Journal of Hematology and Thromboembolic Diseases

Michiels, J Hematol Thrombo Dis 2014, 2:4
http://dx.doi.org/10.4172/2329-8790.1000e113

Editorial Open Access

Aspirin Resistant Autosomal Dominant Familial Erythermalgia: 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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Received date: June 12, 2014, **Accepted date:** June 13, 2014, **Published date:** June 18, 2014

Editorial

The concept and pathologic basis of erythromelalgia outlined by Mitchell in 1878 remained elusive for one century until Michiels discovered aspirin responsive erythromelalgiain thrombocythemia 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 occuring in the hands and feet.
2. The attacks were iniated or aggravated by standing, or exposure to heat.
3. Relief was ontained 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 erythermalgia available
6. Smith and Allen substituted the term erythromelalgia for erythermalgia to denote the importance of heat = therme. Since than both terms are confoundedly used indiscrinimately as synonyms in the primary and seconday forms irrespective of aspirin-responsiveness [3]. There are a multitude of clinical conditions with secondary eythermalgia-like signs and symptoms not responsive to aspirin, which originate from side effects of drugs(verapami), or arise from cutaneous vasculitis, vasculitis in lupus erythematodes, cryoglobuliemia, gout, polyarthritis nodosa, diabetes, artherosclerosis, and rheumatoid arthritis or autoimmune disorders of undetermined significance [4,5]. In our population of erythromelalgia patients we could indentify the idiopathic entity in the complete absence of any detectable uderlying disorder and labeled it as primary erythermalgia 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 asprin resistant idiopathic erythermalgia (symmetric erythromelagia 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 erythermalgia since early childhood in a young woman and her mother as a congenital disorder and reviewed 13 case histotories of familiar primary incurable erythermalgia from the literature [Table 2] [7]. The primary incurable erythermalgia arises early in life or during the puberal period as bilateral more or less ymmetric burning distress in both feet, ankles and lower legs [8-16]. There is relative sparing of the toes and there is no progresion to peripheral acrocyanotic ischemia, occlusive thrombosis or gangene. The incurable and disabling burning red distress of primay congenial erythermalgia is easily elicited by excercise and byexposure to heat or warmth to such a degree that there is frquently an need for cooling of the extremities because of unbearable pain. Most caes of congenital erythermalgia suffer lifelong, are refractory to any treatment and become disabled, indicating that primary congenital erythermalgia is a distinct disorder of unknownetiology. Our experiences and research studies undoubtedly confirm that the clinical manifestations of primary incrable congenital erythermalgia are in essence completely different from aspirin-responsive erthromelalgia in thrombocythemia vera. In extension to the six postulates of Brown, we could add five additional specific features of primary erythermalgia [8-16] :

Authors	Year	Gender	Age at	Age at	Burning	Erythermalgia
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 erythermalgia from the literature

Dermis							
Patients	Epidermis	Perivascular mononuclear cells	Endothelial swelling	Perivascular Edema	Thickening of Basal membrane of Capillaries	Occulusive 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 primarycongenital erythermalgia (Drenth et al. [18])

1. Primary erythermalgia spontaneously arises in children with symmetric bilteral localization in both legs adults. In the earlier series from the Mayo Clinics by Babb et al. only 2 of 30 patients were youg (<20 years) at the time of onset [17]. Early onset is concieved by us in the 1980s to be essential for primary erythermalgia [6,7].
2. In primary erythermalgia 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].
3. Primary erythermalgia has a spontaneous onset in early childhood and the persistence throughout life further support the congenital nature of primary erythermalgia [7,17].
4. The histopathologic findindings in skin biopsies from erythermalgic areas of patients with primary congenital erythermalgia are non-specific, even showing the complete absence of any underlying disorder [Figure 1], and thus do not reveal a clue to its pathophysiolgy [Figure 1] [7-18].
5. From our literature analysis and various other studies, the hereditary basis of primary erythermalgia 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 eythermalgia has become evident in several families [6,7,17].
6. 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 erythermalgia and could in collaboration with the Department of Medical Genetics Erasmus University Medical Center, Rotterdam localize the primary erythermalgia susceptibility gene on chromosome 2q31-32 [19].
7. 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 erythromelalgia in 2 families with autosomal dominant primary erythermalgia [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 congentital utosomal dominant primary erythermalgia has been confirmed in several families [20-25]. In the large USA family with autosomal dominant primary erythermalgia 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 erythermalgia, Drenth detected a novel C1185A mutation as the cause of severe primary congenital erythermalgia showing the complete absence of any underlying disorder in skin punch biopsies [Figure 1].
8. 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, cinnarizie, ketanserin, antihistaminics, the 5-lipoxygenase inhibitor nafazatrom, corticoids, nifedine, prazosine, nitusside, percutaneous regional nerve stimulation, and psychtherapy.

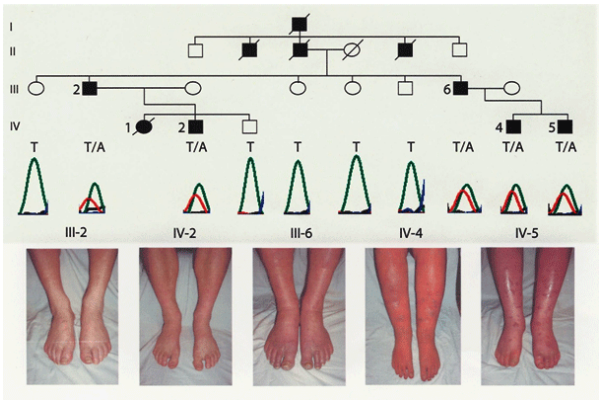

Figure 1: Pedi gree structure, sequencing and phenotype of the Nav1.7 mutation in familial primary erythermalgia, Michiels et al. The pedigree and electrpherograms of part of SCN9a exon 6. Filled symbols indicate individuals affected by primary erythermalgia. DNA sequence for the affected family members revealed a heterozygous substitution of serine (TCA) for threnine (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 aminor transient effect. In view of the excruiating 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 attacks9lasting 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, whicg wasbearable 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 toa similar degree as IV-1. Case III-6 could reasonable handle the distress during adult life by avoiding all circumstances that could elicit erythermalgia at workas factory laborerat ambient tempratu of 61-65 F, but used to cool his feet during lunch time on a metal plate and at home by air coolong or immersion in cold-water baths. Cae IV-4 and IV-5 cool their feet by ventilator, day and night and are treated with anagesics and sedatives y a multidisciplinary team. Case IV-5 developed severe skin lesions due to daily cold waterbaths, but the multidisciplinary team managed totop this practice with acorktail of analgesics, sedatives and lumbar implanted neurostimulator, which resulted in healig 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 missence mutation (T>A) at position 721 of the SCN9a gene [Figure 1]. This mutation results in a serine to threoine 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 possed the mutation (T).

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