The Phenotypic spectrum of dermatological manifestations of the Cardiofaciocutaneous syndrome. First two cases reported in Colombia

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Resumen

El síndrome cardiofaciocutáneo es un desorden genético de baja prevalencia. Los pacientes presentan dimorfismo facial, defectos cardiacos congénitos, retardo en el crecimiento y hallazgos dermatológicos variables. Nuestro reporte incluye una descripción y comparación fenotípica de dos pacientes con síndrome cardiofaciocutáneo con manifestaciones dermatológicas.

Key words: síndrome cardiofaciocutáneo, rasopatía, mutación, fenotipo.

Abstract

The Cardiofaciocutaneous syndrome (CFC) is a genetic disorder with a very low prevalence. Patients present with facial dismorphism, congenital heart defects, growth retardation and variable dermatologic findings. Our report includes a phenotypic description and comparison of two CFC patients with dermatologic manifestations.

Palabras claves: Cardiofaciocutaneous syndrome, rasopathy, mutation, phenotype

The Cardiofaciocutaneous syndrome (CFCS) was first described in 1986 by Reynolds *et al.*[1] CFCS is a genetic disorder with a very low prevalence, classified as a Rasopathy. Less than 200 cases have been confirmed by molecular genetic testing around the world, due to underestimation of diagnosis in mildly affected individuals. Although this condition has an autosomal dominant pattern of inheritance, all cases reported are caused by de novo mutations in genes along the Ras/mitogen-activated protein kinase (MAPK) pathway. Patients present with characteristic facial dysmorphisms, congenital heart defects, growth retardation and intellectual disability.[2] Herein, we present two patients with a diagnosis of CFCS caused by mutations in two different genes. Our report includes a phenotypic description and comparison of their dermatologic manifestations.

Case Presentation

The first patient is a 41-year-old female who was born from non-consanguineous parents. She presented with severe cognitive delay, short stature and facial dysmorphism characteristic of CFCS. A multigene panel for Rasopathies identified a pathogenic variant in BRAF c.1406G>A (p.Gly469Glu). On physical examination she presented sparse, curly hair, regression of the implantation hair line, absence of eyebrows, ulerythema ophryogenes, extensive keratosis pilaris, xerosis, multiple melanocytic nevi, and longitudinal melanonychia with a pseudo-Hutchinson`s sign (Figure 1).

The second patient is a 16-year-old female, born from non-consanguineous parents, also with severe cognitive delay and short stature. A multigene panel identified a pathogenic variant in MAP2K1 c.389A>G (p.Tyr130Cys). On physical examination she presented sparse, curly hair, regression of the implantation hair line, scarcity eyebrows (madarosis), ulerythema ophryogenes, extensive keratosis pilaris and multiple melanocytic nevi (Figure 2).

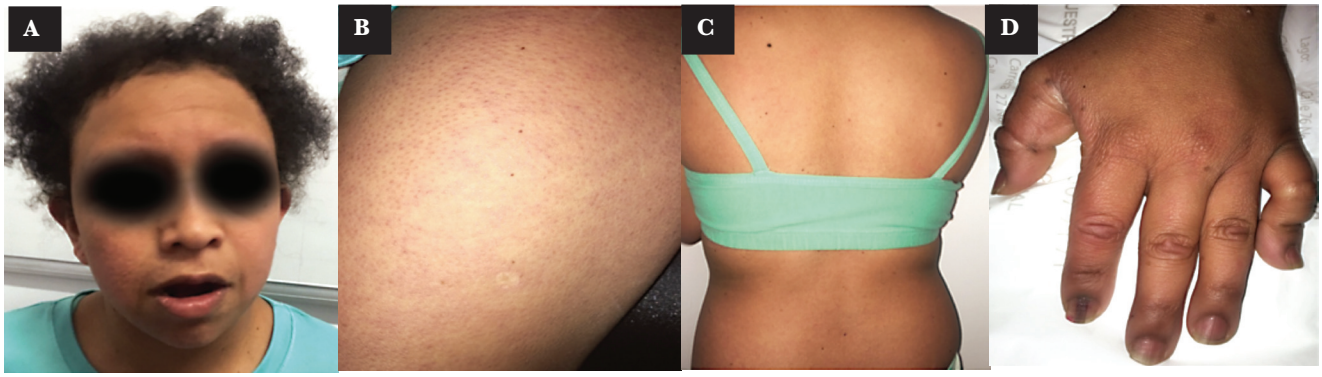

Figure 1
A. Setback of the implantation line and madarosis.
B. Multiple keratotic papules.
C. Melanocytic nevus.
D. Longitudinal melanonychia and pseudohutchinson.

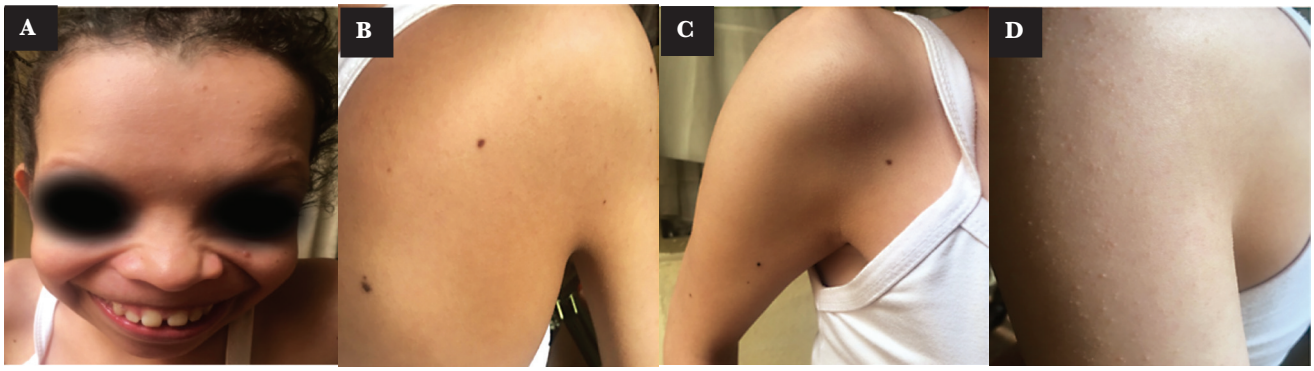

Figure 2
A. Retraction of the frontal implantation, madarosis and arched eyebrows.
B and C. Melanocytic nevi.
D. Keratotic follicular papules.

Discussion

CFCS is a rare genetic entity, classified within the group of Rasopathies, caused by de novo heterocygote mutations in different genes along the Ras/MAPK pathway: BRAF, KRAS, MAPK1 and MAPK2. This pathway has been widely studied and is involved in the processes of cellular proliferation, differentiation and apoptosis.[2]

The clinical manifestations of CFCS are heterogeneous, but characteristically, all patients have short stature and delayed development. Moderate to severe cognitive disability is present in 90-100% of the individuals with this condition.[3–5] The patients with CFCS usually present with relative macrocephaly, sparse, curly hair, high forehead and coarse facial features. Approximately 75% have cardiovascular involvement, the most frequent of them is pulmonary valve stenosis.[6]

Regarding dermatologic findings, these are common but variable in presentation. In a prospective multicentric study, Bessis D et al described the dermatological manifestations of 45 patients with CFCS, which include multiple melanocytic nevi (>10) 93%, hair abnormalities 89%, keratinization disorders 84%, pigmentary disorders 36%, and connective tissue disorders 36%; the least frequent manifestations include hyperhidrosis, nail abnormalities and lymphedema.[2,7]

In our study, similar dermatologic characteristics were found in both patients. The differences were found in the severity of skin manifestations being more severe on the first patient who had extremely curly hair, absence of eyebrows, keratinization disorders represented by ulerythema ophriogenes, and keratosis pilaris in whole body surface accompanied by global xerosis.

The BRAF c.1406G>A (p. Gly469Glu) missense variant found in the first patient has been reported as pathogenic, and affects the kinase domain of the BRAF protein, leading to decreased ability to induce MEK and ERK phosphorylation, components of the Ras/MAPK pathway. However, the mechanism by both activating and inactivating BRAF mutations give rise to the same clinical phenotype is not completely understood, but it may be related to a paradoxical activation of the MAPK pathway.[8,9,10]

Previous studies have described that patients with BRAF mutations have more severe hair abnormalities, especially absent eyebrows, and sparse, curly hair, as our first patient. Bessis D et al, described that 97% of the patients with BRAF mutation had hair abnormalities vs 60% of the patients with MAP2K1 mutation. Regarding melanocytic nevi there were no statistical differences between both groups, representing 91% of patients with BRAF mutation vs 100% in MAP2K1/MAP2K2 group.[7]

On the other hand, the MAPK1 c.389A>G (p.Tyr130Cys) variant observed in the second patient, stimulates an excessive phosphorylation of ERK. Patients with a pathogenic variant in MAP2K1 have a higher probability of developing keratosis pilaris and progressive nevi appearance than those with a pathogenic BRAF variant.[8] In the cases presented there were not significative differences in nevi appearance, only in the severity of keratosis pilaris in patient whit BRAF mutation which was previously discussed.

A wide spectrum of extracutaneous manifestations had been reported, however the most frequent are neurological with intellectual disability, developmental delay, cardiac anomalies include pulmonic stenosis and atrial septal defects and craniofacial dimorphisms.[1,2,3] Among the differential diagnosis are other Rasopathies, mainly Costello Syndrome where they have coarser facies than CFCS, also, but less common lentigines and café-au-lait spots. Another differential diagnosis is Noonan Syndrome (previously named Leopard) which has less coarse fascies than CFCS but xerosis, lentigos and café-au-lait spots are more severe.[10]

There is no treatment for this syndrome, only the prompt identification and early initiation of stimulation for delayed neurocognitive development and preventive measures for cancer risk. It has been considered the use of oncology treatments, particularly the inhibitors of Ras/MAPK pathway, however, continues under research.[10]

Conclusions

Cutaneous manifestations in CFCS are heterogeneous but frequent in patients with this condition. In this study we detailed the dermatological findings in accordance with an altered RAS/MAPK pathway, that should be known to allow accurate diagnosis, preventive treatment, and adequately timed referrals to avoid complications in affected individuals. We are not able to establish a genotype-phenotype correlation with 2 cases, but publishing always helps to expand the phenotype in rare diseases. The dermatologic manifestations described above are pathognomonic, but no life threatening, health care professionals must give supporting treatment to enhance quality of life of individuals with this syndrome.

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