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Autosomal Dominant Erythromelalgia

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We present a kindred of 29 persons affected with erythromelalgia (erythermalgia) in 5 generations. This paper updates the family reported by Burbank et al. [1966]. Patients have symptoms of intermittent intense burning limb pain related to increased skin temperature. No successful treatment has been identified, and the pathogenetic mechanism has not been established. Most affected individuals are female.

KEY WORDS: Erythromelalgia, limb redness and pain, autosomal dominant

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INTRODUCTION

More than a century has passed since *erythromelalgia* was suggested as the term for a disorder characterized by intermittent intense burning pain in the limbs [Mitchell, 1878]. Mitchell reported several patients and considered the manifestations to be bilateral burning foot pain initiated by exercise or exposure to heat and relieved by elevation of the foot or exposure to cold. The affected parts would show local heat and would become flushed or congested. Brown [1932] was convinced that Mitchell had described a clinical entity or syndrome and that erythromelalgia was a rare condition. Brown also recognized a tendency to use *erythromelalgia* to describe a symptom seen in various vascular disorders. Lewis [1933] did not consider *erythromelalgia* as having a precise definition, and thought that this diagnosis should not designate a specific disease, and that *erythralgia* could be used to describe any painful redness of the skin. Erythromelalgia was thought to be a symptom-complex by Mufson [1937] when he concluded that the symptoms were due to intrinsic hypertension and dilatation of minute skin vessels. The symptoms of redness, heat, pain, and swelling of the limbs, when not associated with organic disease, constitute the primary form of erythromelalgia, termed *erythermalgia* by Smith and Allen [1938] because of the significance of heat and confusion of terms in the

literature. The secondary form has been reported in various disorders [Smith and Allen, 1938; Babb et al., 1964; Alarcon-Segovia et al., 1966; Michiels et al., 1985]. The importance of aspirin in relieving symptoms is well known, and this therapeutic response has been used to distinguish the primary from the secondary form [Smith and Allen, 19381; however, no uniformly successful therapy yet has been found [Mandell et al., 1977; Levine and Gustafson, 1987].

Attacks vary in severity and duration, and in some individuals may be incapacitating. Relief has been sought usually by cooling the limb, since symptoms appear to be triggered by increases in skin temperature. Thermographic examination showed the toes and ankles to be warmer than the legs in these patients, and this heat distribution differed from that of normal individuals [Mandell et al., 1977]. Cross [1962] reported on a pedigree with occurrence of erythromelalgia in 3 generations; some affected persons in this family also had nephritis. Since then some of the relatives affected with nephritis have been shown to have Fabry disease [Opitz et al., 19651, which remains an important nosologic consideration in all cases of hereditary erythromelalgia. Additional evidence for the familial occurrence of erythromelalgia and its occurrence as a clinical entity was provided by Burbank et al. [1966], who reported 19 affected relatives in this Alabama family. Burbank et al. concluded erythromelalgia to be either an X-linked or autosomal dominant disorder. Burbank et al. [1966] studied 5 affected persons in this family who showed no evidence of renal or hematological disease. By study of 2 with venous occlusion plethysmography, he concluded that the distress was due not to increased blood flow in the limbs but to local heating. Since our proband was different from Burbank's, we did not realize we were studying the same extended family.

PEDIGREE AND CLINICAL REPORTS

The pedigree (Fig. 1) includes 29 affected persons (22 females, 7 males) in 5 generations. An affected male (IV-13) has 2 unaffected daughters (V-7; V-9). V-23, a 5-year-old-boy, has shown some symptoms of the disorder; however, at this time, it is not certain that he is affected. In some relatives symptoms have occurred even before age 5 years, but in some they have occurred later. If V-6, V-8, or V-23 prove to have the disorder, then male-to-male transmission would make this an autosomal dominant disorder. Within the next few years, it should be possible to obtain definite information about the inheritance in this family.

Patient 1 (IV-22)

This 26-year-old Caucasian woman, the proposita, dated onset at age 9 years of an intense burning sensation of her feet while walking. Gradually the frequency of episodes, correlated with increased heat of the limbs, increased through the years, and relief of symptoms by cooling the limbs or taking aspirin became more difficult. Symptoms of pain and redness have become more pronounced and now extend almost to the knees and elbows. Symptoms characteristically included pain, redness, increased skin temperature, and slight swelling of the ankles and feet, and occasional involvement of hands. These symptoms have been produced by anxiety and occasionally have been accompanied by nausea and diarrhea. The onset of symptoms was reported to be related to exercise, warm weather, dependent position of the lower limb, and other conditions that caused increased skin temperature of the limbs. Humidity aggravated symptoms. Hand symptoms could be produced by placing them in warm water. Examples of relief included placing the feet in

a bucket of ice, arranging for a fan to blow across the feet during the sleeping hours, replacing carpets in the home with tile, and extensive use of air conditioners. Aspirin seemed to be the best medication, and up to 100 tablets were taken per week. While she was a college student, efforts were made to schedule classes late in the day. Episodes were more frequent and severe while residing in central Florida Than in Alabama, where the humidity was less. Symptoms were milder in Arizona, where there was low humidity. There is no history of chronic diseases.

On examination, both feet and ankles had a reddish brown discoloration, with small scattered bright-red spots. Bright-red spots appeared during walking to the clinic, and the onset of pain and swelling were expected to follow. Some scarring was noted on the feet but none on the hands. The scarring was presumed to have resulted from scratching the involved areas. This discoloration and scarring gradually became more pronounced during our follow-up period of approximately 4 years.

Patient 2 (V-16), Daughter of Patient 1

This 8-year-old girl had onset of symptoms at about age 1 year. These symptoms were redness, pain, and elevated skin temperature of the ankles and feet. The severity of the symptoms resulted in more absences from school in the fall and late spring than in the winter. Her toes became bright red on walking on a concrete sidewalk for a few minutes during the examination. No permanent discoloration about the limbs was noted. Her growth and development were normal, and there was no history of other health problems other than the usual childhood illnesses.

Patient 3 (V-17), Daughter of Patient 1.

This 7-year-old girl had onset of intense burning of feet at about the time she learned to walk at approximately age 1 year. She had more episodes than her sister and missed more days of school. She had been troubled with bouts of diarrhea and required Ritalin® for her hyperactivity. The family associated the bouts of diarrhea with episodes of burning feet. Participation in physical education had been a problem, since exercise precipitated the episodes of intense burning pain of the feet and ankles. Her growth and development were normal, and there was no history of other health problems, other than the usual childhood illnesses. Physical examination showed bright redness of toes after brief walking on a sidewalk. Normal skin color returned within a few minutes.

Patient 4 (IV-36)

This 22-year-old woman resided in southern California but visited Alabama occasionally. She was in good health except for intermittent pain, redness, and burning of feet and ankles. She dated the onset of these episodes from age 4-5 years, when the symptoms were initiated by exercise on the playground. Pain radiated from the foot and ankle to the knee. These episodes would occur in winter and summer, and especially after walking 3-4 blocks. Stopping exercise would alleviate both pain and burning. Occasionally symptoms would occur in the hands with radiation to the elbows. Some of the conditions that caused the onset of symptoms included wearing leather shoes, using excess bed clothing at night, drinking alcoholic beverages, and taking examinations in school. Hand symptoms were brought on by wearing gloves, ironing clothes, or placing them in hot water. Pain and burning were aggravated by humidity. Her feet developed a reddish purple color when painful. Approximately 200 episodes occur per year. At night there was a dull aching pain about the feet. Physical examination did not show any permanent discoloration of the hands or feet.

A number of medications had been prescribed. Aspirin afforded some relief, and it was not uncommon for 100 tablets to be consumed per week. Treatment without benefit included Clinoril®, Indocin®, L-tryptophan, diuretics, and estrogen.

Patient 5 (IV-21)

This 29-year-old woman was evaluated at age 18 years by a neurosurgeon because of intermittent burning, stinging, and perspiration of her feet and hands. During the summer she would have severe discomfort in both feet after walking one-half block. She complained also of pain in her hands, but this was less severe than in her feet. Her feet were warm, dusky, and wet. Reflexes, sensation, and pulses were normal. Redness has not recurred since bilateral lumbar sympathectomy surgery; however, the burning pain associated with heat has continued. Pain during the episodes seemed to worsen after her only pregnancy. Excessive burning at the incision site following cesarean section was treated with ice packs and cortisone.

Patient 6 (III-8)

This 55-year-old woman, mother of the proposita, dated her onset of symptoms of ankle pain, swelling, and redness at about age 6 years. These symptoms were most severe during her youth when she was on the playground. She now attributes the decrease in episodes to wider use of air conditioning in the home. She wears sandals without socks to reduce the onset of symptoms. She has had hand involvement when ironing clothes. She was unable to continue a typing position because of the persistence of the symptoms. During her last 3 of 4 pregnancies she believes symptoms were milder. She has used aspirin for the relief of symptoms. Otherwise her health is good. On examination her ankles have slight scarring but no permanent discoloration.

Patient 7 (IV-13)

This 39-year-old man, brother of the proposita and a heavy-machine operator, had onset of episodic ankle pain, swelling, and redness at about age 7 years. Symptoms first appeared on the school playground, and the episodes gradually became more severe until age 10 years, when he quit participating in sports. He tries to avoid sunlight in order to lessen the chances of the onset of symptoms. Shoes too large are worn purposely for more comfort. Symptoms are brought on after immersing feet in warm water for about 10 minutes. A fever will initiate symptoms. There is no history of chronic diseases

DISCUSSION

Familial primary erythromelalgia or erythermalgia seems to be a specific diagnostic entity that must be separated from secondary causes of the symptoms. The pedigree (Fig. 1) shows this disorder to have appeared in successive generations and to have affected more females than males. Since affected males had unaffected daughters, it does not appear to be an X-linked dominant trait in this family. A correlation between the onset of skin redness caused by heat and the distressful symptom of foot pain is reported in all of our patients. Environmental influences increasing skin temperature caused the onset of the burning sensation, redness, and some swelling, and symptoms were alleviated gradually by lowering the skin temperature. The symptoms may occur throughout the year and seem to be aggravated by increased humidity and to be lessened by a dry climate. Vasodilation does not seem to explain the symptoms, since blood flow reduced by a cuff did not improve them [Mandell et al., 1977]. Uno and Parker [1983] attributed the clinical findings to a disturbance in sympathetic innervation.

Treatment is not very satisfactory. Although lowering the skin temperature helps, the pain and redness can persist and can be debilitating. Medications of many categories have been unsuccessful [Mandell et al., 1977; Levine and Gustafson, 1987]. Although no successful treatment has been identified, some relief of symptoms, in addition to aspirin [Smith and Allen, 1938], has been reported. Anti-inflammatory agents [Mandell et al., 1977], antiserotonin agents [Catchpole, 1964; Pepper, 1968; Jelinek, 1970], hydantoin [Mandell et al., 1977], beta-blocking agents [Bada, 1977), vasodilators [Cross, 1962], vasoconstrictors [Jelinek, 1970], and sodium nitroprusside [Ozsoylu et al., 19791 have been temporarily helpful, as has biofeedback [Putt, 1978]. Medications reported to be ineffective are in the following groups: barbiturates [Mandell et al., 1977], anti-hypertensive agents [Mandell et al., 1977], antihistamines [Catchpole, 1964], acetylcholine-blocking drugs [Catchpole, 1964], antiserotonin agents [Mandell et al., 19771, tranquilizers [Mandell et al., 19771, vasodilators [Catchpole, 1964], vasoconstrictors [Mufson, 1937], and indomethacin [Thompson et al., 1979]. Sympathectomy has been tried in some of the severely affected cases, but this has not been beneficial in all cases [Telford and Simmons, 1940]. Two of our patients (IV-10, IV-21) had sympathectomies without permanent benefit. It has been suggested that the temporary response to aspirin may be a useful diagnostic criterion for separating primary from secondary causes [Smith and Allen, 1938].

Only a few patients with primary erythromelalgia have been reported. Table I summarizes case reports with regard to symptoms and limbs involved. In the family we studied, the onset of symptoms was in childhood, and episodes seemed to increase in frequency and severity with age. The age of onset varied greatly in the patients reported, and it was difficult to be sure if all the individuals listed had the same disorder. It is possible that the older patients in Table I may have had symptoms that preceded disorders with vascular complications. A series of 30 cases of primary erythromelalgia was summarized by Babb et al. [1964], and in this group there was a wide range in the age of onset. As Mandell et al. [1977] concluded, patients who had an onset of symptoms over age 40 years were more likely to have the secondary form of this disorder. In fact, secondary erythromelalgia can precede hematological disorders by more than a decade [Alarcon-Segovia et al., 1966].

Recently Drenth and Michiels [1990] have considered patients with erythromelalgia to be of 3 types. The members of the family we have studied are in the type referred to as primary erythermalgia, a rare disorder, which has its onset in childhood and adolescence. These family members affected meet the 6 diagnostic criteria proposed by Drenth and Michiels [1990], namely, attacks of local red vasodilation and congestion with increased local skin temperature and burning pain; bilateral occurrence; attacks aggravated by exercise and heat; relief provided by cooling, rest, and raising limbs; absence of primary or associated disease; and refractoriness to drug treatment. A second type included those patients who have thrombocytopenia and erythromelalgia. There is no history of thrombocytopenia or bleeding disorders in our family. The third type was referred to as *secondary erythromelalgia*, which is found in association with a number of disorders, including grout, rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, vascular diseases, and other disorders. A review of the causes of death of members at increased risk in the family we have studied (Table II) and the health history of those

above the age 50 years does not indicate the presence of chronic diseases that have been associated with erythromelalgia (Table III).

An epidemic of erythromelalgia has been reported among school children in China [Zheng et al., 1988]. The symptoms were preceded by respiratory infections. The episodic occurrence in the family we have studied and its appearance in successive generations does not suggest an infectious etiology.

Several patients with erythromelalgia were reported by Lazareth et al. [1988], and in his group were 9 patients who had primary erythermalgia. These patients with the primary form were younger than those with the secondary form and had paroxysmal bilateral attacks that sometimes were severe and occurred over a period of years. The patients we studied are similar in that the bilateral episodes had onset by age 10 years and continued to occur throughout life.

The family reported by Cross [1962] had members affected with erythromelalgia in successive generations, and some of them also had nephritis. The major disorder was renal disease; however, the patient described had episodic blotchy, redness, and tenderness of hands and feet. Opitz et al. [1965] referred to this Toronto family as having Fabry disease. Female members of the family we studied reported bouts of red and painful feet that differed from the occasional bouts described by Cross [1962]. More males than females were affected in this Toronto family, which had some members affected with Fabry disease, while in our family there were more affected females and possibly an autosomal dominant disorder or a disorder with a more complex pattern of inheritance. Fabry disease and fucosidosis were considered in this family with hereditary erythromelalgia. a-D-galactosidase A and a-Lfucosidase levels were determined in 4 affected family members: 2 male and 2 female (Table IV). The proposita, IV-22, the most severely affected of the family members examined, her mother, brother, and a first cousin had normal enzyme levels. Therefore, symptoms in our patients were not due to Fabry disease. The normal enzyme levels for a-L-fucosidose and the absence of other characteristic features of this syndrome in these patients rules out fucosidosis.

Additional families need to be located to gain more information about the degree of variation in clinical severity and about the penetrance. Some of the affected family members we studied could have been undetected because of the mildness of the symptoms. For example, whereas one of our patients (III-15) reported mild symptoms and improvement in them over a period of years, others, including the proposita, apparently have scarring secondary to scratching the ankles. IV-36, a college student, is so severely affected that she has sought psychiatric help. Several other relatives with less severe disease have sought an excuse from physical education classes during grade school. Of the several members examined in this family, the females were more severely affected than the males.

In reviewing the literature, a mother, her daughter, and 2 brothers were all affected, with the daughter being more severely affected [Thompson et al., 1979]. The most extreme cases reported required amputations as a result of nonhealing secondary to infected ulcerations [Thompson et al., 1979; Kirby, 1987]. Finally, with regard to the issue of penetrance, Cross [1962] reported a pedigree with 2 autosomal disorders, erythromelalgia and nephritis, and in this family reduced penetrance was noted for erythromelalgia. Levine and Gustafson [1987] concluded that this disorder was rare in adults over 40, and that it was more common in males than females. It appears from a literature survey

(Table I) and from this family study that females are more likely to be affected. This sex distribution differs from that considered by Juergens et al. [1980]. Perhaps this diagnosis should be restricted to those cases with a childhood onset and no evidence of other vascular diseases.

The mechanism for initiation of pain is not yet known. What information does exist is based on published observations in only small numbers of patients. For instance, Burbank et al. [1966] concluded that these symptoms were not caused by increased blood flow but rather by local heating. Cuff pressure applied to a symptomatic limb to interrupt blood flow did not relieve symptoms [Mandell et al., 1977]. Erythromelalgia with thrombocythemia has been shown to be caused by plateletmediated arteriolar inflammation [Michiels et al., 1985]. In contrast, a patient with erythromelalgia and without thrombocythemia was reported to lack any evidence of microvascular occlusive disease [Priollet et al., 1985]. Finally, the response to aspirin prompted the study of prostaglandin synthesis in 2 patients who showed an increase in synthesis in skin biopsies [Jorgensen and Sondergaard, 1987]. Thus far, the underlying mechanism for this disorder is obscure, and satisfactory treatment has not been identified.

We conclude that this family studied by us almost 25 years after the Burbank et al. [1966] report and other studies show a symptom complex that constitutes a specific diagnostic entity. Erythermalgia in this family with 29 affected members may be an autosomal dominant trait. The variation in clinical severity in this family is from rather mild with tolerable symptoms to those who had sympathectomy for possible pain relief. Additional families must be studied to learn about penetrance, expressivity, and sex distribution.

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