

Aspirin Resistant Autosomal Dominant Familial Erythralgia: A Congenital Incurable Neuropathic Disorder Caused by a Gain of Function Mutation in Exon 26 of the SCN9a Gene on Chromosome 2q24.3

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Editorial

The concept and pathologic basis of erythromelalgia outlined by Mitchell in 1878 remained elusive for one century until Michiels discovered aspirin responsive erythromelalgia in thrombocytopenia in 1978. On the basis of the description of Mitchell [1] and clinical observations in 81 cases in which burning pain in the hands or feet was a prominent or disabling symptom, Brown postulated in 1932 five basic criteria for the diagnosis of true primary variant of burning red congested extremities [2].

1. Attacks of bilateral or symmetric burning pain occurring in the hands and feet.
2. The attacks were initiated or aggravated by standing, or exposure to heat.
3. Relief was obtained by elevation and exposure to cold.
4. During the attacks, the affected were flushed and congested and exhibited increased local heat.
5. The pathogenesis is unknown and there is no treatment available for primary erythromelalgia available
6. Smith and Allen substituted the term erythromelalgia for erythralgia to denote the importance of heat = therme. Since then both terms are confoundedly used indiscriminately as synonyms in the primary and secondary forms irrespective of aspirin-responsiveness [3]. There are a multitude of clinical conditions with secondary erythralgia-like signs and symptoms not responsive to aspirin, which originate from side effects of drugs (verapami), or arise from cutaneous vasculitis, vasculitis in lupus erythematoses, cryoglobulinemia, gout, polyarthritis nodosa, diabetes, atherosclerosis, and rheumatoid arthritis or autoimmune disorders of undetermined significance [4,5]. In our population of erythromelalgia patients we could identify the idiopathic entity in

the complete absence of any detectable underlying disorder and labeled it as primary erythralgia to emphasize the importance of heat (therme) and pain (algos) as the most prominent specific signs and symptoms [6,7].

Following the six postulates of Brown, the rare and incurable variant of symmetric red, painful extremities in the absence of any detectable underlying disorder has been recognized by Michiels since 1975 as a distinct clinical entity Michiels first described aspirin resistant idiopathic erythralgia (symmetric erythromelalgia as a congenital autosomal dominant incurable disorder in 1988/1989 [Table 1] [6]. Michiels and van Joost described in 1988 the clinical symptoms of incurable idiopathic erythralgia since early childhood in a young woman and her mother as a congenital disorder and reviewed 13 case histories of familiar primary incurable erythralgia from the literature [Table 2] [7]. The primary incurable erythralgia arises early in life or during the pubertal period as bilateral more or less symmetric burning distress in both feet, ankles and lower legs [8-16]. There is relative sparing of the toes and there is no progression to peripheral acrocyanotic ischemia, occlusive thrombosis or gangrene. The incurable and disabling burning red distress of primary congenital erythralgia is easily elicited by exercise and by exposure to heat or warmth to such a degree that there is frequently an need for cooling of the extremities because of unbearable pain. Most cases of congenital erythralgia suffer lifelong, are refractory to any treatment and become disabled, indicating that primary congenital erythralgia is a distinct disorder of unknown etiology. Our experiences and research studies undoubtedly confirm that the clinical manifestations of primary incurable congenital erythralgia are in essence completely different from aspirin-responsive erythromelalgia in thrombocytopenia vera. In extension to the six postulates of Brown, we could add five additional specific features of primary erythralgia [8-16]:

Authors	Year	Gender	Age at Onset	Age at diagnosis	Burning grade	Erythralgia localization
Single cases		F/M	Onset	diagnosis	grade	localization
Degos et al.	1963	F	1 ½	14	severe	feet/hands
Bureau et al.	1964	F	2	8	severe	feet/lower legs
Mandell et al.	1977	F	3 ½	11	severe	feet/hands
Catchpole	1964	F	11	13	severe	feet
Uno and Parker	1983	F	12	17	severe	feet
Priollet et al.	1985	F	13	19	moderate	feet

Jelinek et al.	1985	M	16	25	moderate	feet/loer legs/arms
Jorgensen et al.	1970	M	15	20	moderate	feet/lower legs
Familial occurrence probands						
Cross	1962	M	12	26	severe	hands/feet
Cohen et al.	1982	M	7	20	moderate	feet/hands
Cohen et al.	1982	F	10	14	moderate	feet/hands
Thompson et al. 1978	F		3	14	severe	feet/lower legs
Michiels et al.	1988	F	2	14	severe	feet/lower legs/hands

Table 1: Review of 13 cases histories of primary erythralgia from the literature

Dermis							
Patients	Epidermis	Perivascular mononuclear cells	Endothelial swelling	Perivascular Edema	Thickening of Basal of membrane of Capillaries	Occlusive thrombi	Subcutis
1	Hyperkeratosis hyperplasia	Minimal	Moderate	Mild	Moderate to severe homogeneous	Absent	Normal
2	Normal	Moderate/Severe	Moderate	Moderate	Moderate to severe laminar	Absent	Normal
3	Hyperkeratosis	Minimal	Moderate	Marked	Severe laminar	Absent	Normal

Table 2: Cutaneous pathology in three cases of primary congenital erythralgia (Drenth et al. [18])

- Primary erythralgia spontaneously arises in children with symmetric bilateral localization in both legs adults. In the earlier series from the Mayo Clinics by Babb et al. only 2 of 30 patients were young (<20 years) at the time of onset [17]. Early onset is conceived by us in the 1980s to be essential for primary erythralgia [6,7].
- In primary erythralgia there is relative sparing of the toes ; acrocyanotic ischemia and peripheral gangrene as the result of peripheral vessel (thrombotic) obstruction is never seen [6-15].
- Primary erythralgia has a spontaneous onset in early childhood and the persistence throughout life further support the congenital nature of primary erythralgia [7,17].
- The histopathologic findings in skin biopsies from erythralgic areas of patients with primary congenital erythralgia are non-specific, even showing the complete absence of any underlying disorder [Figure 1], and thus do not reveal a clue to its pathophysiology [Figure 1] [7-18].
- From our literature analysis and various other studies, the hereditary basis of primary erythralgia became clear to us as documented in several contributions by Michiels, Drenth, Van Joost and Van Genderen [4-15]. A hereditary basis of incurable primary erythralgia has become evident in several families [6,7,17].
- Drenth and Michiels designed a study to search for the location of a genetic defect by lodge score analsis in families reported in the literature [19]. Drenth et al. [12] of the Erasmus University Medical Center collected blood samples from European families and the large US family (Finley et al.) [17] with autosomal dominant primary erythralgia and could in collaboration with the Department of Medical Genetics Erasmus University Medical Center, Rotterdam localize the primary erythralgia susceptibility gene on chromosome 2q31-32 [19].
- In view of this paper by Drenth et al. [19], Yang et al. [20] discovered in 2004 two heterozygous gain of function mutations in exon 26 of the SCN9A gene located on chromosome 2q24.3 as the cause of dominant primary erythralgia in 2 families with autosomal dominant primary erythralgia [20]. The SCN9A codes for the human Nav1.7 high voltage dependent sodium channel alpha subunit (Nav1.7) [21], which is preferentially expressed at high levels in two types of neuron : nociceptive DRG neurons Heterozygous mutations in the SCN9A gene as the cause of congenital utosomal dominant primary erythralgia has been confirmed in several families [20-25]. In the large USA family with autosomal dominant primary erythralgia in 5 generations [17], in which linkage to chromosome 2q31-24 has been reported by Drenth et al [22], the heterozygous gain of function mutation T4393G in the SCN9A gene (Nav1.7) was found in 14 of 14 investigated family members affected family members [22]. In the family described by Michiels & van Joost with autosomal dominant primary erythralgia, Drenth detected a novel C1185A mutation as the cause of severe primary congenital erythralgia showing the complete absence of any underlying disorder in skin punch biopsies [Figure 1].
- Michiels et al. investigated 10 members of a Flemish family and found a novel heterozygous S241T mutation in the SCN9A gene (Nav1.7) in all 5 investigated affected family members [Figure 1] [24]. The pedigree of the Flamish family included 10 affected members, who fulfilled the diagnostic criteria for primary

erythermalgia [Figure 1]. Five patients cases III-2, III-6, IV-2, IV-4 and IV-5 in figure were investigated. Patient IV-1 has been described previously by us as case 1 with showing the complete absence of any underlying disorder in skin punch biopsies of this and a second patient with primary congenital erythermalgia [Figure 1]. Between 1983 and 1986, she was treated with aspirin, cinnarizine, ketanserin, antihistaminics, the 5-lipoxygenase inhibitor nafazatrom, corticoids, nifedine, prazosine, nitusside, percutaneous regional nerve stimulation, and psychotherapy.

neurostimulator, which resulted in heal of the ski lesions of the involved lower legs and feet.

The affected members III-2, III-6, IV-2, IV-4 and IV-5 were evaluated by sequencing and found to have a missense mutation (T>A) at position 721 of the SCN9a gene [Figure 1]. This mutation results in a serine to threonine replacement at codon 241 (S241T) of the voltage-gated sodium channel alpha subunit Nav1.7 as the cause of congenital autosomal dominant erythermalgia. None of the unaffected subjects possessed the mutation (T).

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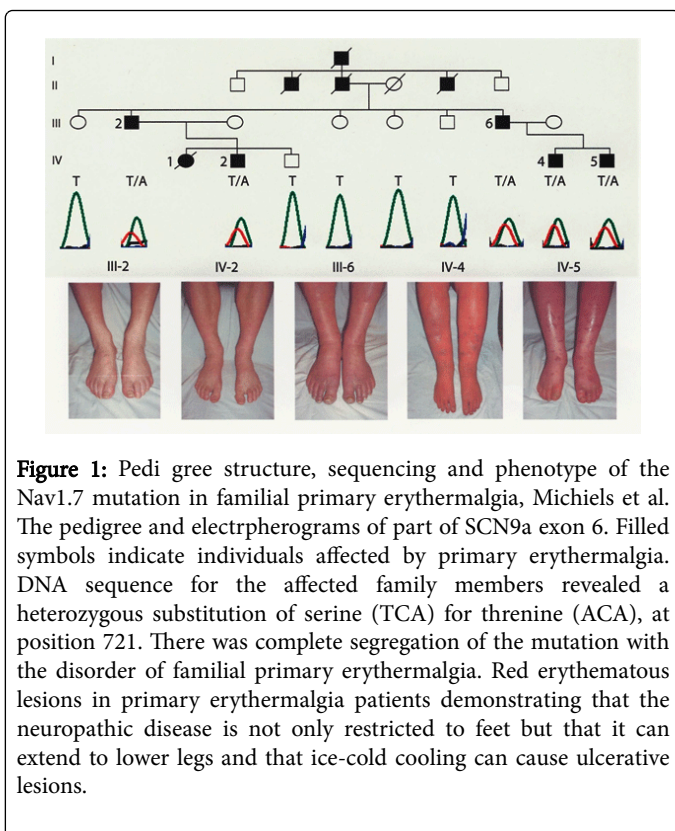


Figure 1: Pedigree structure, sequencing and phenotype of the Nav1.7 mutation in familial primary erythermalgia, Michiels et al. The pedigree and electropherograms of part of SCN9a exon 6. Filled symbols indicate individuals affected by primary erythermalgia. DNA sequence for the affected family members revealed a heterozygous substitution of serine (TCA) for threonine (ACA), at position 721. There was complete segregation of the mutation with the disorder of familial primary erythermalgia. Red erythematous lesions in primary erythermalgia patients demonstrating that the neuropathic disease is not only restricted to feet but that it can extend to lower legs and that ice-cold cooling can cause ulcerative lesions.

None of these approaches had more than a minor transient effect. In view of the excruciating pain and lack of any therapeutic relief, the patient became more and more depressed and desparately passed away by suicide in 1986. Case III-2 and IV-2 suffer from moderate attacks (lasting for a few days or week) of typical erythermalgia elicited by warmth, exercise and standing and relief was always provided by cold. A typical episode is featured by red symmetrically swollen, feet associated with burning to aching pain, which was bearable in case III-2, but IV-2 needed morphinomimetics. Exposure of feet to ice-cold water or after prolonged air cooling was always followed by intense burning to aching pain. Case III- suffered from severe erythermalgia and his two sons, IV-4 and IV-5 suffer continuously from severe erythermalgia to a similar degree as IV-1. Case III-6 could reasonably handle the distress during adult life by avoiding all circumstances that could elicit erythermalgia at work as factory laborer at ambient temperature of 61-65 F, but used to cool his feet during lunch time on a metal plate and at home by air cooling or immersion in cold-water baths. Case IV-4 and IV-5 cool their feet by ventilator, day and night and are treated with analgesics and sedatives by a multidisciplinary team. Case IV-5 developed severe skin lesions due to daily cold waterbaths, but the multidisciplinary team managed to stop this practice with a cocktail of analgesics, sedatives and lumbar implanted

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