A rare report of cardiofaciocutaneous syndrome and ulerythema ophryogenes

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Abstract

Cardiofaciocutaneous syndrome is a rare genetic disorder. It is characterized by craniofacial dysmorphism, congenital heart disease, ectodermal abnormalities, developmental delay, and central nervous system disorders. We discuss the case of an 11-year-old boy with cardiofaciocutaneous syndrome presenting with ulerythema ophryogenes and phenotypic features similar to Noonan syndrome.

Introduction

Cardiofaciocutaneous (CFC) syndrome is a rare autosomal dominant inherited disorder, though it can also manifest as a de novo mutation in a family without a history of a similar condition (1). The syndrome was first described by Reynolds et al. in 1986 (2). It results from a mutation in genes encoding the rat sarcoma (RAS)/mitogen-activated protein kinase (MAPK) signaling pathway and is known as one of the RASopathies (3). The most common mutations in Cardiofaciocutaneous (CFC) syndrome , including BRAF, MAP2K1 and MAP2K2, or rarely KRAS genes. Multiple organs can be involved, manifesting with distinctive facial features, cardiac abnormalities, neuromotor delay, intellectual disability, and ectodermal abnormalities (4). The phenotypic features overlap with other RASopathies, especially Noonan syndrome and Costello syndrome (5). Ulerythema ophryogenes also known as Keratosis pilaris rubra atrophicans faciei, is a rare dermatological disorder of keratinization .the etiology is still unclear although it has been associated with several congenital anomalies such as cardiofaciocutaneous (CFC) syndrome ,Noonan syndrome, Cornelia De Lange syndrome and Rubinstein-Taybi syndrome. and It manifests with perifollicular erythema and multiple inflammatory keratotic facial papules, which my result in alopecia ,scars and atrophy(6).

Case Presentation

The patient was an 11-year-old male Iranian who came to our dermatology center with a chief complaint of eyebrow hair loss since five years earlier. Past medical history revealed he was the product of a Cesarean section with a gestational age of 31 weeks. He had anemia, growth retardation, and developmental delay during infancy. His mother had one history of abortion before his birth.

On the physical examination, the boy had short stature, low-set ears, bilateral ptosis (operated four years earlier) (Fig. 1), inflammatory keratotic papules and hair loss on eyebrows (Fig. 2), hypertelorism, high-arched palate, severe dental caries, mandibular prognathism, and curly hair. Pectus carinatum was seen, and the boy's intelligence quotient was at the lower limit of normal.

Echocardiography showed minimal mitral valve prolapse and minimal mitral regurgitation.

A skin biopsy was taken from the keratotic inflammatory papules of the eyebrows. The pathology report stated a slightly dilated infundibulum filled by basket-weave keratin layers, focal perifollicular fibrosis in the papillary and reticular dermis, and increased telogen follicles, compatible with ulerythema ophryogenes

(Fig. 3). The cardiofaciocutaneous (CFC) syndrome was confirmed by genetic testing. The patient was referred to multidisciplinary team consisting of a dermatologist, geneticist, cardiologist, and orthopedist and ophtalmologist evaluated the patient and devised the management and follow-up plan.

Discussion:

Cardiofaciocutaneous (CFC) syndrome was first described by Reynolds et al. in 1986 (2). This syndrome is a genetic disorder with autosomal dominant transmission caused by germline pathogenic variants in the*BRAF* (75%), mitogen-activated protein kinase kinase 1 (*MAP2K1*), mitogen-activated protein kinase kinase 2 (*MAP2K2*), or *KRAS* genes (3). No epidemiological studies accurately estimate the worldwide prevalence of the CFC syndrome (4).

The syndrome is a member of a family of syndromes referred to as RASopathies. RASopathies are caused by germline mutations in genes encoding the RAS/MAPK signaling pathway and share overlapping clinical features. It is difficult to make a diagnosis based solely on the physical examination (7); therefore, a molecular genetics study is necessary for a definitive diagnosis.

Various organs can be involved in CFC syndrome. Clinical features include:

- Craniofacial dysmorphism with a short webbed neck, relative macrocephaly, high forehead, bitemporal constriction, supra-orbital hypoplasia, hypertelorism, epicanthal folds, ptosis, down slanting of palpebral fissures, low-set ears, and a short nose with a depressed nasal bridge (9);
- A short stature;
- Neurological involvement such as developmental delay, cognitive impairment, hypotonia, and epilepsy;
- Gastrointestinal problems such as gastroesophageal reflux, oral aversion, and gastrointestinal dysmotility (2);
- Congenital cardiac defects;
- Ectodermal abnormalities such as short, thin, and curly hair, ichthyosis, ulerythema ophryogenes, alopecia of the eyebrows and eyelashes, follicular hyperkeratosis, palmoplantar hyperkeratosis, and hyperplastic skin (3, 4, 9);
- Other cutaneous manifestations: slow growth of nails, folding of the earlobes, acanthosis nigricans, hyperplastic nipples, hyperpigmentation, and hemangioma (4).

The clinical findings of CfC syndrome often overlap with other RASopathies, particularly Noonan syndrome. However, substantial mental disorders and cutaneous ectodermal abnormalities like ulerythema ophryogenes (seen in our case) suggest CFC syndrome (8). Other differential diagnoses that CFC syndrome can be mistaken with include Noonan syndrome, Costello syndrome, Leopard syndrome, Noonan-like syndrome with loose anagen hair, and Turner syndrome (7).

The RAS/MAPK pathway plays an essential role in regulating cell proliferation, differentiation, survival, and death. Therefore, somatic mutations in genes encoding proteins from this pathway can be oncogenic. Unlike other RASopathies, CFC syndrome does not increase the risk of malignancy (5). However, the potential risk should not be ignored, and patients should be followed up.

Ulerythema ophryogenes, also known as keratosis pilaris atrophicans faciei, is a rare dermatologic disorder presenting with inflammatory keratotic papules in the outer portion of the eyebrows. It has been associated with several genetic syndromes caused by dysfunction of the MAPK/Ras–signaling pathways, such as cardiofacio-cutaneous syndrome and Noonan syndrome. Treatment of ulerythema ophryogene is challenging, and topical medications have been used including topical steroids, tacrolimus, and pimecrolimus, retinoids, and topical keratolytics such as such as urea, lactic acid, or salicylic acids had little effect (6).

As CFC syndrome is a developmental condition, abnormalities in vital organs may present from infancy to adulthood, so making the diagnosis is crucial in planning the patient's management and monitoring (10). Therefor, in childrens presenting with ulerythema ophryogenes, if there are any suspicious findings, clinicians should consider several genetic syndromes such as CFC syndrome and refer the patient for further workup.

In our case, a multidisciplinary team consisting of a dermatologist, geneticist, cardiologist, and orthopedist and ophthalmologist evaluated the patient and devised the management and follow-up plan.

Consent

The patient's guardian signed a written informed consent form to permit the publication of the case report without identifying data and to use the patient's photographs in this publication. Confidentiality was maintained throughout this research.

Conflicts of interest statement:

The authors have no conflicts of interest to declare.All co authors have seen and agree with the contents of the manuscript and there is no finanial interest to report.

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