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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The concept and pathologic basis of erythermalgia outlined by Mitchell in 1878 remained elusive for one century until Michiels discovered aspirin responsive erythromelalgia in 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 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 erythermalgia available.
6. Smith and Allen substituted the term erythromelalgia for erythermalgia to denote the importance of heat = thermes. Since then both terms are confoundingly used indiscriminately as synonyms in the primary and secondary forms irrespective of aspirin-responsiveness [3]. There are a multitude of clinical conditions with secondary erythromelalgia-like signs and symptoms not responsive to aspirin, which originate from side effects of drugs (verapamil), or arise from cutaneous vasculitis, vasculitis in lupus erythematoses, cryoglobuliemia, gout, polyarthritis nodosa, diabetes, artherosclerosis, and rheumatoid arthritis or autoimmune disorders of undetermined significance [4,5]. In our population of erythermalgia patients we could indentify the idiopathic entity in the complete absence of any detectable underlying 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 aspirin resistant idiopathic erythermalgia (symmetric erythromelalgia as a congenital autosomal dominant incurable disorder in 1980/1989 [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 histories 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 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 erythermalgia 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 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 incurable congenital erythermalgia are in essence completely different from aspirin-responsive erythromelalgia in thrombocythemia vera. In extension to the six postulates of Brown, we could add five additional specific features of primary erythermalgia [8-16]:
2. In primary erythermalgia there is relative sparing of the toes;

5. From our literature analysis and various other studies, the

Jelinek et al. 1985 M 16 25 moderate feet/loer legs/arms
Jorgensen et al. 1970 M 15 20 moderate feet/lower legs

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age at onset</th>
<th>Duration</th>
<th>Severity</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross</td>
<td>M</td>
<td>12</td>
<td>26</td>
<td>severe</td>
<td>hands/feet</td>
</tr>
<tr>
<td>Cohen et al. 1982</td>
<td>M</td>
<td>7</td>
<td>20</td>
<td>moderate</td>
<td>feet/hands</td>
</tr>
<tr>
<td>Cohen et al. 1982</td>
<td>F</td>
<td>10</td>
<td>14</td>
<td>moderate</td>
<td>feet/hands</td>
</tr>
<tr>
<td>Thompson et al. 1978</td>
<td>F</td>
<td>3</td>
<td>14</td>
<td>severe</td>
<td>feet/lower legs</td>
</tr>
<tr>
<td>Michiels et al. 1988</td>
<td>F</td>
<td>2</td>
<td>14</td>
<td>severe</td>
<td>feet/lower legs/arms</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Epidermis</th>
<th>Dermis</th>
<th>Subcutis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross</td>
<td>Hyperkeratosis, hyperplasia</td>
<td>Minimal</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cohen et al. 1982</td>
<td>Normal</td>
<td>Moderate/Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>Thompson et al. 1978</td>
<td>Hyperkeratosis</td>
<td>Minimal</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

1. Primary erythermalgia 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 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 findings in skin biopsies from erythermalic 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 pathophysiology [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 erythermalgia 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 lod score analysis 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 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 Flemish 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, nitrouside, percutaneous regional nerve stimulation, and psychotherapy.

None of these approaches had more than a minor transient effect. In view of the excreting pain and lack of any therapeutic relief, the patient became more and more depressed and despairingly passed away by suicide in 1986. Case III-2 and IV-2 suffered from moderate attacks lasting for a few days or week) of typical 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 works factory laborer ambient tempratu 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 angesics and sedatives a multidisciplinary team. Case IV-5 developed severe skin lesions due to daily cold waterbaths, but the multidisciplinary team managed totop this practice with acortkail of analgesics, sedatives and lumbar implanted neurostimulator, which resulted in healing of the skin 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 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).

References

1. Mitchel SW (1878) On a rare vaso-motor neurosis of extremities and on the maladies with which it may be confounded. Amer J Med Sc 76: 2-36.
