IRAK4 gene polymorphism and odontogenic maxillary sinusitis

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Abstract

Background: The posterior maxilla may suffer a severe resorption and sinus pneumatization. The latter can lead to an inadequate bone height for the placement of implants. To overcome this obstacle short implants and sinus floor elevation are performed. Complications like perforation of the sinus membrane, bone loss, sequestrum development and dental implant migration into the sinus have been reported. The implant may act as a foreign body and will turns into an inflammatory focus of the maxillary sinus.

Aim: Odontogenic maxillary sinus inflammation may have different etiologic factors. The authors highlight the implant placement in atrophic maxilla, periodontal disease and the inflammatory host response to Gram-positive bacteria in the presence of IRAK4 gene polymorphism.

Material and Methods: One hundred and fifty-three Caucasian portuguese patients were included and performed a CT scan evaluation, medical data analysis, a clinical examination and a genetic test. Statistical methodology was done through independent Chi2 test, Fisher's exact test and binary logistic regression.

Results: The prevalence of the IRAK4 gene polymorphism (c.1282G>A (p.Ala428Thr), variant region) found in the sample was 26.8% (confidence interval of 95% [20.1%, 34.7%]. The Fisher exact test ($p = 0.030 < 0.05$) showed statistically significant association between the presence of the IRAK4 gene polymorphism and the mucosal thickening on CT.

Conclusion: The eventual influence of this IRAK4 gene polymorphism on host response against gram positive bacteria together with known risk factors for development of biologic complications in atrophic maxillary implant rehabilitation may raise new suspicions on understanding some particular patients response. This study lies in trying to achieve a model to assist the clinician in dental implant treatment plans in complex cases, with probable involvement of the maxillary sinus.

Fig.1 - Patients' genotypes were determined by real-time PCR and the DNA sequencing resorted to the Sanger method.

Methods and Materials

Retrospective study - study subjects

A retrospective study review was initially conducted to identify and characterize computed tomography (CT) imaging findings of a Portuguese Caucasian population. Institutional Review Board approval was obtained, and appropriate measures were taken to safeguard patient privacy.

The CT scans were performed according to the following indications: implant planning, study of impacted maxillary teeth, suspected lesion/cyst on the maxillary sinus, ankylosis of the anterior teeth, suspected foreign body in the maxillary sinus, endodontic lesions, oroantral fistula, orthodontic planning, local trauma and dental or bone fractures.

The criteria for patient selection were based on etiological factors of the maxillary sinusitis of odontogenic origin and the pathologic changes present in the maxillary sinus. The CT's observed were from the period between 1993 and 2013. Two observers with over 20 years experience in the field of oral surgery identified the eventual changes present on CT.

In the analysed maxillary sinus, only the adjacent teeth to the maxillary sinus were evaluated and the following signs were identified—opacity, presence of fluid, mucosal thickening, cortical bone loss and potential etiologic factors to develop sinusitis of odontogenic origin—teeth protruding into the maxillary sinus (maxillary sinus communication), dental caries, periodontal disease, apical periodontitis, endodontic treatment, iatrogenic signs, dental implants, cysts, foreign bodies, ectopic teeth, oroantral fistula and inclusion of teeth associated with maxillary sinus.

These completed a total of 504 patients, corresponding to 1008 analysed maxillary sinus.

From this base, 153 patients were randomly selected, according to the value of 13 % for the maxillary sinusitis prevalence, with 95 % CI and estimated error of 5.3 % to perform a genetic test.

According to the classification of Maillet et al. (2011)¹⁰, the patients were divided and included into four groups.

Inclusion criteria

All adult Caucasian patients (>18 years) who had at least one CT scan performed were included in this study. The patients with immune-compromised conditions, patients with CT without sufficient slices or poor quality image to analyze the maxillary sinus and patients with CT that did not allow analyzing the maxillary teeth were excluded.

Selection of polymorphism in the human IRAK4 gene

The IRAK4 gene analysis was initially performed by sequencing all gene (Fig.1). The latter was done by polymerase chain reaction (PCR) amplification and sequencing of the entire coding region, including the adjacent intronic regions of the IRAK4 gene. In this first analysis, pathogenic mutations were not detected in the IRAK4 gene. However, the variant c.1882G>A (p.Ala428Thr) was found in heterozygosity (a single nucleotide polymorphism—SNP). This SNP was the same reported to be related with the host susceptibility for development of Gram-positive bacteria infection¹¹.

After this SNP identification, the following samples were studied directly target to the c.1282G>A (p.Ala428Thr) variant region (reference sequence: NM_001114182.2, being the A of the ATG start position 1). Furthermore, the D (down) was considered the forward, the U (up) the reverse and the 12/13 were together in just a fragment

Statistical analysis

Using the software IBM® SPSS® Statistics 22.0, the sample was characterized, an analytical study of association was conducted and data modelling was performed using the binary logistic regression, for dependent variable “diagnosis” corresponding to two categories, one for healthy individuals and the other for individuals with sinusitis of odontogenic origin.

Results

The prevalence of the polymorphism c.1282G>A (p.Ala428Thr) in the variant region of the IRAK4 gene in this sample was 26.8 %, with a confidence interval of 95 % [20.1, 34.7 %]. The Fisher exact test ($p=0.030<0.05$) showed statistically significant association between the presence of the IRAK4 gene polymorphism and the mucosal thickening on CT imaging. The Fisher exact test ($p=0.040<0.05$) revealed statistically significant association between the presence of the IRAK4 gene polymorphism and the diagnosis of sinusitis of odontogenic origin (Fig.2). The final sample to construct the prevision model was accomplished through the selection of two groups of the main sample. So, the latter consisted of 84 individuals, including 38 (45.2 %) healthy and the remaining 46 were diagnosed with sinusitis of odontogenic origin (54.8 %). The prevalence of the polymorphism c.1282G>A (p.Ala428Thr) in the variant region of the IRAK4 gene in this final sample was 32.1 %, with a confidence interval of 95 % [22.6, 43.3 %].

Using the forward conditional stepwise (with $pE=0.2$ and $pR = 0.25$), we obtained a decision model in order to predict the result according to presence of a set of considered risk factors. The choice of pE and pR was made in accordance with Hosmer and Lemeshow that recommend, in models containing more variables, the use of a large p value to provide a more complete picture of possible models.

The area under the curve $AUC=0.911$ means that the model could predict the outcome in 91.1 % of cases. Thus, for the proposed model, an individual without sinusitis diagnosed, without complaints of feeling nasal congestion in the region of the maxillary sinuses, with cortical bone loss observed on CT, with a positive genetic test result and radiographic examination that reveals the roots of the teeth in communication with the maxillary sinus (maxillary sinus communication), it is estimated, by the model, a probability value of 0.977, to triggering an inflammatory response in the maxillary sinus.

Fig.2 - Relation between the IRAK4 gene polymorphism (positive genetic test) and maxillary sinusitis of odontogenic origin.

Conclusion

Demonstration of a genetic association does not prove causality, which must be established by subsequent experiments showing the altered function of the gene and mechanistic impact in the disease. This IRAK4 gene polymorphism may amplify the response of the innate immunity to Gram-positive bacteria, thus increasing the cytokines production and leading to a more severe inflammatory state of the nasal/sinus mucosa. Hence, our study may be give rise to an initial tool (decision model), to be improved in order to help the diagnosis and the therapeutic decisions, particularly in cases of atrophic maxillary implant placement, where there is an anatomic proximity to maxillary sinus.

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