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Crouzon syndrome and celiac disease: A possible association? A case report

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Abstract

Crouzon Syndrome (CS) is a rare genetic disorder, due to mutation in Fibroblast Growth Factor Receptor 2 (FGFR2) and Receptor 3 (FGFR3) genes. Clinical features include craniosynostosis, craniofacial malformation, proptosis of the orbits, ocular strabismus, hearing defects, maxillary hypoplasia and mandibular prognathism. FGFR2 and FGFR3 are widely expressed in the gut and play an essential role in maintaining homeostasis, development, proliferation and differentiation of gut cells.

Celiac Disease (CD) is an immune-mediated disease characterized by gluten-dependent intestinal damage in genetically susceptible individuals. The etiopathogenesis is not completely clear and a combination of triggers, genetic and environmental factors are needed to develop the auto-inflammatory process leading to intestinal damage.

We report the first case of a patient with CS who received a CD diagnosis and hypnotized a connection between these two conditions. We deeply investigated in literature the role and the functioning of FGFR2 and FGFR3. Mutations in these receptors induce macro and microscopic intestinal abnormalities that could disrupt the gut balance, favoring CD.

We are aware that this association may only be random considering the high prevalence of CD in the general population; however, we were stimulated to publish this case because of the possible pathogenetic mechanism that could contribute to the onset of CD in genetically susceptible patients with CS. We believe that it is necessary to study in depth the role of FGFR2 in the pathogenesis of celiac disease and in the intestinal repair process to acquire knowledge that can be applied in clinical practice.

Keywords: Crouzon syndrome; Celiac disease; FGFR2; FGF ligands; Craniosynostosis.

Introduction

Crouzon Syndrome (CS) is one of the most common craniosynostosis syndromes characterized by premature fusion and ossification of the cartilage of cranial sutures. CS is a rare autosomal dominant disorder (1 in 60000 live births) with complete penetrance and variable expressivity. This syndrome is responsible for several congenital anomalies such as craniofacial malformations, proptosis due to shallow orbits, ocular strabismus, hearing loss, maxillary hypoplasia and mandibular prognathism [1]. CS is caused by mutation in the fibroblast growth factor receptor 2 (FGFR2) gene, which is mapped on chromosome locus 10q25-10q26 and by the fibroblast growth factor receptor three gene (FGFR3) responsible for CS with acanthosis nigricans [1].

In CS, FGFR2 and FGFR3 gene mutations induce a gain of function and constitutive activation of the receptors independently from the ligand binding. All FGFRs are expressed in the intestine; in particular, FGFR2 and FGFR3 play an essential role in maintaining homeostasis, development, organogenesis, proliferation and differentiation [2]. Murine models with a mutation in FGFR2 Heterozygosis (HET) compared to Wild-Type mice (WT) show: a) shorter oesophagus with a broader lumen, b) thinner oesophagus epithelium, c) different epithelium cells shape, d) thinner and altered orientation of muscular fibers, e) disorganized amount of collagen in muscle tissues. All these abnormalities are responsible for an alteration of gut motility [3].

Celiac Disease (CD) is a systemic autoimmune-mediated disorder characterized by gluten-dependent intestinal damage in genetically susceptible individuals. The etiopathogenesis is not completely clear, and a combination of genetic and environmental triggers is needed to intervene to develop the auto-inflammatory process leading to intestinal damage.

Herein, we report the first case of a pediatric patient with CS and CD.

Case Presentation

The patient is a 4-years-old female patient with Crouzon syndrome and severe failure to thrive. At 18 months, MRI revealed craniosynostosis, and genetic counselling resulted in the diagnosis of CS based on a de novo mutation (FGFR2 c. 1061 C>G – p. (Ser345Cys)]. At four, she presented with severe failure to thrive and intractable constipation. The patient's weight was 10,7 kg [(-3,27 Standard Deviations (SD)] and her height was 88,5 cm (-3,49 SD). She was in overall fair clinical condition, flat abdomen and a hard faecal mass.

At the end of the diagnostic process, the patient was positive for celiac serology in two separate determinations [anti-tTG-IgA 160 U/mL (nv<10) and 422 U/mL (nv<10), respectively) and genetic predisposition (HLA DR7-DQ2); therefore, we diagnosed CD without intestinal biopsy according to the latest ESPGHAN guidelines [4]. The patient started a Gluten-Free Diet (GFD), and after three months, her weight had improved (11,7 Kg, -2,88 SD), while her height (89 cm, -3,8 SD) remained stable. After nine months of GFD on the latest outpatient visit, her weight remained stable, while her height increased by

four centimetres (93 cm -3,48 SD). Blood tests showed a decrease in serology title [anti-tTG-IgA 37 U/mL (nv<10)] and persistently low ferritin level (14 ng/mL) despite iron supplementation. She resolved constipation on a gluten-free diet and was weaned off stool softeners. At the latest follow-up celiac serology was negative.

Discussion

Crouzon syndrome and celiac disease have never been reported in the literature, and we believe that the scientific community should be informed about this possible association that we believe might not be only related to chance.

Meyer et al. [5], using a model of knock-out mice for FGFR1 and FGFR2 genes, demonstrated a loss of FGF-induced expression of claudins and occludins responsible for abnormalities in tight junction formation with a concurrent deficit in epidermal barrier function, followed by activation of γδ T cells and enhanced expression of pro-inflammatory cytokines and growth factors resulting in dermal fibrosis. FGFR2 and FGFR3 are expressed in the gastrointestinal tract [2]. An alteration of cellular adhesion can lead to abnormal gut permeability, facilitating the passage of gliadin peptides into the lamina propria, which could trigger a cascade of events that ultimately lead to the sensitization of the immune system responsible for the mucosal damage and specific serological response [6]. In patients with active inflammatory bowel disease (IBD), Kristiansen et al. found overexpression of miR-595 and miR-1246 which are responsible for the inhibition of FGFR2 and Neural Cell Adhesion Molecule-1 (NCAM1) expression [7]. The downregulation of these two factors may result in decreased intestinal epithelial repair capacity and altered tight junctions' function. Interestingly, miR-1246 has been found in a patient with CD [8], contributing to an enhancement of intestinal damage secondary to the downregulation of FGFR2.

The abnormal function of FGFR2 might also explain why the catch-up growth in a patient with CS and CD might be slow, as in our case report. Many studies have focused on the effects of FGF ligands and receptor signalling on intestinal epithelial crypt cells, showing that it is essential for maintaining and differentiating intestinal stem cells to replace damaged or old enterocytes [2]. It is possible to speculate that a mutation in the FGFR2 gene could facilitate the onset of celiac disease in genetically susceptible individuals and compromise the repair process after initiating a gluten-free diet.

We are aware that this association might be solely casual considering the high prevalence of CD in the general population; however, we have been stimulated to publish this case because of the possible pathogenetic mechanism that might contribute to the onset of CD in genetically susceptible patients with CS. We believe that it is necessary to deeply study the role of FGFR2 in the pathogenesis of celiac disease and the intestinal repairing process to gain knowledge that can be applied in clinical practice, especially under particular conditions. Our next goal will be to screen an extensive series of patients with CS for Celiac Disease in the national territory to confirm our hypothesis.

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