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Original Research

Association between Haematological Parameters and Recurrent Apthous Stomatitis

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Abstract

Objectives: Recurrent apthous stomatitis (RAS) one of the most common diseases affecting the oral mucosa. The etiology is multifactorial. The aim of this study was to establish the relationship between recurrent apthous stomatitis and Vitamin B12, folic acid and Hemoglobin levels in patients with recurrent apthous stomatitis.

Materials and Methods: This observational study was conducted for a period of two years. Patients with systemic conditions exhibiting oral ulcers were excluded. Serum levels of Vitamin B12, FA and Hb was evaluated.

Results: Fifty two percent of the patients were females. The mean age of the patients was 35.3+10.28. Based on the size, 90% of the ulcers were of the minor type. RAS was seen in 56% of patients with low normal and 21% patients with deficient Vitamin B12 level compared to five patients with normal Vitamin B12 level. RAS was observed in 47% patients with normal and low normal level of FA and 4% patients with deficient FA level. Two female patients and one male patient were anemic compared to ten female patients and ten male patients with normal Hb levels. The mean Vitamin B12, FA and Hb levels among the patients with RAS were 387.74 +264.88, 7.02+4.95ng/ml, 13.23+ 2.15 g/dl respectively.

Conclusion: The results show that Hematinic deficiencies are observed in patients RAS. Hence, hematinic deficiencies should be considered in diagnosis and management of RAS.

Keywords: *Recurrent apthous stomatitis, Vitamin B_{12}, Folic acid, Heamoglobin, Apthous ulcer*

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INTRODUCTION

Recurrent apthous stomatitis, one of the most common diseases affecting the oral mucosa is a chronic inflammatory disease of the oral cavity. A review of literature suggests that 20% of the general population are affected by recurrent apthous stomatitis (RAS) but incidence varies from five to 50 % depending on the ethnic and socioeconomic groups studied [1]. They present clinically as painful, sharply circumscribed fibrin covered mucosal defects with a hyperemic border. Apthous ulcers are classified as minor (Mikulicz), Major (Sutton), and Herpetiform based on the size of the ulcer. They are also classified as simple, comprising of limited number of small, quickly healing, minimally painful ulcers limited to the oral mucosa with a reported recurrence of 3-6 months annually whereas in cases of complex apthosis, the ulcers are found on the oral and genital mucosa or perigenital areas affecting the scrotum, vulva, perineum and inguinal region [2].

The etiology of RAS is multifactorial. Local trauma, genetic, microbial, immunological factors and hematinic deficiencies seem to be major predisposing factors. Vitamin B_{12}, Folic acid and iron deficiency causes nutritional anaemia and is more common in infants, young children, menstruating and pregnant women. These deficiencies cause atrophy of the oral epithelium. This thinning makes them vulnerable to trauma, which increases the penetration of exogenous bacterial antigens leading to RAS [3]. It has been recently reported that CD4 (+) and CD25 (high) T regulatory cells are functionally and quantitatively compromised in patients with RAS [4]. Hematological studies on patients with RAS have also found that nutritional deficiencies most commonly low levels of Vitamin B_{12} and folic acid and replacement therapy with the deficient vitamins have resulted in improvement of the signs and symptoms [5].

The aim of this study was to establish the relationship between recurrent apthous stomatitis and Vitamin B_{12}, folic acid and Hemoglobin levels in patients with recurrent apthous stomatitis.

MATERIALS AND METHODS

This conformational study was conducted on patients referred to the Department of Dental and oral surgery, for a period of two years from November 2016 to December 2018 with complaints of recurrent apthous stomatitis. Patients with a confirmed history of systemic disease in which oral ulcers could be one of the manifestations such as coeliac disease, Behcets syndrome, Crohns disease, ulcerative colitis or AIDS or a pattern of oral ulceration not consistent with recurrent apthous stomatis and evidence of any other oral ulcerative and vesiculo bullous lesions such as oral lichen planus, pemphigus were excluded from the study. A complete physical and clinical examination of the patients were done. The diagnosis of RAS was made based on the clinical appearance of the ulcers and the history regarding the duration of the ulcers using Lehners criteria. Blood samples were taken and serum Vitamin $B_{12,}$ Folic acid and haemoglobin (Hb) was evaluated.

RESULTS

Twenty-three patients diagnosed with RAS were included in the study. Their details along with the results of their hematological parameters are given in the Table 1. Fifty two percent of the patients were females (n=12). The mean age of the patients was 35.3$\pm$10.28 years. Considering the classification based on the size 90% of the ulcers were of the minor type, all cases were of the simple chronic recurrent oral apthous ulcers, and none of the patients was of the complex apthosis type, as they reported no evidence of ulcers other than the oral cavity. The level of serum Vitamin B_{12} considered as normal was 501-950 pg/ml. Levels of 200-500pg/ml was considered as low normal and levels < 200pg/ml were considered as Vitamin B_{12} deficiency. RAS was seen in 56% of patients (n=13) with low normal and 21% patients (n=5) with deficient Vitamin B_{12} level compared to five patients with normal Vitamin B_{12} level. Normal level of serum folic acid was >5ng/ml. Folic acid levels of

3.1 to 5ng/ml was considered as low normal level. Levels <3ng/ml were considered as folic acid deficiency. RAS was observed in 47% patients (n=11) with normal and low normal level of folic acid compared to 4% patients with deficient folic acid level. Hemoglobin level of < 13gm% in males and < 11gm% in females were considered as anaemic. In the present study, two female patients and one male patient were anaemic, compared to ten female patients and ten male patients with normal Hb levels. The mean Hb, Vitamin B_{12}, and Folic acid level among the patients with RAS was 13.23±2.15 gm%, 387.74 ±264.88pg/ml, 7.02±4.95ng/ml respectively.

Table 1. Haematological parameters of the study participants.

S.No	Age	Sex	Serum Folic acid level in ng/ml	Serum Vitamin B12 pg/ml	Haemoglobin gm%
1.	33	Female	5.6	571	11.3
2.	37	Female	3.6	410	14.8
3.	24	Male	4.4	179	14.6
4.	32	Female	4.7	341	12.6
5.	45	Male	10	514	13.5
6.	35	Male	7.3	397	13.2
7.	36	Male	5.2	362	13.8
8.	28	Male	4	279	14.9
9.	44	Male	3.2	238	15.2
10.	41	Female	6	169	5.6
11.	31	Female	4.3	254	15.1
12.	34	Male	3.5	428	16
13.	50	Female	4.9	486	12.5
14.	44	Female	5.9	393	11.4
15.	31	Male	4.3	357	13.5
16.	25	Male	4.2	194	12.4
17.	50	Female	5	131	13.4
18.	18	Female	1.5	554	10.6
19.	36	Female	12.5	298	12.9

20.	17	Female	18.3	705	14.8
21.	37	Female	18.2	202	14.3
22.	27	Male	7	86	13.5
23.	59	Male	17.9	1370	14.4

DISCUSSION

Recurrent apthous stomatitis or recurrent apthous ulcer commonly referred to as canker sores is one of the most common ulcerative and vesiculobullous condition affecting the oral cavity. The ulcers heal spontaneously. The factors proposed as possible causative agents can be broadly classified as host and environmental factors. The host factors may be genetic, food allergy, haematinic deficiencies, immune dysregulation and physical or emotional stress. The environmental factors are microtrauma, local trauma, chemical injury, infections and smoking. The ulcers are usually found on the mobile mucosa such as the labial and buccal mucosa, soft palate, tongue or floor of the mouth. Unlike the minor forms, which heals without scarring, the major apthae heal with scarring. Major apthae are seen in HIV infections and HIV should be considered in the differential diagnosis when major apthae are present [6].

Histologically they are seen as mononuclear infiltrate with a fibrin coating [7]. It has also been found that RAS more often affects younger people and these are mostly correlated to stressful periods. In a study conducted by McCullough et al [8], 87.1 % had minor ulcers, 8.6% had major ulcers and 43% had herpetiform ulcers. The results of the current study are in accordance with the above-mentioned study wherein 90% of the cases were of the minor type. Warnun et al [9] in their study on recurrent apthous stomatitis in Thai dental patients found that the incidence was maximum in 20-30 years. Ghafoor et al [10] reported a mean age of 31.3 years in their study on association of serum ferritin and folate levels with recurrent oral ulceration. In a study by Volkov et al [11] on successful treatment of RAS with Vitamin B_{12}, the mean age of the patients was 38.7 $\pm$18.8 years. Claire et al [12] reported the mean age group of the patients as 32.4 $\pm$14.8 years in a study on hematinic deficiency in RAS. The mean age group of the patients in the present study was 35.3$\pm$10.28 years concurrent with the above-mentioned studies. These results show that RAS is more common in younger people and several factors such as stress, nutritional deficiency, and smoking can be attributed to it.

Considering the sex ratio, Waranu et al [9] noticed that the prevalence of RAs was slightly higher in women (48.2%) compared to men (44.1%). Piskin et al [13] found almost no difference in incidence between males (n=18) and females (n=17) similar to our study where the number of female patients were 12 and male patients 11. Wray et al [14] on their study on treatment of recurrent apthae with Vitamin $B_{12,}$ Folic acid and iron reported more female patients (n=78) than males(n=52). Ghafoor et al [10], Claire et al [12] also reported higher incidence among females. Some conflicting studies [15] report that a minor subset of women with RAS have cyclical oral ulceration related to the onset of menstruation or the luteal phase of the menstrual cycle. This could be one of the reasons for the higher incidence among the females in many studies. On the contrary, Mc Cullough et al [8] noticed that males were affected more than females.

A study conducted by Rogers [16] revealed anaemia in six out of 102 patients with RAS. Helay [17] reported a incidence of anaemia in 10.5 % RAS patients. In contrast, Burgan et al [18] observed no statistical difference

of Hemoglobin between cases and controls as 14 % of patients with RAS were anaemic as compared to 10.5 % of controls. In our study, 13% of patients were anaemic.

A Study byVolkov et al [11] suggested that patients with RAS were deficient in Vitamin B_{12}. Intramuscular cobalamine injection prevented recurrence of the lesion over 18months. Garcia BG et al [19] reported that 74.1% patients with RAS when treated with cobalamine were free from apthous ulcers at the end of the treatment. They concluded that since Vitamin B_{12} administration diminished the occurrence of the RAS lesion, Vitamin B_{12} deficiency should be considered in all patients with RAS. In accordance with this protocol, Vitamin B_{12} was assessed in all patients with RAS in our study.

Kamran Sari [20] in their study reported that 29.7% patients were Hb deficient in the study group as compared to 9.7% in healthy controls. On the other hand, Vitamin B_{12} deficiency was 32.3% as compared to 14.7% in healthy controls. They found that RAS stomatitis patients had statistically low Hb level compared to the control ($p<.001$). Vitamin B_{12} plays a key role in carbohydrate and fat metabolism, hematopoiesis, and protein synthesis. Vitamin B_{12} causes suppression of cell-mediated immunity thereby leading to changes in the cells of oral mucosa. Anaemia and lower Hb levels in RAS causes reduction in oxygen supply to the oral mucosa resulting in atrophy of the oral mucosa. Vitamin B_{12} and folic acid play a crucial role in DNA synthesis and cell division. Hence, the hematinic deficiencies make the patients at a higher risk for RAS.

Lopez jornet et al [21] investigated iron, folic acid, ferritin and Vitamin B_{12} in RAS patients and controls. They showed deficiency of folic acid and Vitamin B_{12} in 4.3% and 5.4 % cases respectively wherein in the control group it was 1.06 % and 1.06% respectively. The overall frequency of hematinic deficiencies was 14.14% in RAS and 6.39 % in controls. In a study by Sun et al [22] 20.9%,20.15 and 4.8% and 2.6 % patients with RAS had deficiencies of Hb, Iron, Vitamin B_{12}, and folic acid respectively. There was a statistically significant higher frequency of hematinic deficiencies in RAS group compared to the control group. In contrast Piskin et al [13] found that only serum Vitamin B_{12} levels were statistically significantly lower in RAS patients compared to the control group. Kozlak et al [23] investigated dietary intake of vitamins in RAS patients in a case- control study and reported that RAS patients had a significantly lower daily intake of Vitamin B_{12} and folate than controls.

Wray et al [14] reported that 17.7% patients with RAS were found to be deficient in iron, Vitamin B_{12}, folic acid as compared to 8.5% in the control group. Out of 23 patients, 15 were deficient in iron, seven in folic acid and five in Vitamin B_{12} and 4 patients had more than one deficiency. Four of the five patients with Vitamin B_{12} deficiency were promptly relieved free of symptoms and remained free of ulcers during the follow up period. Of the six patients with folic acid deficiency, six were completely relieved of ulcers and remained symptom free during the follow up. Ghafoor et al [10] in their study reported anemia in 24 patients out of 57 patients with RAS. They found 46.5% had low level of RBC folate and 50.1 % patients had Vitamin B_{12} deficiency. They concluded that patients with RAS had more hematinic deficiencies particularly of B12 as compared to controls. Nabiha et al [24] observed anemia in 58.3 % cases, Vitamin B_{12} deficiency in 45% cases and low serum folate in 51.7% cases. Burgan [18] reported Vitamin B_{12} deficiency in 26.6% cases. Cobalamine injections made 74.1% of these cases free from ulcers at the end of the treatment. Nabiha et al [24] concluded that there was statistical difference in RBC folate levels between Apthous group and non-apthous. These results correspond with that Barnadas [25]. In the present study RAS was seen in 56% of patients (n=13) with low normal and 21% patients (n=5) with deficient Vitamin B_{12} level and 47% patients (n=11) with normal and low normal level of folic acid.

In a study by Claire Healy et al [12], deficiency state was identified in 28.9% of RAS with iron deficiency accounting to 96% of these, 4.6% were Vitamin B_{12} deficient, and 3.7% have combined iron and Vitamin B_{12} deficiency. Nil patients had folate deficiency. They suggested that the prevalence of hematinic deficiency was

high in the study population. Barnadas et al [25] found that folic acid deficiency was the commonest deficiency in RAS in their study. Oslon et al [26] disputed the role of hematinic deficiency in RAS showing a prevalence of just 3%. Rogers Hutton [16] in contrast reported a high prevalence of 37% RAS in patients with hematinic deficiencies. The results of the present study also showed that there are hematinic deficiencies in patients with RAS.

CONCLUSION

The etiology of RAS is multifactorial. The results of our study show that Hematinic deficiencies are present in patients with recurrent apthous stomatitis. However, the sample size is small and the study that we did was an observational study. Interventional studies with larger samples and case control studies are needed for affirmative results. Other studies have reported correlation between RAS and hematinic deficiencies. Hence, we conclude that hematinic deficiencies of Vitamin B_{12}, Folic acid and Hemoglobin should be considered in the diagnosis and management of recurrent apthous stomatitis.

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