Meige Disease (Familial Lymphedema Praecox) and Cleft Palate: Report of a Family and Review of the Literature

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This is a report of a family with lymphedema praecox and cleft palate. The mother had only lymphedema of the lower extremities; she gave birth to five sons, 3 of whom had both lymphedema of the lower extremities and cleft palate. Others have reported similar associations in the literature without calling attention to their relationship. In familial cases, an autosomal dominant mode of transmission with variable expression has been suggested. A common pathogenetic mechanism that might account for the localized lymphedema and associated cleft palate can only be speculated at this stage of our understanding of the condition.

The association of facial clefts with other malformations may be coincidental or may connote a common pathogenetic mechanism. When such associations recur in families, they merit particular attention. The purpose of this report is to draw attention to the association of primary lymphedema and clefts of the secondary palate in a family, and to review the literature that lends support to the association and suggests an autosomal dominant mode of inheritance.

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Review of the Literature

Primary lymphedema is a rare disease that results from impaired lymphatic drainage. The disease is usually limited to the legs, but arms, hands and feet can also be affected (Fonkalsrud and Coulson, 1969; Fonkalsrud, 1979; and Saijo et al., 1975). The cause of primary lymphedema is believed to stem from congenital absence, hypoplasia or underdevelopment of the superficial lymphatic channel system inhibiting effective drainage leading to enlargement of the affected limb (Kinmonth et al., 1957; Esterly, 1965; Stone and Hugo, 1972; Fonkalsrud and Coulson, 1973; Saijo et al., 1965; and Fonkalsrud, 1979). Children with involvement of the upper extremities frequently have lymphatic abnormalities in other areas of the body, i.e., external genitalia, intestinal lymphangiectasia, etc. (Milroy, 1928; Esterly, 1965; Fonkalsrud, 1979; and Miller and Motulsky, 1978). The association of lymphedema with other malformations such as distichiasis, myopia, ptosis, sensorineural hearing loss, cholestasis, cerebro-vascular malformation, yellow nails, cleft palate, etc. has been reported (Higgins, 1927; Strauss, 1929; Jennett, 1931; Schroeder and Helweg-Larsen, 1950; Kinmonth et al., 1957;

Jester, 1977; McKusick, 1978; and Wheeler et al., 1981).

Three forms of primary lymphedema have been described: (1) lymphedema tarda, with onset in the late second or third decade of life; (2) lymphedema praecox with onset at or near puberty; and (3) congenital lymphedema, noticed at birth or soon thereafter (Kinmonth et al., 1957; Esterly, 1965; Stone and Hugo, 1972; and Fonkalsrud and Coulson, 1973). There is a rare form of congenital lymphedema associated with amniotic band constrictions, but this is a separate entity (Goodman, 1962; and Fonkalsrud, 1979).

Lymphedema can cause severe cosmetic deformity as well as impaired ambulation. Treatment depends on the severity of the condition. It includes dietary management, physical and drug therapy for mild forms and surgical intervention for severe forms (Schroeder and Helweg-Larsen, 1950; Ersek, 1966; Fonkalsrud, 1969, 1979; Stone and Hugo, 1972; Fonkalsrud and Coulson, 1973; Saijo et al., 1965; Jester, 1977 and Wheeler et al., 1981). Spontaneous remission has been reported (Saijo et al., 1975).

Both sporadic and familial forms of primary lymphedema have been reported (Jennett, 1931; Kinmonth et al., 1957; Goodman, 1962; Esterly, 1965; Ersek, 1966; Fonkalsrud and Coulson, 1973; Jester, 1977; Miller and Motulsky, 1978; Fonkalsrud, 1979; and Wheeler et al., 1981). When lymphedema is of the hereditary form, and its onset has been at or near birth (congenital), the eponym Milroy disease is applied. When the familial lymphedema appears at or about puberty (lymphedema praecox), the eponym Meige disease is utilized (Milroy, 1928; Schroeder and Helweg-Larsen, 1960; Goodman, 1962; Esterly, 1965; Stone and Hugo, 1972; and Wheeler et al., 1981).

Several modes of inheritance have been suggested. According to Ersek et al. (1966) the extensive pedigree of Milroy's original family did not conform to the expectations of Mendelian inheritance. This same author reported a family in which congenital lymphedema appeared to follow a sex-linked dominant pattern. However, males were not reported to be more severely affected than females, which would be expected in a sex-linked dominant pattern. The family analyzed by Esterly (1965) excluded X-linked dominant inheritance. Other authors have suggested autosomal dominant inheritance with variability in expression (Schroeder and Helweg-Larsen, 1950; Esterly, 1965; Jester, 1977; Miller and Motulsky, 1978; and Wheeler et al., 1981). Autosomal recessive inheritance was suggested by Goodman (1962) for the Meige type. Wheeler et al. (1981) reported that the two forms of familial lymphedema breed true, that is families with the late onset type (Meige disease) do not include individuals with early onset disease (Milroy disease), and conversely. Reported chromosome analyses yielded grossly normal karyotypes (Ersek et al., 1966 and Jester, 1977). In the earlier study banding was not available and it was not mentioned in the later report.

Cleft palate as an associated finding with both Milroy and Meige diseases has been reported (Higgins, 1927; Strauss, 1929; Jennett, 1931; and Jester, 1977) (Figure 1). Such reports included "cleft palate-like speech with arch deformity in the posterior portion of the hard palate" (Jennett, 1931); bifid uvula with and without submucous cleft of the hard palate (Jester, 1977); and complete cleft of the hard and soft palate (Higgins, 1927; Strauss, 1929). It is interesting to note that in no instance was cleft of the lip reported.

Differential diagnosis for primary lymphedema includes: lymphedema secondary to tumors, amniotic bands, irradiation, parasitic infestation, infection, allergies, posthrombotic causes, nodal resection, and trauma (Kinmonth et al., 1957; Goodman, 1962; Fonkalsrud, 1969, 1979; Stone and Hugo, 1972; Saijo et al., 1975; Miller and Motulsky, 1978). Certain genetic conditions should be considered in the differential diagnosis, i.e., Noonan syndrome, Turner syndrome, yellow nail syndrome, etc. (Miller and Motulsky, 1978).

Case Presentation

CCFA #12: This white male was first seen at the University of Illinois Center for Craniofacial Anomalies at the age of 3 years and 5 months, for an unrepaired cleft palate (Figure 2). The rest of the physical examination was unremarkable. At the age of 16 years, he was seen in the pediatric department clinic where the diagnosis of lymphedema of both legs was made. The condition persisted and was

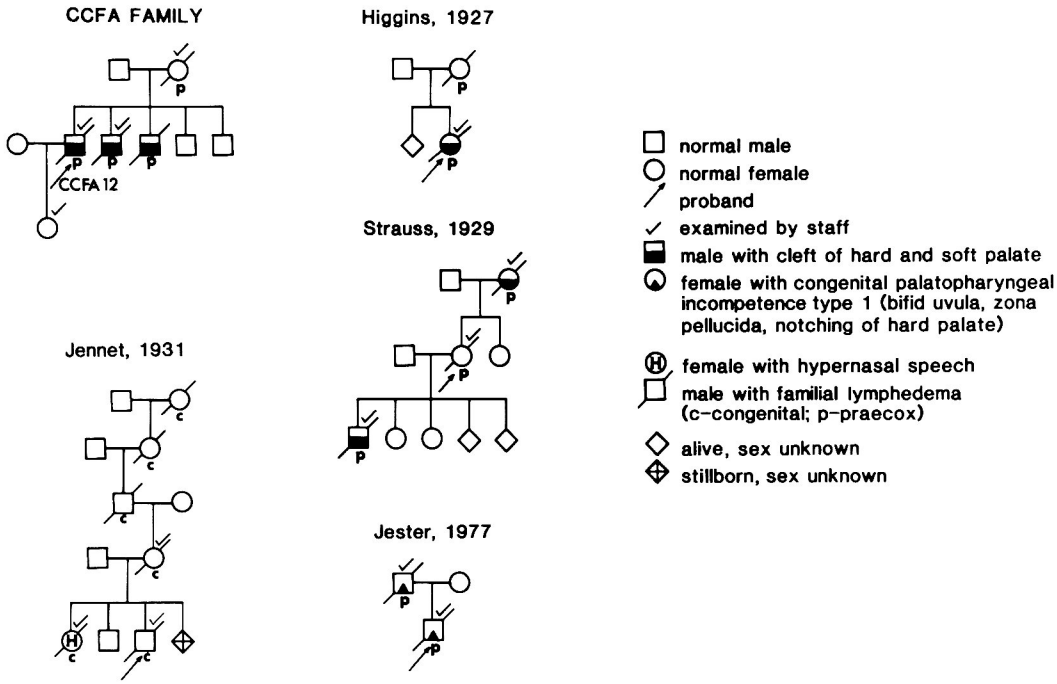

FIGURE 1. Pedigrees obtained from CCFA family and families reported in the literature affected with cleft palate and congenital lymphedema or lymphedema praecox.

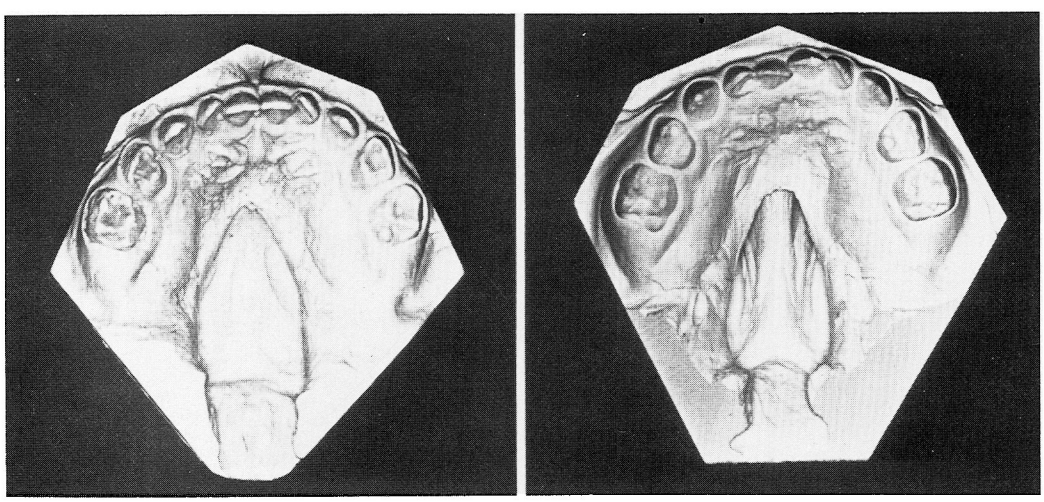

FIGURE 2. Dental study casts showing isolated palatal cleft in the two brothers examined at the Center.

judged to be severe at 23 years of age (Figure 3).

CCFA #382: The younger brother of CCFA #12, was first seen at the age of 10 months for an unrepaired cleft palate (Figure 2). The cleft palate was repaired at the age of 4 years. At the age of 8 years, the patient was seen at the pediatric clinic for swelling of the right lower leg. At age 13, it was reported that the swelling affected both legs. Swelling of both legs persisted and it was reported to be mild at the age of 22 years (Figure 4).

CCFA #1136: The mother of the two previous cases (CCFA #12 and #382) was also affected

with severe lymphedema of both legs (Figure 5). This condition was first detected at the age of 12 years. She does not have a cleft palate. The medical history of this family included a report of a third brother affected with cleft palate and lymphedema of both lower extremities. This individual was not examined by our staff and therefore not included in this report.

Family History: This family has been lost to follow-up and no complete pedigree is available. Other first degree relatives have not been examined by our professional staff, although they are reported to be unaffected.

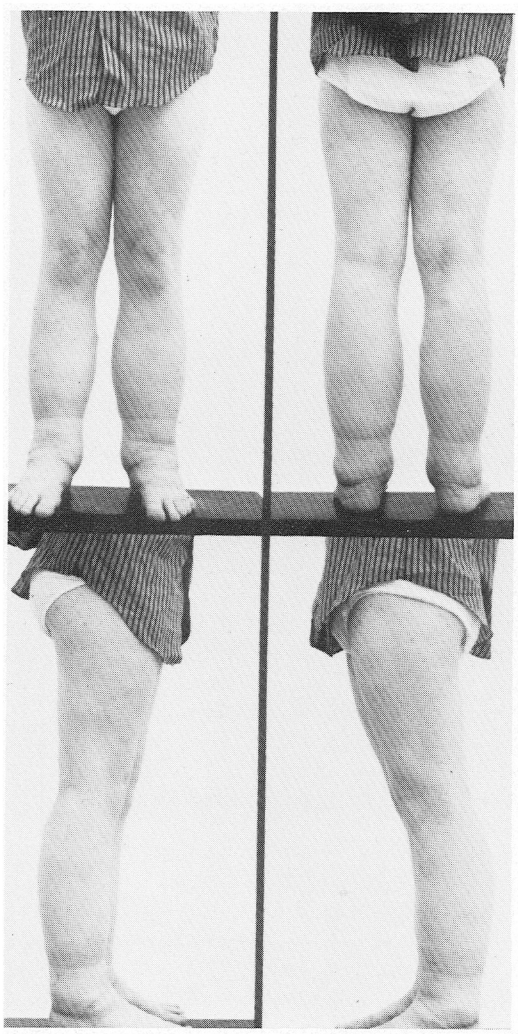

FIGURE 3. CCFA #12. Severe lymphedema affecting both lower extremities (from the knee down) in white male, 23 years and 5 months of age. The left lower leg is larger than the right. Dorsum of both feet is affected.

Discussion

This case report, coupled with a review of the literature, suggests an association between familial lymphedema and isolated cleft palate. However, the nature and frequency of this association are clouded by several factors. For example, primary lymphedema is probably phenotypically and etiologically heterogeneous. Cleft palate may represent part of a broad phenotypic spectrum of one subgroup of the disorder, which may also be characterized by other associated malformations. Alternatively, the association of cleft palate and primary lymphedema may represent a distinct association which has been underreported due to failure to recognize the potential significance of the association or to identify microforms such as submucous cleft palate and bifid uvula. Conversely, patients or families observed in cleft palate clinics may not have been thoroughly examined and history taking may have been incomplete, thereby failing to identify or recognize the significance of associated primary lymphedema. In addition, patients undergoing surgical repair of the cleft palate may be lost to subsequent follow-up prior to the onset of lymphedema.

Ideally, one would like to identify a common pathogenetic mechanism to elucidate the possible association between cleft palate and primary lymphedema. One suggested mechanism is based on a report by Kinmonth et al. (1957) of a group of patients affected with primary lymphedema in which the frequency of associated congenital anomalies was higher than might have been expected in the general population. The associated anomalies most commonly encountered were blood-vascular malformations. The authors indicated that the vascular anomalies were often trivial in nature (i.e., capillary hemangiomata of the skin). They also stated that lymphatic deformities were frequent in patients with gross vascular anomalies such as congenital arteriovenous fistulae. These observations led Kinmonth and coworkers (1957) to suggest that the lymphatic abnormality might be due to some error in fetal development, during which the lymphatic and vascular systems are closely associated.

It is thought that primary lymphedema results from congenital underdevelopment of the superficial lymphatic channel system (Es-

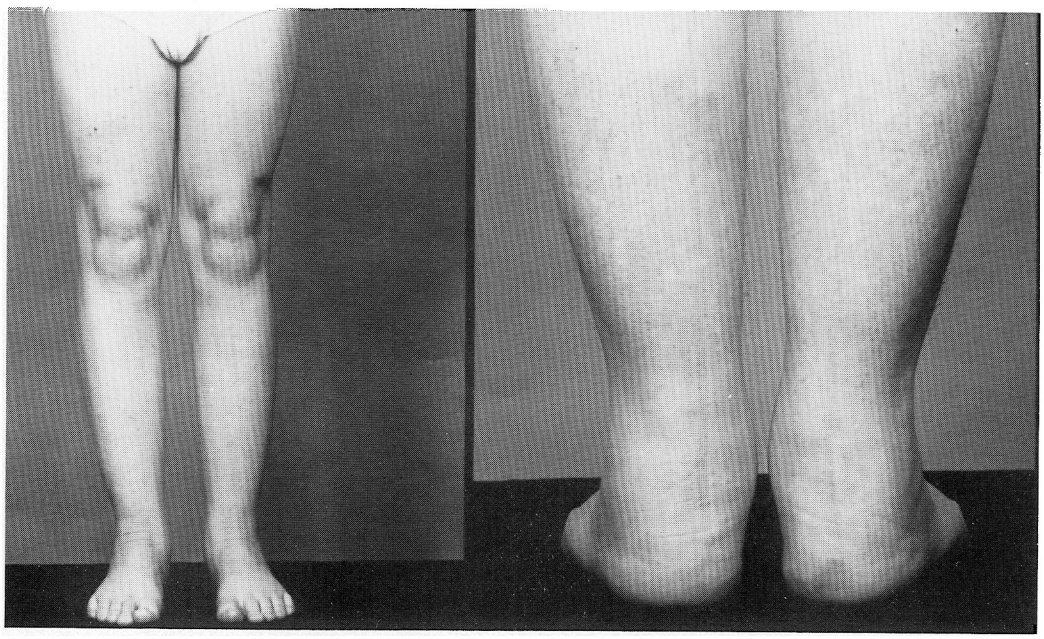

FIGURE 4. CCFA #382. Mild form of lymphedema affecting primarily the medial aspect of both ankles in white male 21 years and 6 months of age.

terly, 1965; Saijko et al., 1965; Kinmonth et al., 1957; Stone and Hugo, 1972; Fonkalsrud and Coulson, 1973; and Fonkalsrud, 1979), and it occurs in association with lymphatic abnormalities in other areas of the body (Milroy, 1928; Esterly, 1965; Miller and Motulsky, 1978; and Fonkalsrud, 1979). In experimental animal models, selected teratogens may cause alterations (i.e., reduced lumen of the vascular and palatine arteries, positional alterations of the palatine neurovascular bundle, etc.), as well as delayed development of the palatal vascular system, which in turn may interfere with growth and elevation of the palatal shelves, resulting in cleft palate (Gregg and Avery, 1971; and Diewert, 1976). From these studies we can speculate that a possible abnormality in the vascular and lymphatic systems of the secondary palate could account for a greater than expected frequency of cleft palate in patients affected with primary lymphedema which present obvious lymphatic malformations, and usually malformations of the vascular system (Kinmonth et al., 1957).

The mode of inheritance of familial lymphedema in association with cleft palate is compatible with autosomal dominant transmission with variable expressivity. For example, in our family a female is affected only with primary lymphedema while three of her five sons are affected with both primary lymphedema and cleft palate. Several expectations of autosomal dominant inheritance are met by our family and the reviewed pedigrees such as, vertical transmission from female to male/female and male to male/female. The exact ratio of affected to unaffected and male to female family members is not known due to the limited number of case reports and inadequate pedigree data. Combining our family with the limited data from the literature, a 2:1 male to female ratio (6 males and 3 females) was observed. The significance of this finding is unclear. Sex-linked dominant transmission is unlikely because male to male transmission has been reported (Jester, 1977) (Figure 1), and males are not reported to be more severely affected than females. In the family reported herein, sex-linked dominant transmission cannot be ruled out because an affected male (Figure 1) had an unaffected daughter, since at this time we cannot exclude lymphedema of teenage onset.

The possible association between primary lymphedema and cleft palate and its micro-

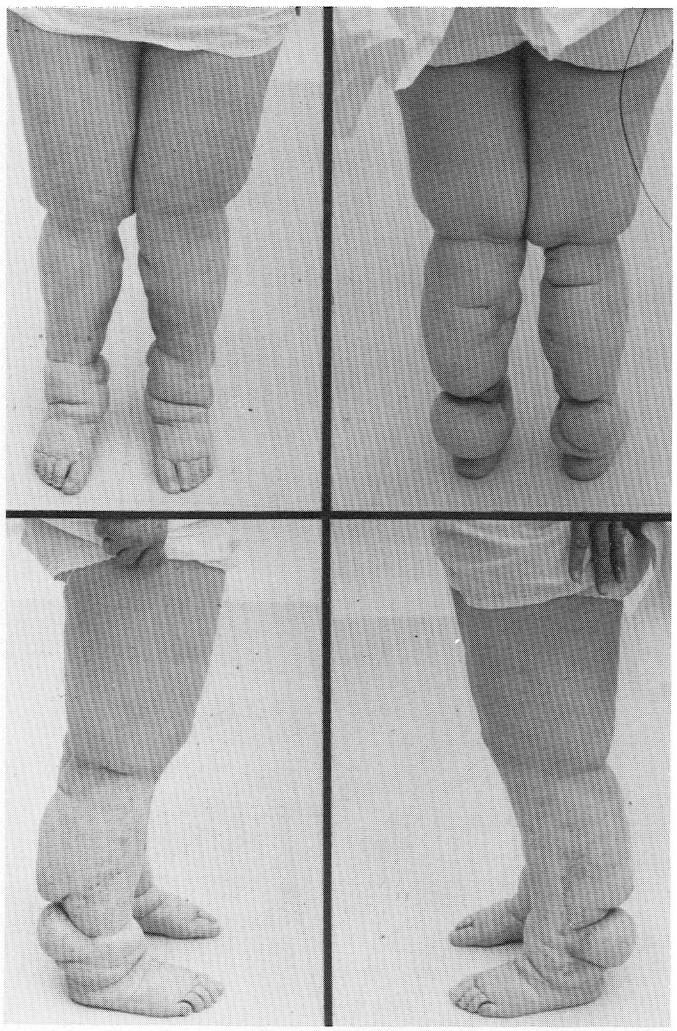

FIGURE 5. CCFA #1136. Thirty-eight year old mother of CCFA #12 and CCFA #382 was severely affected with lymphedema of both lower extremities (from knee down).

forms has not been emphasized in the literature, and is not included in compendia of genetic syndromes and craniofacial anomalies (Gorlin et al., 1976; Cohen, 1978; and McKusick, 1978). Family studies designed to search for cleft palate and its microforms in patients affected with primary lymphedema and their first degree relatives might yield additional cases of the association. At the same time, lymphedema should be considered in the history taking of patients with cleft palate and their families.

Clefting syndromes merit identification and description for purposes of genetic counseling and for elucidation of pathogenetic mechanisms involved in cleft palate formation.

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