, 2005). In a study of 10 members of a Flemish family with 5 affected and 5 unaffected members it was demonstrated a mutation on the SCN9A gene (S241T) in all affected members and none of the unaffected members (Michiels et al, 2005). On the other hand, a study by Drenth et al identified an SCN9A mutation in only 1 of 15 patients with a clear family history of the disease, concluding that hereditary EM may have a polygenic basis (Drenth et al, 2008). Another study concluded that in inherited EM the Nav1.7 mutations are preferentially expressed by the dorsal root ganglion and the sympathetic ganglion neuron. Most cases have been associated with onset in early childhood. This study of a patient with onset of EM in the second decade suggests a genotype–phenotype relationship at three levels (clinical, cellular and molecular/ion channel), with mutations that produce smaller effects on sodium channel activation being associated with a smaller degree of dorsal root ganglion neuron excitability and later onset of clinical signs (Han et al, 2009).

Therapy

Reviews of current therapeutic approaches have been published (Mørk and Kvernebo, 2009; Cohen, 2000). No treatment apart from cooling is consistently effective, and the level of evidence for effect of most proposed therapies is low, based on experiences with series with ≤ 5 subjects (category D) or anecdotal case reports (category E).

Effect of acetylsalicylic acid has been reported (Michiels, 1999) but in our material of 87 patients only 2 patients had therapeutic effect. The anticonvulsant drug gabapentin have been reported to have effect in a few cases (Pipili and Cholongitas, 2007; Ceyhan et al, 2008). Effect of the orally active anti-arrhythmic drug mexiletine on EM has also been reported in two cases (Iqbal et al, 2009). Sympathectomy (Seishima et al, 2000; Nakajima, 2004) has also been reported beneficial, but based on our own experience of one severe, but well documented case, we find it contraindicated (Kvernebo; 1998). Effect of lidocain patch (Davis and Sandroni, 2005), a combination gel of 1% amitriptyline and 0, 5% ketamine (Sandroni and Davis 2006), amitriptyline and naftidrofuryl oxalate (Belch, 1996) has been reported. In case studies, sodium nitroprusside has been reported to be of effect (Özsoylu et al, 1979; Özsoylu and Coskun, 1984; Kvernebo, 1998), propranolol (Bada, 1977), as well as parenteral

prostaglandin E1, prostacyclins and prostacyclin analogues (Kvernebo, 1998; Belch, 1992). A randomized blinded study using oral misoprostol (a prostaglandin E1 analogue), with vasodilatory, cytoprotective and thrombocyte aggregation inhibitory effects, demonstrate beneficial clinical and microvascular effects (Mørk et al, 2004a).

AIM OF THE THESIS

Based on an EM-registry of 87 patients gathered from 1983 to 1995 we studied:

1. Clinical findings
2. Light, immunofluorescence and electron microscopy findings
3. Neurogenic and vascular function
4. The effect of prostacyclin in a double-blinded, placebo-controlled, randomized trial

These studies were performed to deepen the understanding of the pathogenetic mechanisms of EM: The vasculogenic and the neurogenic pathway, and to study the effect of treatment with a drug that could redistribute microvascular skin perfusion in EM patients.

SUMMARY OF PAPERS I-IV

Paper I: Erythromelalgia: a clinical study of 87 cases.

Aim of the study

To report on epidemiology, etiological factors, clinical findings and prognosis.

Material and Methods

87 EM-cases with a follow up for up to 11 years, all seen by two doctors were recorded with a full, family history of EM, age, sex, age at onset of symptoms and at time of diagnosis, sites of affection, development of disease severity according to an extended version of a previously introduced severity scale (Kvernebo, 1998).

Results

Classification. About 2/3 of the patients were primary cases and around 3/4 had a chronic condition, Fig. 7.

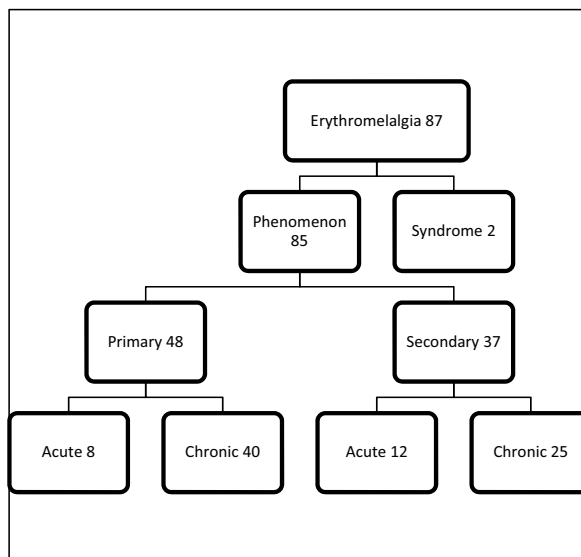


Fig.7. Classification of the EM patient material.

Secondary EM. A variety of underlying diseases deemed to be etiologically linked to the development of EM was found in the 37 cases and defined as secondary EM.

Inheritance. In addition to a mother and daughter with erythromelalgic syndrome (ES), nine other patients had mostly female relatives with a possible history of EM.

Prognosis. With time the trend is that ES gradually gets worse until high severity, primary and secondary acute EM gets better while primary and secondary chronic EM generally have a stable chronic course.

Conclusions

The material was at the time of publication the largest prospective cohort in the literature of western medicine with a long follow-up period by two doctors. The study has demonstrated the heterogeneity of EM in terms of aetiology, severity and prognosis.

Paper II: Nonspecific capillary proliferation and vasculopathy indicate skin hypoxia in erythromelalgia.

Aim of the study

To report histopathologic findings of affected EM skin.

Material and methods

All patients in our database (n=87) were invited to participate, and 49 eligible for inclusion accepted to join the study. In addition, we included one female patient without symptoms at the time of examination. She had previously had a limb threatening EM, and had been treated successfully with prostaglandin E1 (Kvernebo, 1998). Consecutively collected biopsies were examined. Symptoms were recorded according to a clinical severity scale based on the need for cooling described in Paper I. Duration of disease, patient age and sex were also recorded. All biopsies were divided in three equal parts, for light immunofluorescence and electron microscopy.

Results

16/49 patients had normal findings with all three investigational techniques.

Light microscopy. 33 did not show pathological findings. 12 showed increased number of capillaries in papillary dermis compared with control biopsies. Of these patients, 10 were cases of primary EM, 1 with ES and 1 with secondary EM. Other findings were

inflammation, oedema and thickened arteries. Vasculitis and thrombosis were not found in any of the biopsies. Disease severity and duration of disease in the patients with capillary proliferation was not different from the remaining patients without proliferation.

Immunofluorescence (IF) results. Twenty-eight patients showed no pathology, whereas the remaining 21 patients had pathological deposits. Granular or small lumpy deposits of C3c and immunoglobulins were seen in the small vessel walls, while fibrin was usually seen more diffusely in the inner part of the vessel wall. The combination of complement and fibrin deposits in vascular walls is consistent with vasculopathy in terms of IF microscopy, and indicates damage to vessel walls. It may be seen along with vasculitis, but is not diagnostic for this condition. None of these patients, or any other patients, had signs of vasculitis as judged by clinical findings or light microscopy.

Electron microscopy. Forty-eight biopsies from EM patients were examined. 6/30 patients with primary EM showed endothelial pathology, demonstrated as either endothelial cell defects or swollen endothelium, with or without perivascular leukocyte accumulation. One primary EM patient had perivascular leukocyte infiltration only without endothelial cell defects. Of the seven cases with endothelial cell pathology with- or without swelling of endothelial cells, six were found in patients who had capillary proliferation demonstrated by light microscopy. The only significant morphological changes seen among the 17 secondary EM cases were sparse perivascular lymphocyte infiltration observed in two patients; one with chronic myelogenous leukaemia, and one with diabetes mellitus. The ES case showed numerous capillary nests with endothelial cell defects and slight perivascular inflammatory reaction.

Conclusions

Histopathologic analysis is of limited value as a routine diagnostic tool in EM because no morphological changes are specific to EM. Capillary proliferation or vascular damage was demonstrated in 31/49, mainly in patients with primary EM. The capillary proliferation and vasculopathy can be interpreted as a consequence of intermittent skin hypoxia consistent with the shunt hypothesis.

Paper III: Impaired Neurogenic Control of Skin Perfusion in Erythromelalgia.

Aim of the study

To characterize local and central neurogenic, as well as endothelial cell function in EM, as compared with healthy controls.

Material and methods

Inclusion criteria were primary, adult (> 18 y) EM patients and severity group 2-3, 2 implies that the patient feels uncomfortably warm periodically and cools the feet by walking barefoot on cold floors, 3 indicated periods of burning pain and active cooling of the feet in cold water for less than 1 h a day. Laser Doppler flowmetry (LDF) were performed at the pulp of the first toe at rest and following provocations with Valsalva's maneuver, contralateral cooling, dependency or cuff-induced venous stasis, cuff-induced ischemia and local skin heating.

Results

Baseline skin perfusion was significantly reduced in patients with EM ($p < 0, 01$). LDF signals after sympathetic stimulation of reflexes mediated through the central nervous system was significantly diminished in patients with EM as compared with healthy controls (Valsalva's maneuver $p < 0, 01$; contralateral cooling test ($p < 0, 05$). Local neurogenic vasoconstrictor (venous cuff occlusion and dependency of the extremity) and vasodilator reflexes (local heating of the skin), as well as tests for vascular smooth muscle and vascular endothelial function (postocclusive hyperemic response) were maintained.

Conclusions

The results indicate that postganglionic sympathetic dysfunction and denervation hypersensitivity may play a pathogenetic role in primary EM, whereas local neurogenic as well as endothelial function is unaffected.

Paper IV: Prostacyclin Reduces Symptoms and Sympathetic Dysfunction in Erythromelalgia in a Double-blind Randomized Pilot Study.

Aim of the study

To determine whether iloprost, a synthetic prostacyclin analogue, primarily a vasodilator and inhibitor of platelet activation, improves symptoms and sympathetic function in patients with EM.

Material and methods

12 patients with primary EM were allocated to either iloprost infusion (n~8) or placebo (0.9% NaCl) (n~4) infusions according to a weighted randomization schedule. No differences in baseline clinical and demographic characteristics were found. Iloprost infusion was given to hospitalized patients for 6 h (10-40 ml/h determined by the side effects) on 3 consecutive days. Outcome measures were the change in the average one-week cooling score (8-point ordinal scale) and change in LDF flux after central vasoconstrictor tests (Valsalva's manoeuvre and contralateral cooling) before and after intervention. Safety was evaluated by recordings of adverse events and blood tests.

Results

The results show a significant reduction in symptoms ($p < 0,05$) and sympathetic dysfunction ($p < 0,05$) in the iloprost group compared to the placebo group. Mild adverse events were only reported among patients in the iloprost group: erythema (n~5) or warm sensation (n~2) at the injection site, headache (n~5), nausea (n~1) and hypotension (n~1). The symptoms were dose-related and resolved rapidly on reduction of the infusion rate. Maximum dosage was tolerated for three patients in the iloprost group at the third day of intervention. No clinically significant changes in blood tests were demonstrated.

Conclusions

This is the first randomized placebo controlled study in patients with EM. This small pilot study indicates that prostacyclins or analogues have a beneficial clinical and microvascular effect on patients with primary EM. Larger studies are needed.

PART SIX: GENERAL DISCUSSION AND CONCLUSIONS

General discussion

In the introduction part of this thesis an overview of the history and pathogenetic hypothesis of EM is given. Our research group has claimed that all cases of EM have a common final pathway of pathogenesis, where skin microvascular shunting and maldistribution of skin perfusion are central elements. When the work with this thesis started it was well known that primary conditions in patients with secondary EM could trigger this mechanism, and during the work with the thesis both neurophysiological and genetic studies has demonstrated that autonomic nerve dysfunction can lead to EM.

The aim of all individual papers included in this thesis was to broaden the understanding of the pathogenesis.

Paper I gives an overview of the clinical characteristics in 87 EM patients using a clinical classification system severity scale previously introduced. EM is a heterogenous condition concerning etiology, severity and prognosis. The information was used to design the other studies on pathogenesis and therapy.

The main question in paper II was: is there histological evidence for the existence of hypoxia in affected skin? We found capillary proliferation indicative of hypoxia in 12 (EPP=10/31, EPS=1/17, ES=1/2) out of 49 cases, which supports our hypothesis. This may indicate that the pathogenesis in primary EM and secondary EM may differ.

In paper III we asked the question: is there evidence for a neurogenic defect? We tested autonomic vascular reflexes and found impaired central sympathetic control of skin perfusion, intact local neurogenic control and normal endothelial function.

In paper IV EM patients were treated with iloprost, a vasodilator that may improve the hemorheological properties of the blood, and that potentially have beneficial effects on the microvascular maldistribution. A significant clinical improvement in the iloprost group, and a significant improvement in neurogenic dysfunction, compared to the placebo group, was found.

THE POST-STUDY HYPOTHESIS OF THE PATHOGENESIS OF EM (fig.8).

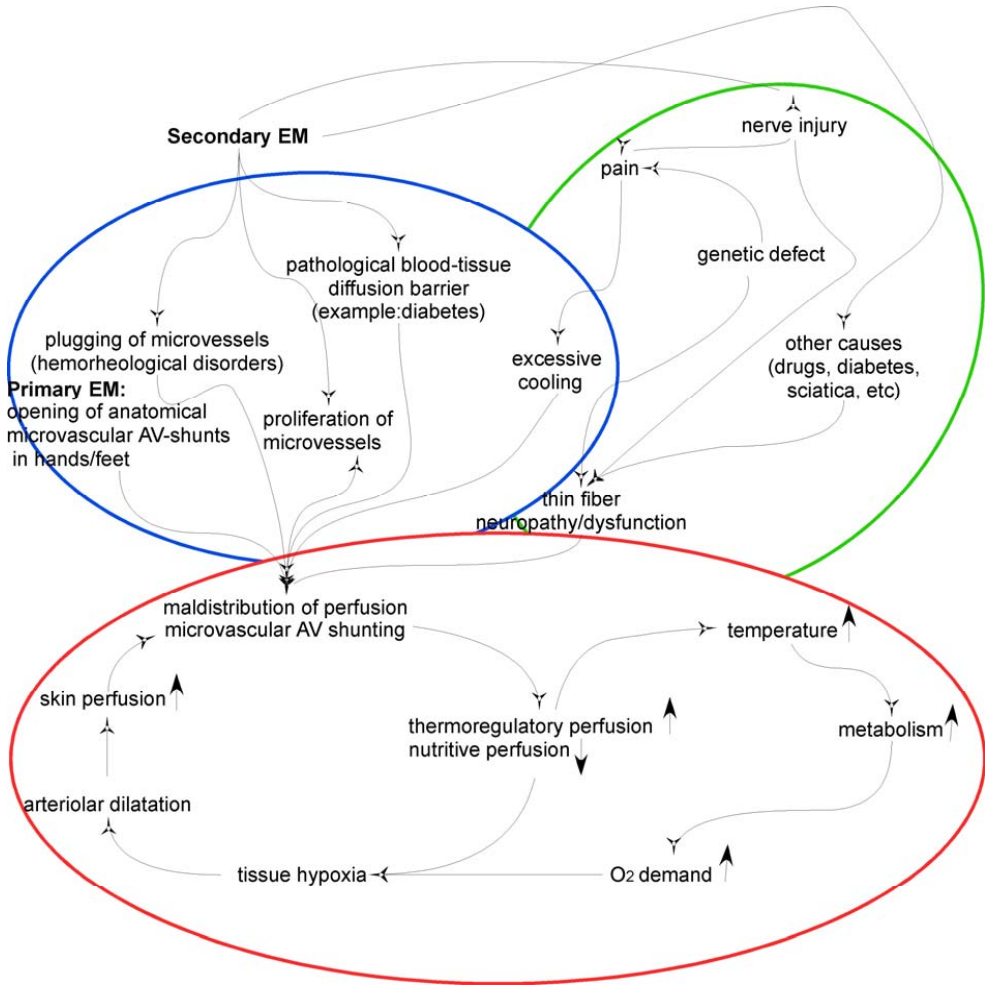


Fig. 8. The post-study hypothesis of the pathogenesis of EM. Red circle: “The common final pathway of pathogenesis”. Blue circle: The vascular pathway. Green: The neurogenic pathway.

THE VASCULAR PATHWAY

Secondary EM

Several authors have described that **hemorheological disorders** (like polycythemia, thrombocythemia and leukemia) may cause secondary EM (Michiels et al, 1985; Michiels et

al 1989; Kalgaard et al, 1997). In such cases, the functional capillary density may be severely reduced, and the spatial heterogeneity of distribution of perfused capillaries increased due to plugging of capillaries. In such patients some cells may have a lack of oxygen supply according to the theories of August Krogh (awarded the Nobel Prize in physiology and medicine in 1920) (Krogh, 1967). One of his achievements was the identification of the “Krogh cylinder,” postulating that all cells need to be located within a critical radius of a perfused capillary to survive. The radius of the cylinder is defined by the limited diffusion capacity of oxygen in the tissue, and cells located outside such a radius will experience insufficient nutrition. In tissues with a large heterogeneity of distribution of perfused capillaries and/or reduced capillary density, some cells will experience low oxygen tension, while cells that are near to perfused capillaries will experience adequate oxygen tension.

Proliferation of microvessels in the skin is a prominent feature of skin histology in our patient with ES (Kalgaard et al, 2011). These microvessels were without a muscular wall, and may probably serve as low resistance microvascular shunts. The proliferated capillaries shown in a number of patients in paper II may be a consequence of tissue hypoxia, and may possibly also serve as shunts.

A **pathological blood - tissue diffusion barrier** may impair oxygen delivery from capillaries. At least one of our patients with severe EM has his condition secondary to a poorly regulated diabetes mellitus, a condition known to impair the function of the capillary wall (Kalgaard et al, 1997).

Nerve injury and drugs can cause nerve dysfunction with a secondary maldistribution (Kalgaard et al, 1997; Mørk et al, 2002b). Other nerve injuries (like disk herniation) may cause severe pain, and cooling may give pain relief (Kalgaard et al, 1997). But excessive cooling can induce both nerve injury and vascular injury. Cooling may therefore possibly induce EM both by the vascular and the neurogenic pathway.

Primary EM

The mechanism triggering symptoms in patients with primary EM is for us uncertain.

THE NEUROGENIC PATHWAY

A neurogenic hypothesis for the pathogenesis of EM has also been proposed. One study has shown degeneration of autonomic nerve plexuses in affected skin of 1 patient with EM, as

compared with unaffected skin of the same individual and with the skin of a control person (Uno and Parker, 1983). A slight and questionable reduction in the density of autonomic adrenergic nerve terminals in the periarterial and glandular plexuses in the skin of one patient was demonstrated in another study (Blanchard et al, 1983). The finding of decreased nerve fibre density associated with dilated capillary loops in 12 of 16 patients with primary EM described by Davis et al supports the hypothesis that patients with primary EM may have a small-fibre neuropathy (Davis et al, 2006). Electrophysiologic studies have demonstrated small, afferent, nerve fibre dysfunction in patients with EM (Ørstavik et al, 2003; Ørstavik et al, 2004).

Sandroni et al have in a large patient material of 97 examined with LDF, TCpO₂, and in sub-studies performed neurophysiologic testing, autonomic reflex screening and recordings of peripheral autonomic surface potentials of patients during symptoms. They demonstrated an increase in LDF perfusion and temperature accompanied by a decrease in TCpO₂ of affected areas, confirming findings proposed by our group. A high proportion of their patients had a distal small fibre neuropathy with selective involvement of cutaneous sympathetic fibres in addition to large fibre neuropathy (Sandroni et al, 1999).

Davis et al have in a prospective study tested nerve and vascular function in patients after provoking symptoms by exercise or by increasing the ambient temperature. During symptoms, the mean temperature of the toe skin increased by 7.8 degrees C, and blood flow increased 10, 2-fold, but in this study transcutaneous oximetry measurements did not change. Results were abnormal for 49 (86%) of the 57 patients who had autonomic reflex screening. They concluded that most patients with EM in addition to other forms of neuropathy, had small-fiber neuropathy (Davis et al, 2003).

Attenuated vasoconstrictor responses to Valsalva's maneuver and indirect cooling demonstrated in paper III imply sympathetic nerve dysfunction. The sympathetic stimuli in these spinal reflexes activate different afferent pathways, but have common efferent pathways. Consequently, our findings are consistent with impaired postganglionic nerve function. Our data are in agreement with previous observations that demonstrated reduced vasoconstriction in response to inspiratory gasp and contralateral cold challenge in EM patients (Littleford et al, 1999b).

Several authors have demonstrated that primary, hereditary EM may be a neuropathic

disorder of small sensory and sympathetic neurons caused by a genetic defect in the gene SCN9A, which codes for Nav1.7, a sodium channel in peripheral thin-fiber neurons. The defect leads to hyper-excitability of sensory small-fibre neurons and reduced lidocaine sensitivity. (Michiels et al, 2005; Sheets et al, 2007). We believe that this dysfunction can cause EM either by pain that is self-treated by excessive cooling, or by affecting distal vasoregulation with a corresponding maldistribution of skin perfusion.

In our opinion, there is no conflict between the vascular and the neurogenic hypothesis. We believe that a primary thin-fibre dysfunction can lead to maldistribution of perfusion and a corresponding hypoxia. Since hypoxia may be a stimulus for capillary proliferation in the skin (Ryan, 1976), capillary proliferation may take place, paper II. Vice versa we believe that a primary vascular maldistribution leading to skin hypoxia can cause a secondary hypoxic-induced neuropathy.

“THE FINAL COMMON PATHWAY OF PATHOGENESIS”

We have previously postulated that the skin becomes intermittently hypoxic with attacks of shunting through anatomical AV anastomoses located in the skin of the hands and feet (Kvernebo, 1998; Mørk et al, 2002). In our material that at present includes more than 200 patients with EM, we have even seen several cases with critical hypoxia and limb loss in spite of open arterial supply.

Previous studies from our group have demonstrated dilated skin circulation measured with laser Doppler flowmetry (post-occlusive hyperemia index), and increased AV shunting and reduced nutritive capillary density in affected skin in primary EM patients during symptomatic attacks of in EM (Kvernebo, 1998, Mørk et al 2002a; Mørk et al, 2004a). Sandroni et al demonstrated has confirmed an increase in flow and temperature, accompanied by a decrease in oxygenation of the affected area in EM during symptoms (Sandroni et al, 1999).

Therapeutic trials with positive effects on EM patients with prostaglandin E1 and sodium nitroprussid have been published (Özsoylu et al, 1979; Özsoylu and Cuscun, 1984; Kvernebo, 1998). In Paper IV a positive effect of iloprost, a prostacyclin analogue, on EM patients was demonstrated in a blinded and placebo-controlled study. Later, a larger

blinded, placebo controlled crossover therapeutic trial with a commercially available oral prostaglandin E1 (misoprostol) showed positive effect on EM patients on both pain, cooling score and physiological measurements (Mørk et al, 2004). The mechanism of action of these vasodilatory drugs may be to redistribute the maldistributed skin perfusion, and thereby enhance the oxygenation delivery to the skin – in other words to interrupt the vicious circle described in fig. 8, the circle we believe represents the **the final common pathway of pathogenesis of EM**.

Conclusions

A better understanding of the clinical picture and the pathogenesis of EM has been the main scope of this thesis.

Paper I has demonstrated the heterogeneity of EM in terms of aetiology, severity and prognosis. We believe this improvement of understanding of the clinical picture and of classification of the patients was necessary for conducting further on pathogenesis and therapy.

In Paper II capillary proliferation and vasculopathy compatible with hypoxia, which was demonstrated in a smaller portion of the patients in the histopathology study, lends support to the vascular hypothesis of EM, AV shunting and the resulting hypoxia. The findings are compatible with the prestudy hypothesis that recurrent episodes of skin hypoxia in selected patients may lead to microvascular injury followed by vascular proliferation. However, it should be emphasized that most of the findings in the histopathology study were in fact normal, and that firm conclusions cannot be drawn. Histology could not be used for the diagnosis of EM.

In Paper III our data demonstrate that asymptomatic patients with primary EM have reduced cutaneous perfusion preceding provocation and impaired central sympathetic vasoconstrictor reflexes. Local autonomic reflexes and endothelial function are intact. The findings provide support for the existence of efferent thin fibre neuropathy and denervation hypersensitivity in at least some patients. Further studies are needed to determine if the EM associated neuropathy is primary or secondary. The vascular and the neuropathic hypothesis of pathogenesis are not mutually exclusive, as arterioles, shunts and venules are partially under neurological control. The findings in Paper III are compatible with the hypothesis of a

“final common vascular pathway”.

In Paper IV a positive effect of the prostacyclin analogue iloprost on EM patients was demonstrated, which gave support to carry out a later therapeutic trials with commercially available oral prostaglandin E1 (misoprostol). This later trial showed positive effect on EM patients and has become a well documented treatment alternative for EM (Mørk et al, 2004). The mechanism of action of prostacyclin may at least in part be to redistribute skin perfusion, and thereby enhance the oxygenation of skin tissue.

PART SEVEN: REFERENCES

- Babb RR, Alarcon-Segovia D, Fairbairn JF: Erythromelgia: review of 51 cases. *Circulation* 29:136-141, 1964
- Bada JL: Treatment of erythromelalgia with propranolol. *Lancet* 2(8034):412, 1977
- Belch JJF: Erythromelalgia: A personal perspective. *J Dermatol Treat* 3:153-8, 1992
- Belch JFF: In Tooke JE, Lowe GDO. Eds. A Textbook of Vascular Medicine. London, UK: E Arnold publishers 342-52, 1996
- Blanchard P, Grenier B, Marchand S, Rochoux MM: Erythromelalgia, arterial hypertension and increased excretion of urinary catecholamines. *Arch Fr Pediatr* 44(9):799-802, 1987
- Boron, WF, Boulpaep, Emile L: Medical physiology: a cellular and molecular approach Book. Published Philadelphia, Penn. Elsevier, 2005
- Ceyhan AM, Gurses I, Yildirim M, Akkaya VB: A case of erythromelalgia: good response to treatment with gabapentin. *J Drugs Dermatol* 9 (5):565-7, 2010
- Chang XZ, Lu HM, Zhang YH, Qin J: Hypertension and erythromelalgia as prominent manifestations of mercury intoxication. *Beijing Da Xue Xue Bao* 18; 39(4):377-80, 2007
- Cohen JS. Erythromelalgia: New theories and new therapies. *J Am Acad Dermatol*; 43: 841-7, 2000
- Cummins TR, Dib-Hajj SD, Waxman SG: Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy *J Neurosci* ; 24(38):8232-6, 2004
- Davis MD, O'Fallon WM, Rogers RS 3rd, Rooke TW: Natural history of erythromelalgia: presentation and outcome in 168 patients. *Arch Dermatol*; 136(3):330-6, 2000

Davis MD, Sandroni P, Rooke TW, Low PA: Erythromelalgia: vasculopathy, neuropathy, or both? A prospective study of vascular and neurophysiologic studies in erythromelalgia.

Arch Dermatol; 139(10):1337-43, 2003

Davis MD, Sandroni P: Lidocaine patch for pain of erythromelalgia: follow-up of 34 patients.

Arch Dermatol; 141(10):1320-1, 2005

Davis MD, Weenig RH, Genebriera J, Wendelschafer-Crabb G, Kennedy WR, Sandroni P: Histopathologic findings in primary erythromelalgia are nonspecific: special studies show a decrease in small nerve fiber density. *J Am Acad Dermatol*; 55(3):519-22, 2006

Drenth JP, Finley WH, Breedveld GJ, Testers L, Michiels JJ, Guillet G, Taieb A, Kirby RL, Heutink P: The primary erythromelalgia-susceptibility gene is located on chromosome 2q31-32. *Am J Hum Genet*; 68(5):1277-82, 2001

Drenth JP, Te Morsche RH, Mansour S, Mortimer PS: Primary erythromelalgia as a sodium channelopathy: screening for SCN9A mutations: exclusion of a causal role of SCN10A and SCN11A. *Arch Dermatol*; 144(3):389-91, 2008

Finley W.H., Lindsey Jr. J.R., Fine J.-D., Dixon G.A., Burbank M.K: Autosomal dominant erythromelalgia. *Am Journ of Medical genetics* 42: 310-15, 1992

Gaur S, Koroscil T: Late-onset erythromelalgia in a previously healthy young woman: a case report and review of the literature. *J Med Case Reports* 4; 3:106, 2009

Graves RJ: Clinical lectures on the practice of medicine. *Fannin & Co*, Dublin, 1834

Han C, Dib-Hajj SD, Lin Z, Li Y, Eastman EM, Tyrrell L, Cao X, Yang Y, Waxman SG: Early- and late-onset inherited erythromelalgia: genotype-phenotype correlation. *Brain* 132(Pt 7):1711-22, 2009

Hval E: Erythromelalgia cum polyglobulia megalosplenica. *N Mag Lægev* 89:31-36, 1928

Iqbal J, Bhat MI, Charoo BA, Syed WA, Sheikh MA, Bhat I: Experience with oral mexiletine in primary erythromelalgia in children. *Ann Saudi Med* 29(4):316-8, 2009

Kalgaard OM, Seem E, Kvernebo K: Erythromelalgia: a clinical study of 87 cases. *J Int Med* 242: 191-7, 1997

Kalgaard OM, Mørk C, Kvernebo K: Prostacyclin Reduces Symptoms and Sympathetic Dysfunction in Erythromelalgia in a Double-blind Randomized Pilot Study. *Acta Derm Venereol* 83:442-4, 2003

Kalgaard OM, Clausen OP, Mellbye OJ, Hovig T, Kvernebo K: Nonspecific capillary proliferation and vasculopathy indicate skin hypoxia in erythromelalgia. *Arch Dermatol* 147(3):309-14, 2011

Krogh A. Nobel Lecture in Physiology and Medicine 1920. Nobel Lectures, Physiology and Medicine 1901-1921, Elsevier Publishing Company, Amsterdam, 1967

Kvernebo K, Seem E: Erythromelalgia -pathophysiological and therapeutic aspects. A preliminary report. *J Oslo City Hosp* 37(1):9-12, 1987

Kvernebo K: Erythromelalgia: a condition caused by microvascular arteriovenous shunting. *Vasa* 51(suppl):1-39, 1998

Kvernebo M: Erythromelalgia- a separate disease or a pathophysiological response? Student thesis, University of Lund, Sweden, 2003

Lazareth I, Priollet P. Coexistence of Raynauds syndrome and erythromelalgia. *Lancet* 335: 853, 1990

Littleford RC: Skin microvascular function and its relevance to erythromelalgia. Thesis. University of Dundee, Scotland, UK, 1997

Littleford RC, Khan F, Belch JJ: Skin perfusion in patients with erythromelalgia. *Eur J Clin Invest.* 29(7):588-93, 1999a

Littleford RC, Khan F, Belch JFF: Impaired skin vasomotor reflexes in patients with erythromelalgia. *Clin Sci* 96:507-12, 1999b

Mescon H, Hurley HJ, Moretti G: The anatomy and histochemistry of the arteriovenous anastomoses in human digital skin. *J Invest Dermatol* 27: 133-45, 1956

Michiels JJ, Abels J, Steketee J, van Vliet HH, Vuzevski VD: Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia. *Ann Intern Med* 102(4): 466-71, 1985

Michiels JJ, Hagemeyer A, Prins ME: Thrombocythaemic erythromelalgia in chronic myeloproliferative and myelodysplastic disorders. *Neth J Med* 35(1-2):4-10, 1989

Michiels JJ: Aspirin and platelet-lowering agents for the presentation of vascular complications in essential thrombocythemia. *Clin Appl Thromb Hemost* 5: 247-51, 1999

Michiels JJ, te Morsche RH, Jansen JB, Drenth JP. Autosomal dominant erythromelalgia associated with a novel mutation in the voltage-gated sodium channel alpha subunit Nav1.7 *Arch Neurol* 62: 1587-90, 2005

Mitchell, SW: Injuries of Nerves and their Consequences. Philadelphia: JB Lippincott, 1872

Mitchell SW: On a rare vaso-motor neurosis of the extremities, and on some maladies with which it may be confounded. *Am J Med Sci* 76:2-36, 1878

Mørk C, Kalgaard OM, Kvernebo K: Erythromelalgia: A clinical study of 102 cases. *Australas J Dermatol* 38:50, 1997

Mørk C, Kalgaard OM, Kvernebo K: Erythromelalgia as a paraneoplastic syndrome in a patient with abdominal cancer. *Acta Derm Venereol* 79(5):394, 1999

Mørk C, Asker CL, Salerud G, Kvernebo K: Microvascular arteriovenous shunting is a probable pathogenetic mechanism in erythromelalgia. *J Invest Dermatol* 114:643-46, 2000a

Mørk C, Kalgaard OM, Myrvang B, Kvernebo K: Erythromelalgia in a patient with AIDS. *J Eur Acad Dermatol Venereol* 14(6):498-50, 2000b

Mørk C, Kvernebo K: Erythromelalgia—a mysterious condition? *Arch Dermatol* 136 (3):406-9, 2000c

Mørk C, Kvernebo K, Asker CL, Salerud EG: Reduced skin capillary density during attacks of erythromelalgia implies arteriovenous shunting as pathogenetic mechanism. *J Invest Dermatol* 119: 949-53, 2002a

Mørk C, Kalgaard OM, Kvernebo K: Impaired neurogenic control of skin perfusion in erythromelalgia. *J Invest Dermatol* 118: 699-703, 2002b

Mørk C, Salerud EG, Asker CL, Kvernebo K: The prostaglandin E1 analogue misoprostol reduces symptoms and microvascular arteriovenous shunting in patients with erythromelalgia. A double blind, crossover, placebo-compared study. *J Invest Dermatol* 122, 587-593, 2004a

Mørk C: Erythromelalgia: Studies on pathogenesis and therapy. *Faculty of Medicine, University of Oslo*, 2004b

Mørk C, Kvernebo K: Erythromelalgia – therapeutic strategies. In: 3rd edition. Treatment of Skin Disease. Comprehensive therapeutic strategies. Edited by Lebwohl M, Heymann WR, Berth-Jones J and Coulson I. Mosby Elsevier 2009

Nakajima Y, Koizumi K, Hirata T, Hirai K, Sakamoto A, Shimizu K: Successful thoracoscopic sympathectomy for primary erythromelalgia in the upper extremities. *Jpn J Thorac Cardiovasc Surg* 52(11):524-6, 2004

Pipili C, Cholongitas E: Erythromelalgia in a diabetic patient managed with gabapentin. *Diabetes Res Clin Pract* 79 (3):15-6, 2008

Porter JM, Moneta GL: Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J Vasc Surg* 21(4):635-45, 1995

Prevost N, English JC 3rd: Case reports: red scrotal syndrome: a localized phenotypical expression of erythromelalgia. *J Drugs Dermatol* 6(9):935-6, 2007

Reed KB, Davis MD: Incidence of erythromelalgia: a population-based study in Olmsted County, Minnesota. *J Eur Acad Dermatol Venereol*; (1):13-5, 2009

Ryan TJ, Wilkinson DS: Angiodyskinesia and osteochondritis dissecans? *Proc R Soc Med* 67(12 Pt 1):124, 1974

Ryan TJ: The blood vessels of the skin. *J Invest Dermatol* 67; (1): 110-8, 1976

Sandroni P, Davis MD, Harper CM, Rogers RS 3rd, Harper CM Jr, Rogers RS 3rd, O'Fallon WM, Rooke TW, Low PA: Neurophysiologic and Vascular Studies in Erythromelalgia: A Retrospective Analysis. *J Clin Neuromuscul Dis* 1(2):57-63, 1999

Sandroni P, Davis MD: Combination gel of 1% amitriptyline and 0.5% ketamine to treat refractory erythromelalgia pain: a new treatment option? *Arch Dermatol* 142(3):283-6, 2006

Seishima M, Kanoh H, Izumi T, Niwa M, Matsuzaki Y, Takasu A, Ban M, Kitajima Y:
A refractory case of secondary erythermalgia successfully treated with lumbar sympathetic
ganglion block. *Br J Dermatol* 143(4):868-72, 2000

Sheets PL, Jackson JO 2nd, Waxman SG, Dib-Hajj SD, Cummins TR. A Nav1.7 channel
mutation associated with hereditary erythromelalgia contributes to neuronal
hyperexcitability and displays reduced lidocaine sensitivity. *J Physiol* 581(Pt 3): 1019-31, 2007

Slutsker G E. Coexistence of Raynaud`s syndrome and erythromelalgia. *Lancet* Vol: 335,
1286, 1990

Smith L A, Allen EV: Erythermalgia (Erythromelalgia) of the extremities: a syndrome
characterised by redness, heat, and pain. *Am Heart J* 16: 175-188, 1938

Stanton-Hicks M, Jänig W, Hassenbusch S, Haddock JD, Boas R, Wilson P: Reflex sympathetic
dystrophy: changing concepts and taxonomy. *Pain* 63(1):127-33, 1995

The Erythromelalgia association (TEA) website: <http://www.erythromelalgia.org>,

Thompson GH, Hahn G, Rang M: Erythromelalgia. *Clin orthopaedics and Related Research*
144:249-54, 1979

Uno M, Parker F. Autonomic innervation of the skin in primary erythromelalgia. *Arch*
Dermatol 119: 65-71, 1983

Waxman SG, Dib-Hajj SD: Erythromelalgia: a hereditary pain syndrome enters the molecular
era. *Ann Neurol* 57(6):785-8, 2005

Yang Y, Wang Y, Li S, Xu Z, Li H, Ma L, Fan J, Bu D, Liu B, Fan Z, Wu G, Jin J, Ding B, Zhu
X, Shen Y: Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with
primary erythermalgia. *J Med Genet* 41(3):171-4, 2004

Zheng ZM, Zhang JH, Hu JM, Liu SF, Zhu WP: Poxviruses isolated from epidemic erythromelalgia in China. *Lancet* 1(8580):296, 1988

Ørstavik K, Weidner C, Schmidt R, Schmelz M, Hilliges M, Jørum E, Handwerker H, Torebjörk E: Pathological C-fibres in patients with a chronic painful condition. *Brain* 126(Pt 3):567-78, 2003

Ørstavik K, Mørk C, Kvernebo K, Jørum E: Pain in primary erythromelalgia-a neuropathic component? *Pain* 110 (3): 531-8, 2004

Ørstavik K, Jørum E: Microneurographic findings of relevance to pain in patients with erythromelalgia and patients with diabetic neuropathy. *Neurosci Lett* 470(3):180-4, 2010

Özsoylu S, Caner H, Göklap A: Successful treatment of erythromelalgia with sodium nitroprusside. *J Ped* 94: 619-21, 1979

Özsoylu S, Coskun T: Sodium nitroprusside treatment in erythromelalgia. *Eur J Paediatrics* 141: 185-7, 1984

Paper I

Erythromelalgia: a clinical study of 87 cases.

Kalgaard OM, Seem E, Kvernebo K

J Int Med 242: 191-7, 1997

Paper II

Nonspecific capillary proliferation and vasculopathy indicate skin hypoxia in erythromelalgia.

Kalgaard OM, Clausen OP, Mellbye OJ, Hovig T, Kvernebo K

Arch Dermatol 147(3):309-14, 2011

Paper III

Impaired Neurogenic Control of Skin Perfusion in Erythromelalgia.

Mørk C, Kalgaard OM, Kvernebo K

J Invest Dermatol 118:699-703, 2002

Paper IV

Prostacyclin Reduces Symptoms and Sympathetic Dysfunction in Erythromelalgia in a
Double-blind Randomized Pilot Study.

Kalgaard OM, Mørk C, Kvernebo K

Acta Derm Venereol 83:442-4, 2003

Appendix I

Erythromelalgia as a paraneoplastic syndrome in
a patient with abdominal cancer.

Mørk C, Kalgaard OM, Kvernebo K

Acta Derm Venereol 79(5):394, 1999

Appendix II

Erythromelalgia in a patient with AIDS.

Mørk C, Kalgaard OM, Myrvang B, Kvernebo K

J Eur Acad Dermatol Venereol 14(6):498-50, 2000

