Crouzon syndrome in association with acanthosis nigricans

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Crouzon syndrome is a rare inherited autosomal dominant syndrome characterized by craniosynostosis, midface hypoplasia. Acanthosis nigricans may be associated with Crouzon syndrome, but it differs from the classic crouzon syndrome. This is a report of a 30-year-old-woman who presented acanthosis nigricans coexist with crouzon syndrome.

Keywords: crouzon syndrome, craniosynostosis, acanthosis nigricans

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INTRODUCTION

Crouzon syndrome is one of the rare syndromes of craniofacial dysostosis caused by premature obliteration of two or more sutures. Crouzon syndrome is characterized by craniosynostosis, exophthalmos and midface hypoplasia. Acanthosis nigricans is the most important dermatologic sign of Crouzon syndrome. This syndrome is inherited in an autosomal dominant pattern.

Mutation of the gene for fibroblast growth factor receptor 2 (FGFR2) could be responsible for Crouzon syndrome. Furthermore, the different mutation in the transmembrane region of FGFR3 was detected in crouzon syndrome associated with acanthosis nigricans [1].

CASE REPORT

A thirty-year-old girl came for a consultation to the dermatology clinic for her facial skin lesions. She knew in advance that they are acanthosis nigricans because a previous skin biopsy confirmed the diagnosis of acanthosis nigricans. The lesions had developed noticeably around her eyes and mouth starting many years ago (Figure 1,2). She was born with crouzon syndrome during the war between Iran and Iraq and that was why she personally has defined chemical weapons which triggered the gene mutation the cause of her disease. Even though there is not any firm confirmation or documentation, but definitely this requires further research to determine if these two can be related.

She had hydrocephalus from birth due to craniosynostosis, so she has had multiple surgeries from early stages of her life. All were done in United States, including midface advancement, moving her lower jaw back and a bone graft transfer from her right leg to her cheeks. She has subsequently had orthodontic therapy and had correction to improve her to class I occlusion. Furthermore she had rhinoplastic surgery as well.

In 2005 she had operations including bilateral canthopexy; bilateral malar augmentation with fat transfers from periumbilical area and left medial thigh; Z- plasty of left eyelid scar and revision of bilateral lower eyelid scars.

Now that she is getting her doctorate degree in physiotherapy. She says "I really understand and feel people when they suffer and that`s why I`m just praying that God will use my hands to heal them, specially kids. But mean while psychologically was difficult for me…"

We treated the acanthosis nigricans with Alexandrite laser and the scar of previous surgeries with Fractional CO2 laser.

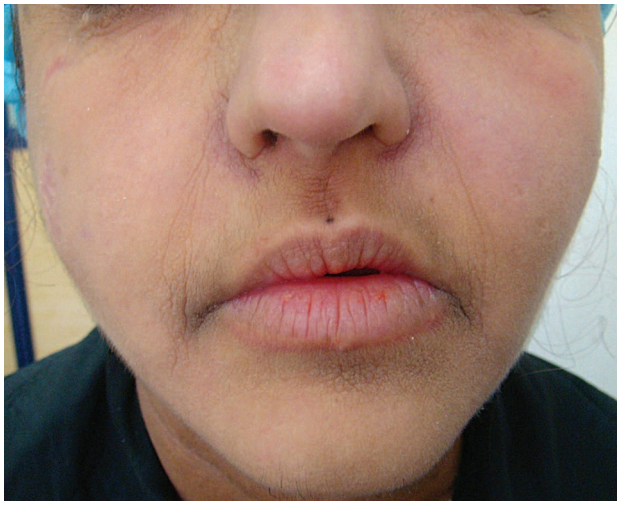

Figure 1. Perioral acanthosis nigricans lesions.

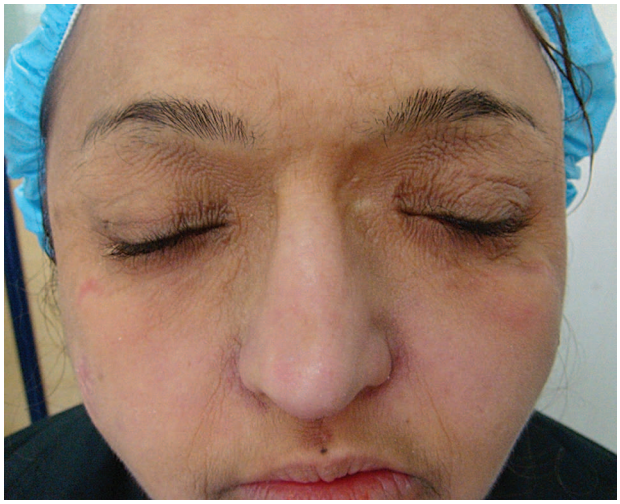

Figure 2. Periorbital acanthosis nigricans lesions.

DISCUSSION

Crouzon syndrome was described in 1912 by a French neurologist, Octave Crouzon as one of the hereditary syndrome of craniofacial dysostosis (craniosynostosis) caused by premature obliteration and ossification of two or more sutures; most often, coronal and sagittal [2]. It is inhereited as an autosomal-dominant disorder with variable expressions so history of consanguinity and family history are essential, although cases due to new mutations have been reported. Positive family history can be detected just in 44 percent to 67 percent of cases [3]. Three affected siblings suggestive of germinal mosaicism have also been reported [4].

Crouzon syndrome is caused by a mutation in the fibroblast growth factor receptor-2 (FGFR2) gene [2]. The mechanisms underlying craniosynostosis remain unknown. However, mutations in FGFR2 are associated with craniosynostotic syndromes [5].

The prevalence is very low, and is currently estimated to occur in 1 in 25,000 people in the general population with no sex and race predilection [6]. craniosynostoses results in skull deformities and the disturbances in the normal brain development, due to the reduced volume of the intracranial space. Patients also have maxillary retrusion, hypertelorism and shallow orbits which give rise to ocular proptosis. There is significant variation of the clinical features, but ocular proptosis is a constant feature even in the absence of craniosynostosis and can be regarded as a diagnostic criterion of Crouzon syndrome [7,8].

Ocular manifestations of Crouzon syndrome include: chronic papillary edema, as a result of increased intracranial pressure with resulting optic nerve atrophy; keratopathy, as a consequence of qualitative changes of the tear film due to the exposure of the exposed part of the globe to external micro- and macroclimate factors of subluxated globes and multifactorial poorsightedness, which is, apart from the above-mentioned conditions, caused by astigmatism (particularly oblique astigmatism), anisometropia or strabismus [9,10].

Other associated features include deafness, cervical spine anomalies, acanthosis nigricans and stenosis of the jugular foramen which may led to herniation of the cerebellar tonsils following craniofacial surgery [11].

Acanthosis nigricans may coexist with Crouzon syndrome, but despite the classic crouzon syndrome here, mutation is in the transmembrane region of fibroblast growth factor receptor 3 (FGFR3) gene (locus 4p16.3). At birth, individuals with this disorder have craniosynostosis, ocular proptosis, midface hypoplasia, choanal atresia, hydrocephalus, and they experience the onset of acanthosis nigricans during childhood. Histologic features of acanthosis nigricans include hyperkeratosis, acanthosis, and papillomatosis. In the basal layer, the amount of pigment cells is also increased in the upper dermis [12,13].

The association of acanthosis nigricans with Crouzon syndrome is believed to be a rare abnormality. Although the true frequency is uncertain, some approximate that acanthosis

nigricans is associated with 5% of all Crouzon cases. In medical literature review, all described patients with acanthosis nigricans had an excess of skin and hyperpigmented lesions in the orbital area (mainly on the lower eyelid), on the perioral area, neck and armpits [3].

A chorionic villus sampling performed early in the 11th gestational week of the first trimester can also diagnose this syndrome by separating the DNA [14]. Recent development of 3D ultrasonography and magnetic resonance imaging provide a more efficient early recognition and diagnosis of fetal malformation [15].

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