

## Prevalência da aftose oral recidivante na população geral portuguesa

Prevalence of recurrent oral ulceration in portuguese general population

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### Resumo

As aftas orais são lesões ulcerosas que aparecem na mucosa de revestimento não queratinizada da cavidade bucal, dos lábios, da língua e da faringe. Quando estas lesões se repetem em número de três ou mais episódios por ano, designam-se como aftose oral recidivante (AOR). Ainda que por vezes a reincidência de aftas esteja associada a patologias que a justificam, o quadro de aftose oral recidivante traduz geralmente um problema primário.

Pretendeu-se, com este trabalho determinar a prevalência de AOR numa população portuguesa geral, constituída por pessoas abordadas aleatoriamente, sem condição de doença aguda conhecida, compará-la com a encontrada noutras países e com a prevalência desta afecção em portadores de doenças sistémicas nas quais está presente a AOR. Foi avaliada uma população de seiscentos indivíduos aos quais foi indagada a idade de aparecimento, o local de residência, as causas precipitantes, o tratamento efectuado e a incidência familiar. Para complemento do estudo, realizou-se um breve despiste de outras doenças que pudessem estar a motivar o aparecimento de AOR, bem como a identificação de antecedentes patológicos relevantes.

Foi encontrada uma prevalência de 19,0% de indivíduos com AOR nesta população, com predomínio de 22,7% de mulheres quando comparado com 14,0% de homens, sendo esta diferença entre sexos estatisticamente relevante ( $p<0,05$ ). Verificou-se que a maioria dos afectados apresenta idade de início antes dos 20 anos. Como factores facilitadores de recidiva das ulcerações, foram identificados alguns alimentos, o trauma, o stress, a febre, a menstruação, alguns medicamentos e a cessação tabágica. Em 9,6% dos indivíduos não foi identificada qualquer causa para a recorrência de lesões. Concluiu-se também que a AOR está presente em familiares directos, até ao 1º grau, de 45,6% dos afectados por esta entidade.

Palavras-chave: Aftose oral recidivante, aftas orais, epidemiologia, prevalência, Portugal.

### Abstract

*Oral aphthae are ulcerous lesions that affect non-keratinized mucosae of the mouth cavity, lips, tongue and pharynx. When these lesions reoccur for three or more episodes per year are named as Recurrent Oral Ulceration (ROU). Although recurring ulcers might be associated with other disorders, ROU usually expresses a primary problem.*

*The main objectives of this study were 1) to determine the prevalence of ROU in the general Portuguese population, composed by people randomly approached without any acute disease; 2) to compare the observed prevalence with the prevalence of ROU in other countries and 3) to compare the prevalence of this problem in patients with other systemic diseases where ROU is included. A population of six hundred persons was enquired regarding the age of the disease onset; place of residence, factors triggering outbreaks, usual treatments and family incidence. Besides, it was carried out the identification of other diseases associated with ROU as well as the relevant pathological background. The prevalence of ROU was 19.0% in this general population, with predominance of 22.7% in women, compared with 14.0% in men, being this difference statistically significant ( $p<0.05$ ). In most of the affected individuals, the first ulceration appeared before the twenties. Certain food, oral trauma, stress, fever, menstrual cycle, presence of acute disease, some medications/drugs and smoking cessation have been identified as precipitation factors associated with ROU. In 9.6% of the affected people it was not possible to identify any cause for recurrent ulcers. We also found that 45.6% of the population with ROU has direct relatives, up to first degree, also affected by this problem.*

*Key words: Recurrent oral ulceration, oral aphthae, epidemiology, prevalence, Portugal.*

### INTRODUCTION

Aphthae are ulcerations affecting the non-keratinized mouth mucosa, especially the areas of the vestibule, palate, tongue and sublingual region although it can also affect the pharynx.

The presentation shows well-defined edges, erythematous ring with pearly background. They are

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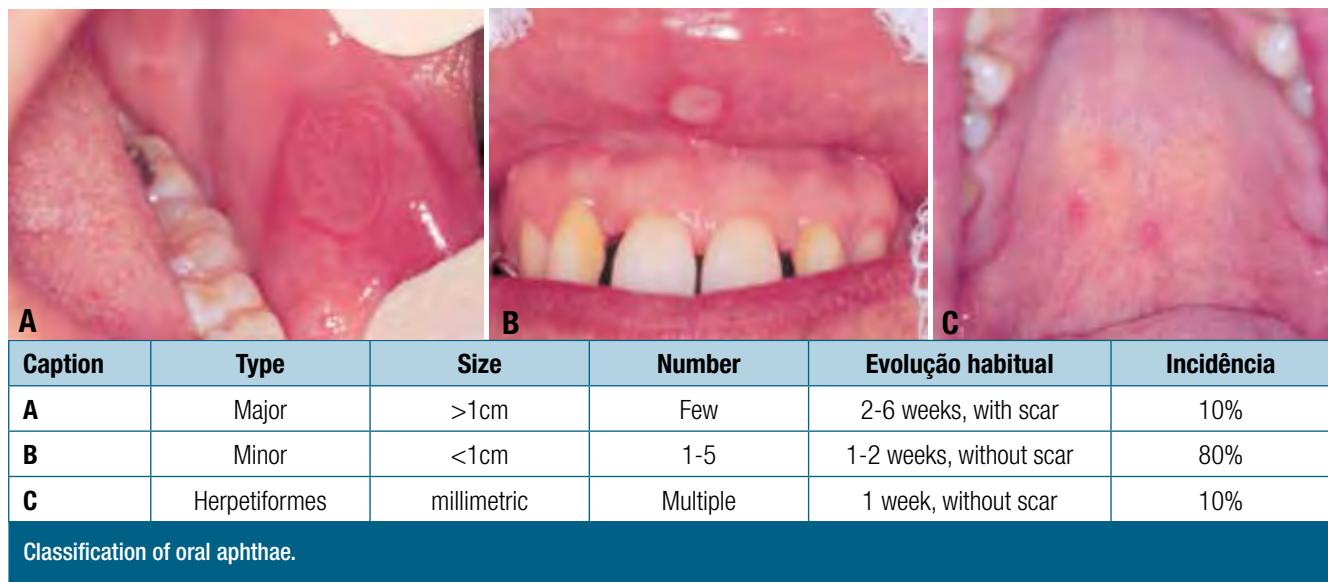


FIG. 1

classified as major, minor or herpetiform, according to the size, and they can emerge in isolate or multiple forms remaining for periods of a few days to 2 to 6 weeks<sup>1</sup> (*Figure 1*). In spite of being benign lesions, ROU can account for food indisposition with relevant discomfort, sometimes very difficult to control.

Studies prove that in the origin of such lesions is a immunologic response mediated by cells, involving T lymphocytes, macrophages and mastocytes producing alpha tumor necrosis factor (TNF- $\alpha$ ).<sup>2</sup> TNF- $\alpha$ , as inflammatory cytokine, it exerts its chemotactic effect in neutrophils,<sup>3</sup> promoting the expression of major histocompatibility complexes<sup>4</sup> and the interventions of several other cytokines.<sup>5</sup> T lymphocytes with gamma delta ( $\gamma\delta$ ) receptors can be implied in a response mediated by antibody dependent cells.<sup>3,6-7</sup> As a matter of fact, it was only in ROU lesions that big densities of T lymphocytes with  $\gamma\delta$  receptors, considering that such lymphocytes only seldom were observed in the epithelium or connective tissue of non-ulcerated areas in the same patients.<sup>3</sup> Previous works verified added proportions of  $\gamma\delta$  lymphocytes in the ROU patients peripheral blood, both in active as inactive stages of the disease.<sup>8</sup> The exact role of such T lymphocytes in ROU lesions is yet to be clarified. They can have an important role to reduce the damage in the mucosa after ulceration or whilst producing a specific fibroblast growing factor.<sup>7</sup>

Regarding the prevalence, it is estimated that around 20% of the general population is affected by ROU.<sup>9-10</sup> The calculation of cumulative prevalence range from 5 to 66% of the population,<sup>11-15</sup> and these change a lot according to the world region and the group studied.

The conclusion from studies that, in the case of both parents being affected, children are at a higher risk of developing ROU (67-90%) and that there is a high correlation in ROU incidence in homozygotic twins.<sup>16</sup> An increased incidence of genetic factors as human leukocyte antigens (HLA) B12, B51, Cw7, DR2, DR4, DR5, DR7, A28 and MT3 were identified in patients of different nationalities.<sup>17-18</sup> The variability in individual susceptibility can be explained in polygenic heredity.

At present, ROU seems to manifest itself as a more common entity in children and adults with better social and economic conditions,<sup>19-20</sup> and might be related to an increase of the associated stress to the new jobs and life styles.

The need to determine the prevalence of such pathology is linked with the strict definition of its importance as a primary entity, and on the other hand, with the differential diagnosis with pathologies where it is included. The ROU differential diagnosis has included: herpes simplex, oral candidiasis, lack of vitamins (B12 and folic acid) or iron,

Behcet's disease, Crohn's disease, ulcerative colitis, celiac disease, systemic lupus erythematosus, pemphigus, MAGIC (Mouth And Genital ulcers with Inflamed Cartilage) syndrome, PFAPA (Periodic Fever Aphthous stomatitis, Pharyngitis, Adenitis) syndrome, Sweet's syndrome, cyclic neutropenia and acquired immunodeficiency syndrome.<sup>1</sup>

## MATERIAL AND METHODS

### Sample population / Questionnaire

A population of 600 individuals was evaluated who were then referred to the two hospitals of the central region of Portugal: 1) Coimbra University Hospital and 2) General Hospital of Coimbra Hospital Centre; and others did not go to these hospitals for reasons of personal health. Therefore, visitors to inpatients and those accompanying patients in appointments were interviewed. A questionnaire identifying individuals with ROU complaints, differentiating gender, current age and the age at the ROU onset, place of residence (country or town), the precipitating causes (stress, trauma, food, medicine, menstruation, fever and smoking withdrawal), the treatment usually carried out and in the presence of relatives up to 1<sup>st</sup> degree. As a study supplement, the questionnaire has briefly tracked other situations that could be confused with ROU (as herpes simplex) and complaints related with pathologies which eventually could be related with the emergence of oral aphthae (for instances, fever, weight loss, arthritis, venous/arterial thrombosis, exanthema, erythema nodosum, folliculitis, inflammatory eye lesions, diarrhea with blood, genital ulcers). The identification of relevant pathological antecedents was also carried out.

A random sampling has included female individuals in a ratio of 57.2% and male individuals in 42.8%, belonging to different age groups (from 8 to 94 years old) or with a mean age of  $49.8 \pm 17.3$  years old.

Individuals at the hospital for any reason of personal health, individuals having no cognitive ability to answer the current questionnaire, individuals with aged 8 years old or less were not included.

### Statistical analysis

To test the occurrence of association between ROU and any of the genders, the Test  $\chi^2$  using MINITAB 12.2 software, considering the following working

hypotheses:

- $H_0$ : ROU is not preferentially associated to one of the genders; and
- $H_1$ : ROU is preferentially associated to one of the genders.

Within the group of individuals affected with ROU, to test the occurrence between gender and the existence of 1st degree relatives with symptoms of this pathology, the Test  $\chi^2$  using MINITAB 12.2 software, considering the following working hypotheses:

- $H_0$ : The existence of 1st degree relatives with ROU symptomatology is not preferentially associated with one of the genders; and
- $H_1$ : The existence of 1st degree relatives with ROU symptomatology is preferentially associated with one of the genders.

In both tests, the null hypothesis was rejected to  $p \geq 0.05$ .

## RESULTS

In a total of 600 people enquired, 114 presented ROU. Such figure results in a 19.0% prevalence, presenting a confidence interval of 95% (IC95%) from 15.9 to 22.1%.

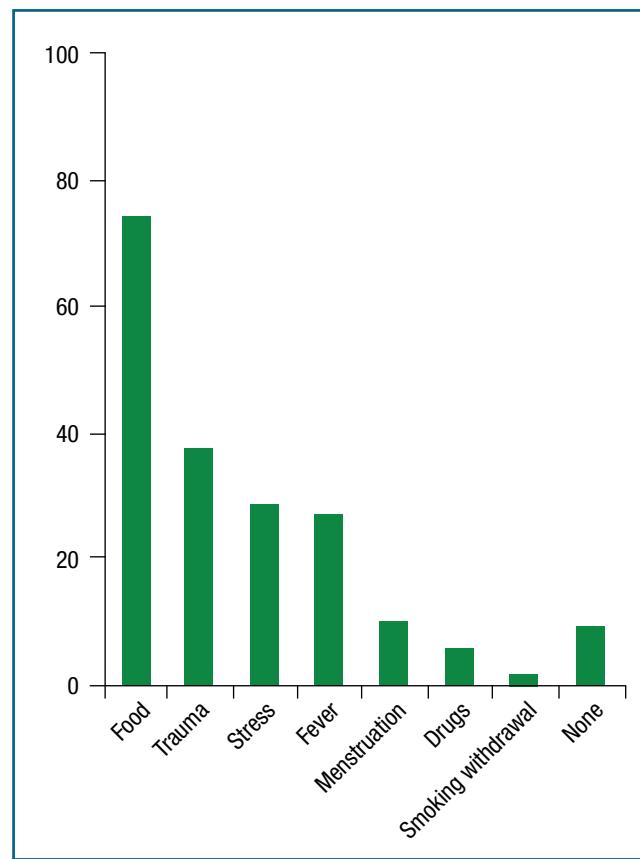
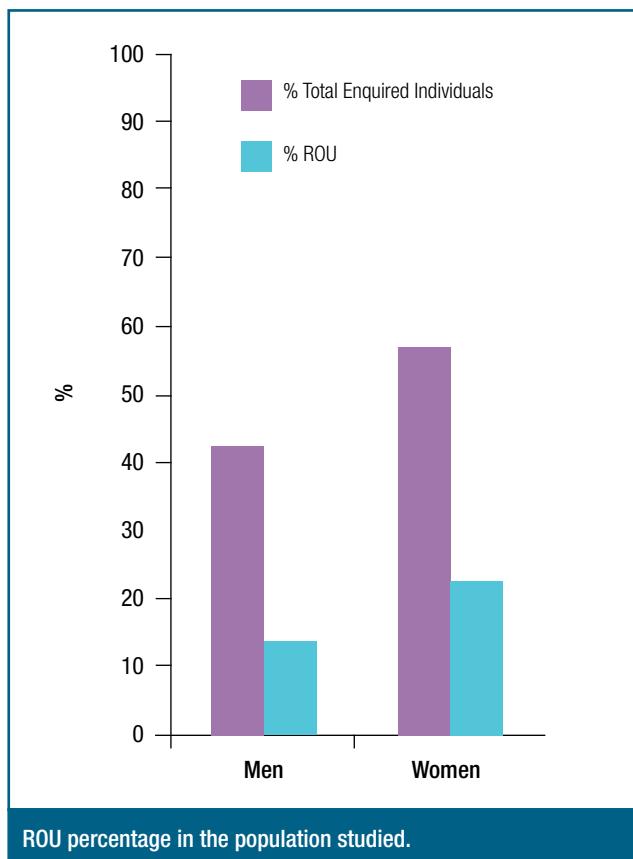
The percentage of women with ROU is 22.7% (IC95% - 18.4 to 27.3%) and the percentage of affected men is 14.0% (IC95% - 9.8 to 18.3%) (Fig. 2). The test  $\chi^2$  results indicate that occur more cases of this pathology in women, therefore the ROU preferential association with the female gender was observed ( $F=6.724$ ;  $p=0.009$ ).

Regarding the place of residence, 19.2% of individuals living in towns had ROU and the individuals living in the countryside presented a prevalence of 19.0% to ROU.

The onset age was divided in 1) children (less than 13 years), with 39.5% of those affected; 2) youngsters (from 13-19 years), with 26.3% of those affected; 3) adults (from the age of 20 years), with 34.2% of those affected. It should be mentioned that 6.1% of affected women associated the ROU onset to puberty.

Regarding the triggering causes, a total of 74.6% of ROU individuals, have identified some foods as predisposing factors to recurrences of oral aphthae (Fig. 3). The most quoted foods are chocolate, cheese, pineapple, citrines, nuts and dried fruits.

Regarding the treatment carried out, 61.4% of



ROU individuals denied the use of any product and 21.1% could not identify the name of the medicine used (Fig. 4). The identified medicines were colchicine, hexetidine, triamcinolone, salicylic/rhubarb acid, choline salicylate and benzydamine. Some patients mention the use of products “traditionally” used for such purpose as honey, sugar, water with salt, beer and even chocolate...

Of a total of 114 affected individuals, 45.6% mentioned to have up to 1st degree ROU relatives. Our data are contrary to an association between gender and the existence of 1st degree relatives with ROU symptoms ( $F=0.604$ ;  $p=0.437$ ).

In ROU individuals an assessment of signs and symptoms of other diseases that may evolve with such manifestations was carried out, similar or identical, from a common herpes simplex (perhaps the situation more confusing but it was duly clarified), up to Behcet's disease, bowel inflammatory disease, systemic lupus erythematosus and other connective

pathologies. From such assessment (Fig. 5) it was verified as a more relevant data than herpes simplex is concomitantly present in 39.5% of ROU carriers.

Relevant chronic diseases identified in the questionnaire were Crohn's disease (1 case), diabetes mellitus (5 cases), peptic ulcers (4 cases), rheumatoid arthritis (2 cases), gouty arthritis (2 cases), neoplasm (uterus cervix: 1 case, hematological: 3 cases), intolerance to lactose (1 case). ROU situations which might be justified as secondary manifestations of an underlying chronic disease were excluded.

## DISCUSSION

This work main target relates to a prevalence study of recurring oral aphthosis in a general population of the central region of Portugal. Being an apparently simple job, the difficulty of dealing with the concept of “oral aphtha” was faced, widely used by the population but often in an unduly or imprecise

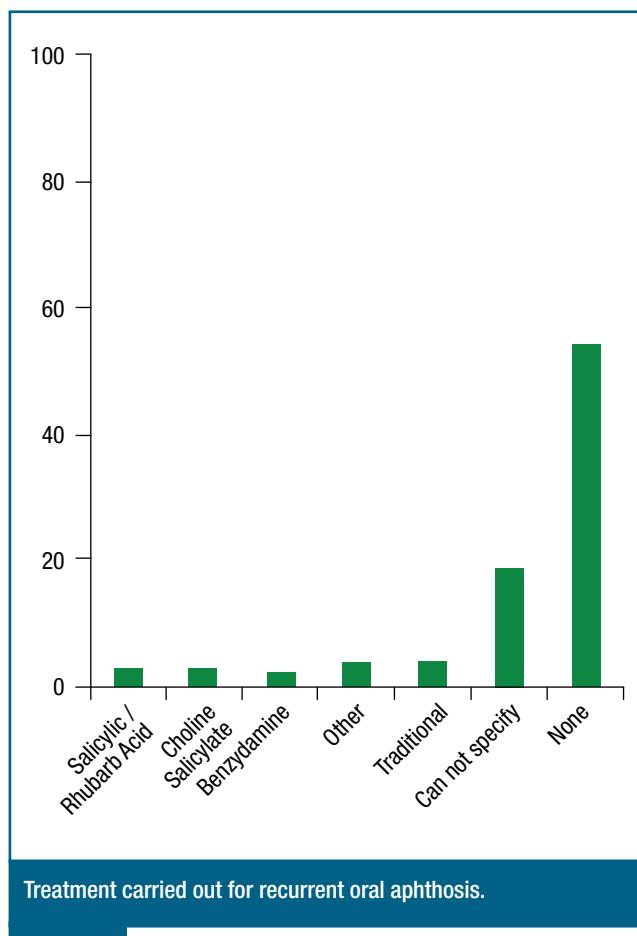


FIG. 4

fashion. Other difficulty presented is related with the fact of being an entity hardly valued by its carriers (and even by physicians) making sometimes difficult to quantify the number of lesions by year or the age of onset of this dysfunction. This is an original work in Portugal, where there is no publication of a similar study, being until now, a gap regarding other European countries.

The prevalence found is within the 20% that some review articles estimate for the general population.<sup>9-10</sup>

However, other studies refer odd prevalence in certain parts of the world or particular groups. For example, a study carried out in Sweden, has considered an ROU story of at least 2 years, defining a prevalence of 17.7% in the general population.<sup>21</sup> An huge study carried out in Kuwait (n=20.000), has ascertained a 27% prevalence in Arab individuals

of different nationalities, the Bedouin Arabs shown a prevalence of a mere 5%.<sup>14</sup> Other studies state that ROU can be three times more frequent in the Caucasian population than in the Afro-American population in the United States of America.

Regarding the gender of the individuals affected, in this work of ours a higher prevalence of ROU in women, is in line with the international literature.<sup>14-22</sup>

Regarding the ROU onset age a higher prevalence is found in ages below 20 years. In literature, the onset peak age is the first and/or second decade of life<sup>11-24</sup> considering that in our study, this happened in around 2/3 of those affected (65.8%).

No significant relationship was found between the place of residence and ROU presence. This can be explained by the fact that life style, food and medication are not very influenced by the place of residence. This factor is yet less relevant when, in the same person, places (country or town) of residence and work can differ.

When the triggering causes were assessed (Fig. 3), a correlation was detected between the emergence of oral aphthae and some foods as chocolate, dried fruit, citrines and cheese.<sup>25-27</sup> In the current study, around 3/4 (74.6%) of ROU individuals relate recurrences with certain foods, being these the most often named.

Several researchers indicate that ROU patients seem to develop inflammatory and immunologic responses different from the general population at the time of a traumatic event, causing the worsening and extending of ulceration, with aphthae being formed.<sup>10</sup> In our study, a significant percentage (37.7%) of ROU individuals confirm trauma as triggering factor.

Stress and anxiety were also named as causing ROU<sup>11-12,28</sup> and, also in this work, a considerable percentage (28.9%) of ROU individuals has confirmed it.

Acute febrile intercurrences were also named by ROU individuals we enquired as potentially triggering new recurrences.

Hormonal changes as ROU cause, are target of studies based in the fact that some women revealed cyclic oral ulceration related with catamenia or with the luteal stage of the menstrual cycle. In spite of Sircus (1957) mentioning that 10% of women pre-

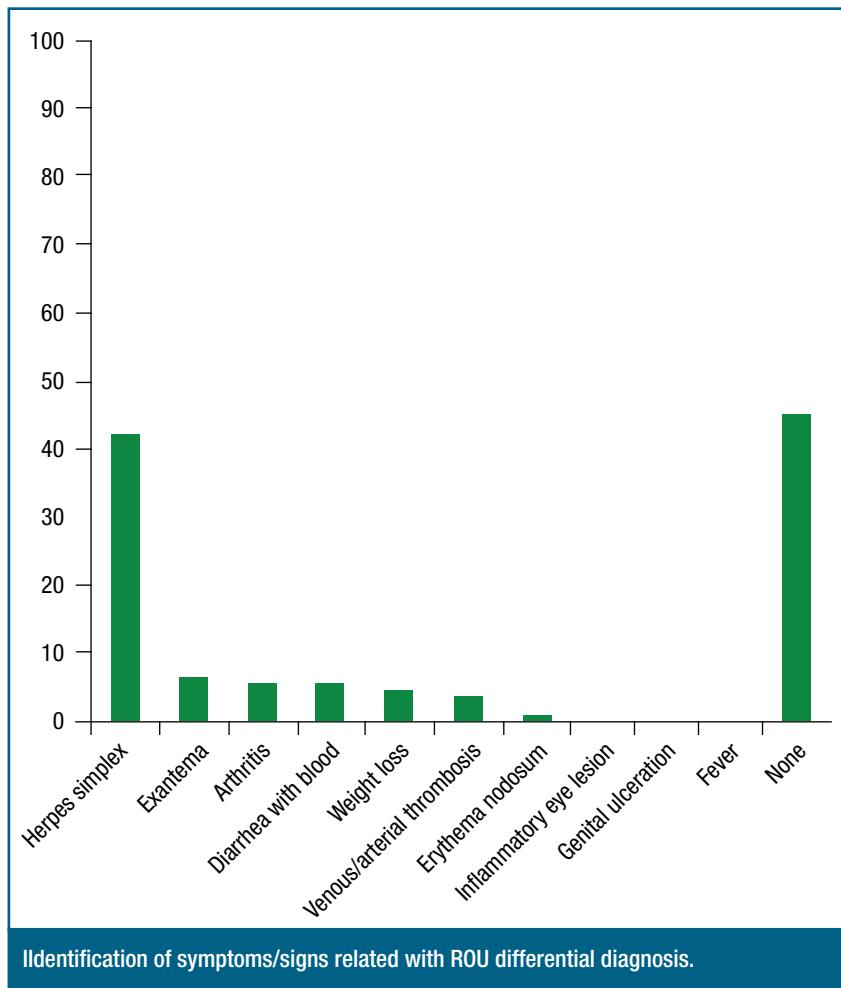


FIG. 5

sented their first ROU episode from 50 to 59 years old, more recent studies did not find any association between ROU and menopause.<sup>29</sup> In this work, a small percentage of women has identified the onset of the oral aphthosis in puberty, and many others did not succeed to confirm or deny such hypothesis. On the other hand, one in every ten women with ROU has referred to have recurrent periods in the peri-menstrual stage. An enquired woman has shown a complete remission during pregnancy, what is interesting because there are studies where a similar situation was documented,<sup>11</sup> with a subsequent exacerbation during puerperium.<sup>30</sup>

Medicines as  $\beta$ -blockers, non-steroidal anti-inflammatory, captopril, salts of gold, phenobarbital, are named as causing ROU.<sup>31-36</sup> In our study, just a small reduced percentage (6.1%) of the total of en-

quired individuals on this hypothesis has confirmed it.

Due to mechanisms not yet clarified, the smokers suffer less of ROU or present a clinical situation with less severity.<sup>37-38</sup> Some smokers present a first episode of oral ulceration after stopping smoking, with remission after a restart of such habit.<sup>9</sup> The current study, a very reduced number of ROU individuals has referred to stop smoking as a predisposing factor to oral aphtha.

The treatments currently anticipated for ROU, do not have yet the ability to cure, targeting the relief of symptoms through reducing the length of lesions and a decrease on reoccurrence. The medicines identified in this study envisage mainly disinfectants, anti-inflammatory and analgesics of topical action recommended by pharmacies. Immunomodulating agents and systemic action anti-inflammatory (as colchicine) presented a very reduced use. Such a high percentage of ROU individuals who denied carrying out any treatment (61.4%) can indicate the lesions limited character and mild aggression, as a reduced valorization of such entity on the part of patients and physicians.

Our study agrees with the literature results, confirming that almost half (45.6%) of ROU carriers presents a family history of identical condition.<sup>11</sup> Such patients can present more severe symptoms than those who do not present such family background.<sup>15,30-39</sup>

Regarding ROU differential diagnosis, it is crucial than physicians do not think in such issue as "only an aphtha". In any ROU patient, a differential diagnosis should be carried out, that can reveal that these "small and troubling" lesions can be an indicator of systemic pathology of a huge complexity. On the other hand, certainly we will find many patients to whom we will not succeed to give an explanation for such problem and should as such, be considered a primary lesion.

Herpes simplex is also a common condition distinct from ROU because it involves the keratinized mucosa and adjacent skin, having a character initially blistery and only after that ulcerative. This presented a high prevalence in ROU individuals (39.5%), translating also a high prevalence in the general population. A French study, for instances, has revealed a serological prevalence of 67% in the general population.<sup>40</sup> We did not find studies recording any kind of prevalence in the Portuguese population.

Regarding chronic diseases identified in this study, relevant for ROU investigation, we highlight Crohn's disease, which can present changes from the oral cavity to the anus. Although not identified in this general population studied, we must name Behcet's disease and SLE as associated pathologies to ROU which is important always to exclude when this is present. ■

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