Oral manifestations, biochemical, and IL-6 analysis of saliva in major depressive disorder patients under treatment

Omar F. Fawzi, B.D.S. [(1)]
Fawaz D. Al-Aswad, B.D.S., M.Sc., Ph.D. [(2)]

ABSTRACT

Background: Major depressive disorder (MDD) is mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem, and by loss of interest or pleasure in normally enjoyable activities. The aims of the study: were to determine the prevalence of oral manifestation among patients with major depressive disorder receiving antidepressant drugs, and detect alkaline phosphatase (ALP), Total Salivary proteins (TSP), and Interleukin-6 (IL-6) in relation to MDD patients under treatment and to compare with healthy controls.

Materials and method: (50) MDD patients; between the ages of 20 years and 60 years.The depression patients are divided into (25) patients under treatment with fluoxetine (Prozac), and (25) patients under treatment with imipramine (Tofranil).The depression patients are diagnosed according to Hamilton depression scale used in the department of psychiatry in Al-Yarmouk Teaching Hospital by a psychiatric specialist.

Results: The most frequent oral manifestations in the patients with MDD, in this study were burning mouth syndrome (72%), and dry mouth (70%), while metallic taste (48%) was fairly frequent, males more effected than females.Burning mouth syndrome, and metallic taste were more frequent in patients with Prozac treatment, while dry mouth was more frequent in patients with Tofranil treatment. increased levels of IL-6, TSP, and ALP in MDD patients receiving treatment as compared to healthy control

Conclusion: frequent oral examination of patients with MDD is mandatory, and these patients should be a major concern in dental practice.

Keywords: Major Depressive Disorder, Oral Manifestations, ALP, TSP, IL-6. (J Bagh Coll Dentistry 2013; 25(2):89-93).

INTRODUCTION

The term "depression" is ambiguous. It is often used to denote this syndrome but may refer to other mood disorders or to lower mood states lacking clinical significance[(1,2)].

The diagnosis is based on the patient's self-reported experiences, behavior reported by relatives or friends, and a mental status examination. There is no laboratory test for major depression[(1)].Saliva has tremendous potential source of biological molecules to some as indicators of many diseases, and also monitoring different types of medications. It may have the potential to replace serum in many analyses[(2,3)].During the last decade several studies were done to determine the prevalence of oral manifestation with emphasis on the different medication of treatment of MDD [(4,5)].Therefore the present study was instigated since no extensive studies have been made in Iraq on oral manifestation allocated with MDD, and in order to show that a routine dental examination for patients with antidepressant medications is necessary.Finally the research is supported with biochemical studies (IL-6, ALP, TSP) to draw comparisons and to test their significant differences between samples.

The aims of the study are to determine the percentage of oral manifestation among patients with major depressive disorder receiving antidepressant medications, and to provide base line information for future studies and comparisons. Correlate the prevalence of the oral manifestations according to age, gender, type and duration of medications.Determine the level of the following markers among antidepressant and control groups in unstimulated saliva:IL-6, ALP, and TSP.

MATERIALS AND METHODS

The study sample consists of (50) MDD patients receiving treatment for more than 1 month, 20 healthy; according to their personal statement, control group of both genders. The depression patients were divided into (25) twenty five patients under treatment with fluoxetine Prozac, and (25) twenty five patients under treatment with imipramine Tofranil. The depression patients were diagnosed according to Hamilton depression scale (1960) used in the department of psychiatry in Al-Yarmouk Teaching Hospital by a psychiatric specialist; they were examined from the period (6-12-2011----17-3-2012) to detect the prevalence of oral manifestation, biochemical analysis, and salivary IL-6 measurement.

(1) M.Sc. Student, department of oral medicine college of dentistry, university of Baghdad.
(2) Professor , department of oral medicine, college of dentistry, university of Baghdad.

Exclusion criteria

Patients with heavy smoking and alcoholism, pregnant women, diabetic patients, patients received radiotherapy, chemotherapy, and patients receiving combination of Prozac and Tofranil, and any other systemic disease.

Materials used for immunological and biochemical analysis

1.SalivaryInterleukinelisa -6- kit Catalog number:ABIN455601.

2.Total Salivary Proteins Man. Cat #:23225.

3.Alkaline Phosphatase ELISA kit Catalog number: CSB-E09033h

Oral examination

All the patients examined by a single examiner, under standardized conditions; the oral cavity examined in an artificial light by using a mouth mirror. The procedure of examination of oral soft tissue was done in sequence according to directions suggested by the W.H.O.(1987)

Oral Manifestations

A-Xerostomiawas diagnosed according to the subjective complaint of all patients of dry mouth due to a lack of saliva[6].

B-Burning mouth syndromewas identified according to burning or tingling sensation on the lips, tongue, or entire mouth[7].

C-Metallica tastewas diagnosed according to the distortion of the sense of taste, the distortion in the sense of taste is the only symptom, and diagnosis is usually complicated since the sense of taste is tied together with other sensory systems[8].

Immunological and biochemical analysis

Salivary Interleukin-6, and salivary alkaline phosphatase levels was determined using ELISA technique.

Total salivary proteins level was determined using BCA technique.

Statistical Analysis

Data are analyzed through the use of SPSS (Statistical Process for Social Sciences) version 10.0 application Statistical analysis system, Excel (Statistical package) and Microsoft word.

Descriptive data analysis

1. Tables (Frequencies, Percentages and Cumulative Percentages)
2. Mean, Trimmed Mean, Median.
3. Standard Deviation (Std. D.), Standard Error (Std. Error), Range, Interquartile range .
4. (95%) Confidence interval for population Mean values.
5. Two Extreme values (min. and max.) respondents.
6. Contingency Coefficients for the causes correlation ship of the contingency tables.
7. Odds Ratio coefficient for represents the number of times that the target factor (increased /or decreased) by the other factor in the association table.
8. Cohort group study for represents the risk estimate.
9. Graphical presentation by using:Bar- charts, Custer Bar Charts.Pie - charts.Stem-Leaf Plot.

Inferential data analysis

1-Binomial Test procedure.

2-Mann-Whitney test (a nonparametric equivalent to the t test).

3-Chi-Square test.

4-Contingency Coefficients test.

RESULTS

Prevalence of oral manifestation according to age, gender, type of medication, and duration treatment

As shown in (table 1) the results has reported that with burning mouth syndrome manifestation a significant difference was obtained at P<0.05 with treatment only and with a non-significant at P>0.05 were recorded with the leftover, then followed with dry mouth manifestation a highly significant difference was obtained at P<0.01 with duration only and with a non-significant at P>0.05 were recorded with the leftover, then followed with metallic taste manifestation a significant difference was obtained at P<0.05 with duration only and with a non-significant at P>0.05 were recorded with the leftover.

Immunological Analysis

Salivary IL-6

Higher mean value of IL-6 in patients treated with Tofranil than patients treated with Prozac as shown in (figure 1).

Table 1: Causes correlation ships of the distribution among some related variables (Age, Gender, Treatment, and Duration) and the studied oral manifestation

some related variables X Oral manifestation (*)		Contingency Coefficient	Approx. Sig.	C.S.
Burning mouth syndrome	Age Groups	0.319	0.340	NS
	Gender	0.075	0.594	NS
	Treatment	0.336	0.012	S
	Duration	0.411	0.071	NS
Dry mouth	Age Groups	0.238	0.701	NS
	Gender	0.122	0.384	NS
	Treatment	0.213	0.123	NS
	Duration	0.489	0.008	HS
Metallic taste	Age Groups	0.371	0.157	NS
	Gender	0.125	0.374	NS
	Treatment	0.158	0.258	NS
	Duration	0.439	0.036	S

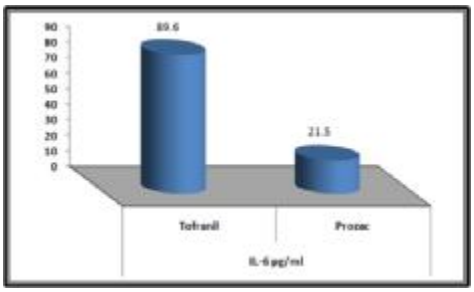

Figure 1: Bar chart for the mean values of IL-6 (pg/ml) parameter distributed between the two different types of treatments of the study sample of depression status

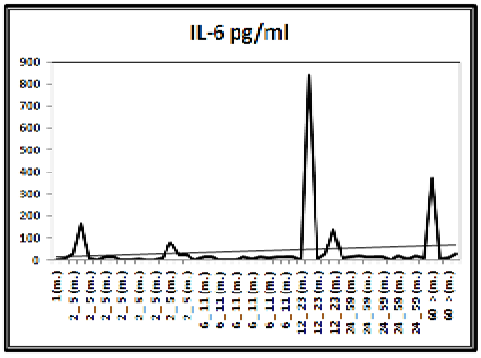

Figure 2: Sequence of IL-6 pg/ml parameter readings a long duration periods of treatment with both drugs (Tofranil and Prozac)

Concerning the duration of treatment, (figure 2) shows slight increase in Il-6 level with increased duration of treatment with both medications Tofranil&Prozac, also with periods of high elevations and demotions.

Biochemical Analysis

Alkaline Phosphatase

A higher mean value of ALP in patients treated with Tofranil that patients treated with Prozac as shown in (figure 3)

An increase in the concentration of ALP according to the duration of treatment in both medications, (figure4) also revealed periods of high elevations and demotions in ALP level at (24-54 months).

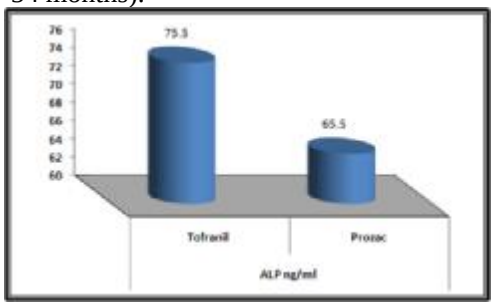

Figure 3: Bar chart for the mean values of ALP (ng/ml) parameter distributed between the two different types of treatments of the study sample of depression status

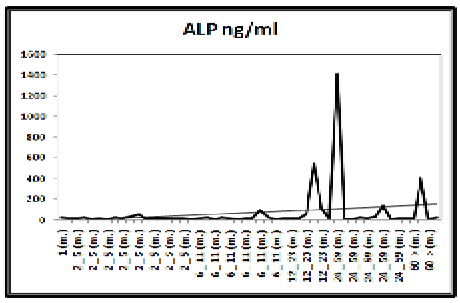

Figure 4: Sequence of ALP ng/ml parameter readings a long duration periods of treatment with both drugs (Tofranil and Prozac)

Total Salivary Proteins

Figure (5) shows that a higher mean value of Total Proteins in patients treated with Prozac than patients treated with Tofranil.(Figure 6) shows Investigations concerning the duration of treatment with both medication Tofranil&Prozac, a slight increase in the concentration of TSP was evident, with periods of elevations and demotions.

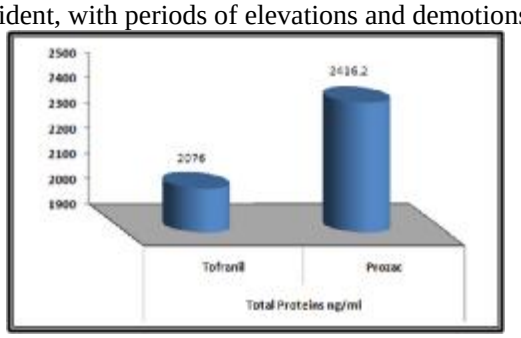

Figure 5: Bar chart for the mean values of Total Proteins (ng/ml) parameter distributed between the two different types of treatments of the study sample of depression status.

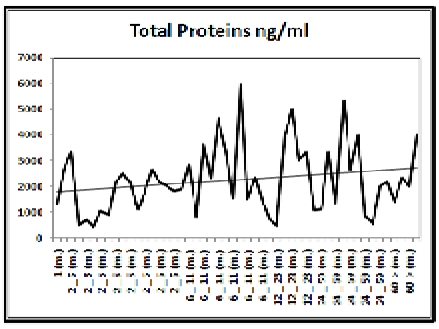

Figure 6: Sequence of Total Proteins ng/ml parameter readings a long duration periods of treatment with both drugs (Tofranil and Prozac)

Biochemical and Immunological analysis compared to healthy groups

Table (2) represents the target of the critical base line of the study sample for abnormal(IL-6 pg/ml), (ALP ng/ml), and (Total Proteins ng/ml)

parameters. High mean values of study parameters when compared to control.

DISCUSSION

Patients that take psychotropic medications for long periods may experience behaviors that have a negative impact on oral health. These medications may cause lethargy, fatigue and lack of motor control and memory that may impair the individual's ability to practice a good oral hygiene technique[9].The present study showed no significant relationship between total oral manifestation and age.

This was also reported by Jorm [10], and disagreed with Snowdon [11] he stated that his findings have been inconsistent, but majority opinion holds that oral manifestations in MDD are common in old age.Regarding the duration of the treatment the oral examination revealed oral complication at the time of the examination and does not give an indication about the past; to go in depth in this parameter, this require a retrospective study with a longitudinal design. This is definitely outside the scope of this study however the interpretation of the duration of treatment when studied should be treated with caution. In our findings BMS, and dry mouth was evident with high statistical significant when compared to healthy group this was also mentioned by Scully [12].It might argue that age of onset of depression may reflect the time when the patient fulfilled the diagnostic criteria of MDD. The mean age of disease onset in males was at young aged, while in females was in middle aged, Hans-Ulrich *et al,* [13] reported the same results.

This may be partially explained by that the environmental factor, life styles, and diet may influence the development of these complications and decrease susceptibility with advancing age.This study showed that the level of salivary IL-6 was higher in MDD patients receiving treatment with both medications Tofranil and Prozac than healthy controls however, this was not statistically significant, Kubera*et al.*[14] found different results, they speculated that the therapeutic activity of these antidepressants is at least partly connected with their effect on the cytokine network and IL-6 production.Salivary ALP activity level was elevated in relation to type of medication, and duration of treatment than control group in all MDD patients receiving treatment with both medications with no statistical significance, this was close to that reported by Diem*et al.* [15], they found that antidepressant medications can profoundly affect bone metabolism. In some scenarios (eg, osteoporosis), these effects are intended, potentially adverse side effects of medications on bone may occur.This study showed higher significant TSP value than control patients in all MDD patients receiving treatment with both medications, these results differed from those of Van Hunsel *et al* [16] they found that TSP was lower in MDD patients. This may be explained by the fact that major depression is accompanied by an acute phase response (APR), characterized by elevated levels of positive acute phase proteins (APPs) and decreased levels of negative APPs.This study showed also higher mean value of TSP in MDD patients treated with Prozac than MDD patients treated with Tofranil with no statistical significance, this was also mentioned by Hunter and Wilson [17] they explained the varyingly increased TSP that have been reported more with Tofranil to the suppressive effects of tricyclic antidepressants and SSRI are profound, and extend beyond suppressing resting parameters to reducing stimulated salivary flow. According to the results presented in the present study TSP was found to be higher in study group as compared to healthy, the difference was statistically significant, actually when the duration of treatment were considered in MDD a significant correlation was found.

REFERENCES

1. Sidana S, Kishore J, Ghosh V, Gulati D, Jiloha R, Anand T. Prevalence of depression in students of a medical college in New Delhi: A cross-sectional study. Austral Med J 2012; 5(5): 247-250.
2. Greabu M, Battino M, Mohora M, Totan A, Didilescu A, Spinu T, Totan C, Miricescu D, Radulescu R. Saliva--a diagnostic window to the body, both in health and in disease. J Med Life 2009; 2(2): 124-132.
3. Kinney JS, Morelli T, Braun T, Ramseier CA, Herr AE, Sugai JV, Shelburne CE, Rayburn LA, Singh AK, and Giannobile WV. Saliva/Pathogen Biomarker Signatures and Periodontal Disease Progression J Dent Res 2011; 90: 752-758.
4. Reddy RS, Vijayalaxmi N, Ramesh T, Raju RR, Reddy RL, Singh TR. Mood and mouth. J Dr NTR Univ Health Sci 2012; 1: 106-110.
5. Joseph TI, Vargheese G, George D, Sathyan P. Drug induced oral erythema multiforme: A rare and less recognized variant of erythema multiforme. J Oral Maxillofac Pathol 2012; 16: 145-148.
6. Jeganathan S, Carey H, Purnomo J. Impact of xerostomia on oral health and quality of life among adults infected with HIV-1. Spec Care Dentist 2012; 32(4): 130-135.
7. Klasser GD, Epstein JB, Villines D. Management of burning mouth syndrome. J Mich Dent Assoc 2012; 94(6): 43-46.
8. Sakagami M. Diagnosis and treatment of taste disorders. Nihon JibiinkokaGakkaiKaiho 2012; 115(1): 8-13.
9. McClain D, Bader J, Daniel S, Sams D. Gingival effects of prescription medications among adult dental patients. Special care in dentistry 1991; 11(1): 15-18.

10. Jorm AF. Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. Psychological Medicine 2000; 30(1): 11-22.
11. Snowdon J. Is depression more prevalent in old age? Aust NZJ Psychiatry 2001; 35(6): 782-787.
12. Scully C. Drug effects on salivary glands; dry mouth. Oral Dis 2003; 9: 165-176.
13. Hans-Ulrich Wittchen, Stefan Uhmann, The timing of depression: an epidemiological perspective. Medicographia 2010; 32: 115-125.
14. Kubera M, Kenis G, Bosmans E, Kajta M, Basta-Kaim A, Scharpe S, Budziszewska B, Maes M. Stimulatory effect of antidepressants on the production of IL-6. Int Immunopharmacol 2004; 4(2): 185-192.
15. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM, Bliziotes MM, Ensrud KE.Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med 2007; 167(12):1240-1245.
16. Van Hunsel F, Wauters A, Vandoolaeghe E, Neels H, Demedts P, Maes M. Lower total serum protein, albumin, and beta- and gamma-globulin in major and treatment-resistant depression: effects of antidepressant treatments. Psychiatry Res 1996; 65(3): 159-169.

Table 2: Summary statistics and the Standardized limitations for the studied parameters by applying the suggested technique of depression status

Statistic		ALP ng/ml		IL-6 pg/ml		Total Proteins ng/ml	
		Study	Control	Study	Control	Study	Control
Mean		70.5	13.8	40.4	12.8	2246.1	1696.6
95% Confidence Interval for Mean	**Lower Bound**	9.5	12.2	3.5	8.9	1865.8	1425.4
	Upper Bound	131.5	15.4	77.2	16.8	2626.4	1967.8
5% Trimmed Mean		29.9	13.6	16.1	12.8	2162.3	1692.3
Median		16.8	14.0	11.4	12.9	2083.0	1689.5
Std. Error		30.3	0.8	18.3	1.9	189.2	129.6
Std. Deviation		214.6	3.1	129.6	7.7	1338.2	579.5
Minimum		9.6	9.1	0.0	1.2	438.0	804.5
Maximum **Standardized Limits : (Cutoff point)**		1408.6	20.8	842.0	25.8	6000.0	2666.0
Range		1399.0	11.7	842.0	24.6	5562.0	1861.5
Interquartile Range		9.2	4.2	15.1	12.4	1989.3	983.3
C.S. **P-value**	**Levene's test**	P=0.063		P=0.079		P=0.003	
	Student's test	P=0.282		P=0.375		P=0.019	
	Statistical Decision	NS		NS		S	