ORIGINAL ARTICLE

Immune markers in oral discomfort patients before and after elimination of oral galvanism

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Submitted: 2013-03-12 Accepted: 2013-05-15 Published online: 2014-01-15

Key words: **oral discomfort; oral galvanism; electro active restorations removal; IgA1; IgA2; sIgA; lysozyme; antiIgA/HSP60**

Neuroendocrinol Lett 2013; **34**(8):802–808 **PMID:** 24522020 NEL340813A03

Abstract

BACKGROUND: An enhanced release of metals in the mouth due to galvanic cell formation is considered to be one of the causes of oral discomfort. The aim of this study was to investigate the influence of galvanic cell on salivary immune defense factors.

MATERIAL AND METHODS: The levels of IgA1, IgA2, sIgA, lysozyme and antiIgA/HSP60 were evaluated in representative samples from 159 patients with galvanism, from 177 patients without galvanism and in two control groups. All the participants underwent personal history taking, clinical examination, galvanic currents measurement and saliva collection.

RESULTS: Electro active dental materials were removed in 30 patients. There was a significant increase in IgA2 level, a significant decrease in antiIgA/HSP60 levels and an increase in IgA1, sIgA and lysozyme levels found after the removal of electro active restorations. Morphological symptoms disappeared in 70% of the treated patients.

CONCLUSION: The study confirmed that pathologic galvanic phenomena influences the immune defense reactions in the oral cavity and thus may cause the symptoms of oral discomfort. A measurement of the galvanism and a subsequent removal of electro active restorations should become a common therapeutic procedure in the patients with oral discomfort.

INTRODUCTION

In the case of patients with oral discomfort an unusual character and intensity of patient´ s complaints combined with negative or very discrete and uncommon findings in the oral cavity often lead to diagnostic as well as therapeutic confusion. Dental materials are in a long-term contact with soft and hard tissues of the oral cavity. Due to specific environmental characteristics of the mouth, metal alloys undergo mechanical and electrochemical changes. These changes may contribute to a development of oral discomfort symptoms (Wataha 2000).

The presence of diverse metallic systems in the oral cavity may induce the development and manifestation of electrochemical corrosion, where various dental alloys function as electrodes and fluids in the oral cavity (saliva, crevicular fluid or dietary fluids) as an electrolyte (Holland 1980; Arvidson

& Johansson 1985; Yontchev *et al.* 1989; Walker *et al.* 2003; Al-Ali *et al.* 2005; Ciszewski *et al.* 2007; Koh *et al.* 2008; Sutow *et al.* 2008). An action of the galvanic current may also manifest itself as morphologic changes of oral tissues. Consequently inflammation of the oral mucosa and tongue, paraesthaesia, glossodynia, stomatodynia, hyperaemia of the pulp or neuralgia may occur (Kucerova *et al.* 2002; Sutow *et al.* 2004). Galvanic effects can be evaluated by measuring galvanic potentials and currents (values over 5 microamperes are considered pathological) (Nilner 1981; Nilner *et al.* 1982; Axell *et al.* 1983; Hampf *et al.* 1987; Kobayashi 1989; Nogi 1989; Kucerova *et al.* 2002; Wataha 2002; Sutow *et al.* 2004; Prochazkova *et al.* 2006; Podzimek *et al.* 2008) and, in addition, it is relatively easy to eliminate galvanism from the oral cavity by removing electro active dental materials and replacing them by non-metallic ones (Lindh *et al.* 2002; Prochazkova *et al.* 2004; Prochazkova *et al.* 2006).

Local toxic activity of metal ions released from dental metal materials to adjacent tissues may lead to the development of inflammation, activation of immunocompetent cells, production of proinflammatory factors, worsened elimitation of metabolic products and, therefore, to the worsening of inflammation (Syrjanen *et al.* 1985; Bumgardner & Johansson 1996). In patients with already developed oral cavity inflammatory disease (periodontitis), especially in special subgroup of these patients (pregnant women), the inflammation can have serious consequences (pre-eclampsia) (Straka *et al.* 2011). The inflammation may become chronic if the causal factor is not removed and an appropriate treatment is not provided. Components of the saliva, such as secretory IgA, IgA1, IgA2 and lysozyme, have a critical role in the mucosal defence against galvanic phenomena (Kerr 1990; Nagler *et al.* 2002).

The objective of this study was to investigate the influence of pathologic galvanic currents and therefore enhanced release of metal ions from oral metal restorations on immune defense factors of the saliva in patients with oral discomfort.

MATERIAL AND METHODS

Study participants from all four groups underwent personal history taking, clinical examination, galvanic currents measurement and saliva collection for establishment of IgA1, IgA2, sIgA, lysozyme and IgA antibodies against heat shock protein 60 (antiIgA/HSP60) levels. Electro active dental materials were removed in 30 patients. For the purposes of this project 397 patients – 91 men and 306 women of an average age of 51 years – were examined.

Patients with oral discomfort

There were 336 patients referred for an examination for suspicious "galvanic problems" (inflammatory or lichenoid efflorescences on the mucosa after dental treatment, metallic pigmentations of the gingiva, prosthetic restorations staining and corrosion, tongue burning, burning and shedding of lips and oral mucosa, sour, bitter, salty sensations, metallic taste) or "oral discomfort of an unknown etiology". Based on the measurement of galvanic currents, these patients were divided into two groups: in 159 patients (34 men and 125 women, an average age of 53.5 years) the pathological values of galvanic currents ranging from 5–50 μA were found and these patients constituted the Group DIS^+GAL^+. Thirty patients from Group DIS^+GAL^+ had their electro active fillings replaced.

The Group DIS^+GAL^- consisted of 177 patients (37 men and 140 women, an average age of 52.5 years) with oral discomfort, with no pathological values of galvanic currents found.

Control groups

Two control groups were established:

The Group DIS^-GAL^- consisted of 40 participants (8 men and 32 women, an average age of 49.5 years) without any pathological values of galvanic currents and without any oral discomfort. Dental materials found in the oral cavities of these participants were similar to those used in patients in the Group DIS^+GAL^+ and in the Group DIS^+GAL^-.

The Group $DIS^-GAL^-MET^-$ consisted of 21 healthy participants (12 men and 9 women, an average age of 32.5 years) without any pathological values of galvanic currents, without any oral discomfort and without any dental metal fillings or other metallic restoration in their oral cavity.

Personal history

All examined persons had a detailed personal history, which focused on the exposure to metals, taken.

Clinical examination

All tested persons underwent a detailed examination of the oral tissues including a panoramic X-ray examination. Their examination focused on the identification of dental metal restorations and morphologic signs of oral discomfort – inflammatory or lichenoid changes of the mucosa, tongue or gingiva. The presence of the metal staining of their oral tissues was also evaluated.

Galvanic currents measurement

The galvanic currents between dental alloys and gum, tongue, lips or buccal mucosa and between different dental alloys were measured using the Odontologic 2000 device (Embitron; Prague, Czech Republic) (Kucerova *et al.* 2002). A threshold for galvanic current pathological values (over 5 μA) was established in previous studies (Kucerova *et al.* 2002; Prochazkova *et al.* 2006; Podzimek *et al.* 2008) based on experimental data and previous publications (Holland 1980; Nilner 1981; Nilner *et al.* 1982; Axell *et al.* 1983; Arvidson & Johansson 1985; Hampf *et al.* 1987; Nogi 1989; Walker *et al.* 2003; Sutow *et al.* 2004; Sutow *et al.* 2008).

Saliva collection and immunologic markers determination

Non-stimulated saliva (1 ml) from all examined participants was collected and frozen at –18 °C.

After defrosting the samples a radial immunodiffusion method was used to determine immunologic marker (IgA1, IgA2, secretory IgA and lysozyme) levels. Commercial kits Human IgA Subclass NL BINDARID™ Combi Kit, Human Secretory IgA RID Kit (The Binding Site Ltd.; Birmingham, UK) and Human Lysozyme NL NANORID™ Kit (The Binding Site Ltd.) were used.

The ELISA method (Lequin 2005) was used to measure IgA antibodies against HSP 60 in the saliva.

The measurement was performed in all the groups in randomly selected patients (Group DIS$^+$GAL$^+$ – 41 samples, Group DIS$^+$GAL$^-$ – 44 samples, Group DIS$^-$GAL$^-$ – 18 samples and Group DIS$^-$GAL$^-$MET$^-$ – 15 samples).

Removal of electro active dental restorations from oral cavity

Electro active dental restorations were removed from the oral cavity in 30 patients of the Group DIS$^+$GAL$^+$, with morphological symptoms in their oral cavity. Electro active restorations were replaced under the shield of strong antioxidants – vitamin C and selenium.

Special precautions were used to eliminate a contact of the patients with released metal ions from the removed electro active metal restorations (Lindh *et al.* 2002; Prochazkova *et al.* 2004).

Statistical analyses

Statistical data analysis was performed using the single sample Student´s t-test after logarithmic transformation y = log10(x+1) for the quantitative data. Qualitative characteristics of the examined samples were compared using the Pearson test χ^2. An analysis was done to determine required number of randomly selected samples from participants from each group in order to determine if statistical differences exists between groups.

All the participants of this study were examined and treated after providing an informed consent statement, with approval of institutional scientific and ethics committees and in accordance with the Helsinki Declaration.

RESULTS

Results of personal history examination

An unfavorable reaction to metals was subjectively perceived by all patients with oral discomfort (the Group DIS$^+$GAL$^+$ and the Group DIS$^+$GAL$^-$), by one woman from the Group DIS$^-$GAL$^-$ (3%) and by no participant from the Group DIS$^-$GAL$^-$MET$^-$. Diverse allergies were found in one half of the patients with oral discomfort (80 participants – the Group DIS$^+$GAL$^+$), in at least one third of patients from the Group DIS$^+$GAL$^-$ (49 participants – 28%), in 7 patients from the Group DIS$^-$GAL$^-$ (18%) and in one patient from the Group DIS$^-$GAL$^-$MET$^-$(5%).

Results of the oral cavity clinical examination

Clinical signs of inflammatory affections, lichenoid changes or metallic pigmentations were found most frequently on the mucosa and gingiva of the patients from the Group DIS$^+$GAL$^+$ (40%). In the Group DIS$^+$GAL$^-$, a significantly lower number of such affections (16%) was found. In the Group DIS$^-$GAL$^-$ only two persons with metallic pigmentations (5%) were found and in the Group DIS$^-$GAL$^-$MET$^-$ no such affections were found, as expected. A statistic analysis did not reveal any significant differences in dental metal restorations within the tested Groups DIS$^+$GAL$^+$, DIS$^+$GAL$^-$ and DIS$^-$GAL$^-$.

Galvanic currents measurement

Among those 397 examined persons pathologic values of galvanic currents were found in 159 patients (Group DIS$^+$GAL$^+$). The mean value of the galvanic current was 13.4±10.3μA. In the remaining three groups, galvanic current values did not reach the limit of 5μA.

When comparing galvanic current maximum values with clinical findings in the patients from the Group DIS$^+$GAL$^+$, we found significantly (p=0.00004) higher values of galvanic currents in the patients with morphological changes on the oral mucosa, tongue and gingiva as compared to the patients without morphological affections. The highest values of galvanic currents were found in the patients with inflammatory and lichenoid changes of the oral mucosa and tongue (22.8±12.5μA; p=0.0001 compared to the patients without the affections; p=0.01118 compared to the patients with pigmentations), lower values in the patients with metallic pigmentations (14.0±9.6μA; p=0.01016 compared to the patients without the affections) and the lowest values in patients with oral discomfort, but without any morphological changes in their oral cavity (1.8±1.3μA).

Immunologic markers determination and comparison

IgA1 levels

The highest mean concentration of IgA1 in the saliva was found in the Group DIS$^-$GAL$^-$ (5506 mg/l) and the lowest in the Group DIS$^+$GAL$^+$ (1154 mg/l). Statistically significant differences were found between the Group DIS$^+$GAL$^+$ and the Group DIS$^+$GAL$^-$ (p=0.036), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$ (p=0.001), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$MET$^-$ (p=0.004) and between the Group DIS$^+$GAL$^-$ and the Group DIS$^-$GAL$^-$ (p=0.012) (Table 1).

IgA2 levels

The highest mean concentration of IgA2 in the saliva was observed in the Group DIS$^-$GAL$^-$MET$^-$ (778 mg/l)

Tab. 1. IgA1 levels [mg/l].

IgA1 (mg/l)	Number of tested samples	Data after logarithmic transformation (Basis = 160, y = log10(x+basis))		Geometric mean
		Mean	Standard error	
Group DIS$^+$GAL$^+$	41	3.12	0.07	1154
Group DIS$^+$GAL$^-$	44	3.36	0.04	2115
Group DIS$^-$GAL$^-$	18	3.75	0.05	5506
Group DIS$^-$GAL$^-$MET$^-$	15	3.52	0.12	3137

Significant difference (p-value ≤0.05) between Group DIS$^+$GAL$^+$ and Group DIS$^+$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$MET$^-$ and Group DIS$^+$GAL$^-$ and Group DIS$^-$GAL$^-$.

Tab. 2. IgA2 levels [mg/l].

IgA2 (mg/l)	Number of tested samples	Data after logarithmic transformation (Basis = 55, y = log10(x+basis))		Geometric mean
		Mean	Standard error	
Group DIS$^+$GAL$^+$	37	2.56	0.05	308.7
Group DIS$^+$GAL$^-$	35	2.85	0.03	647.9
Group DIS$^-$GAL$^-$	18	2.89	0.08	712.1
Group DIS$^-$GAL$^-$MET$^-$	15	2.92	0.07	778.3

Significant difference (p-value ≤0.05) between Group DIS$^+$GAL$^+$ and Group DIS$^+$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$MET$^-$ and Group DIS$^+$GAL$^-$ and Group DIS$^-$GAL$^-$.

Tab. 3. Secretory IgA levels [mg/l].

sIgA (mg/l)	Number of tested samples	Data after logarithmic transformation (Basis = 160, y = log10(x+basis))		Geometric mean
		Mean	Standard error	
Group DIS$^+$GAL$^+$	41	2.52	0.05	266.4
Group DIS$^+$GAL$^-$	44	2.66	0.04	388.6
Group DIS$^-$GAL$^-$	18	2.87	0.04	669.3
Group DIS$^-$GAL$^-$MET$^-$	15	2.82	0.06	597.6

Significant difference (p-value ≤0.05) between Group DIS$^+$GAL$^+$ and Group DIS$^+$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$MET$^-$, Group DIS$^+$GAL$^-$ and Group DIS$^-$GAL$^-$ and Group DIS$^+$GAL$^-$ and Group DIS$^-$GAL$^-$MET$^-$.

Tab. 4. Lysozyme levels [mg/l].

Lysozyme (mg/l)	Number of tested samples	Data after logarithmic transformation (Basis = 0.05, y = log10(x+basis))		Geometric mean
		Mean	Standard error	
Group DIS$^+$GAL$^+$	41	0.05	0.16	1.07
Group DIS$^+$GAL$^-$	44	0.45	0.10	2.77
Group DIS$^-$GAL$^-$	18	0.78	0.20	6.00
Group DIS$^-$GAL$^-$MET$^-$	15	0.77	0.26	5.77

Significant difference (p-value ≤ 0.05) between Group DIS$^+$GAL$^+$ and Group DIS$^+$GAL$^-$, Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$ and Group DIS$^+$GAL$^+$ and Group DIS$^-$GAL$^-$MET$^-$.

and the lowest in the Group DIS$^+$GAL$^+$ (309 mg/l). Differences between the mean levels in the Group DIS$^+$GAL$^+$ and the Group DIS$^+$GAL$^-$ (p=0.018), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$ (p=0.004), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$MET$^-$ (p=0.001) were statistically significant (Table 2).

Secretory IgA levels

The highest mean concentration of secretory IgA was found in the Group DIS$^-$GAL$^-$(669 mg/l) and the lowest in the Group DIS$^+$GAL$^+$ (266 mg/l). Statistically significant differences were found between the Group DIS$^+$GAL$^+$ and the Group DIS$^+$GAL$^-$ (p=0.034), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$ (p=0.001), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$MET$^-$ (p=0.02), the Group DIS$^+$GAL$^-$ and the Group DIS$^-$GAL$^-$ (p=0.027), the Group DIS$^+$GAL$^-$ and the Group DIS$^-$GAL$^-$MET$^-$ (p=0.049) (Table 3).

Lysozyme levels

The highest value of lysozyme mean concentration was found in the Group DIS$^-$GAL$^-$ (6 mg/l) and the lowest in the Group DIS$^+$GAL$^+$ (1.1 mg/l). Statistically significant differences were discovered between the Group DIS$^+$GAL$^+$ and the Group DIS$^+$GAL$^-$ (p=0.038), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$ (p=0.001), the Group DIS$^+$GAL$^+$ and the Group DIS$^-$GAL$^-$MET$^-$ (p=0.002) (Table 4).

Levels of IgA antibodies against HSP 60

The highest mean concentration of IgA antibodies against HSP 60 was found in the Group DIS$^+$GAL$^+$

Tab. 5. AntiIgA/HSP 60 levels [mg/l].

antiIgA/HSP 60 (mg/l)	Number of tested samples	Data after logarithmic transformation (Basis = 0.005, y = log10(x+basis))		Geometric mean
		Mean	Standard error	
Group DIS^+GAL^+	41	–0.56	0.09	0.27
Group DIS^+GAL^-	44	–0.64	0.07	0.23
Group DIS^-GAL^-	18	–1.43	0.24	0.03
Group $DIS^-GAL^-MET^-$	15	–0.99	0.20	0.10

Significant difference (p-value ≤ 0.05) between Group DIS^+GAL^+ and Group DIS^-GAL^- and Group DIS^+GAL^- and Group DIS^-GAL^-.

Tab. 6. Comparison of salivary immune markers in patients before and after removal of electro active restorations.

(mg/l)		IgA 1	IgA 2	sIgA	lysozyme	antiIgA/ HSP 60
Before removal	Mean	1937	374	352	7.0	0.49
	S.D.	2232	251	253	5.6	0.47
After removal	Mean	3236	716	381	9.4	0.23
	S.D.	3427	379	276	10.5	0.30
p-value		0.28	0.02	0.78	0.55	0.05

S.D. - Standard deviation

(0.27 mg/l) and the lowest in the Group DIS^-GAL^- (0.03 mg/l). Statistically significant differences appeared between the Group DIS^+GAL^+ and the Group DIS^-GAL^- (p=0.001) , the Group DIS^+GAL^- and the Group DIS^-GAL^- (p=0.012) (Table 5).

Results of electro active dental restorations removal from oral cavity

After the removal of electro active restorations from the oral cavity, 93% of the patients subjectively claimed that their health improved, while morphologic symptoms objectively disappeared in 70 per cent of the treated patients.

Comparing the levels of immunologic markers in the saliva before and after the removal of electro active dental metal restorations from the oral cavity a significant increase in IgA2 levels, rising from the prior concentration of 374 mg/l to the concentration of 716 mg/l (p=0.0206), was found. A non-significant increase in IgA1, sIgA and lysozyme levels was also registered.

Comparing the levels of IgA antibodies against HSP 60 in the saliva before and after the removal of electro active dental metal restorations from the oral cavity a significant decrease in IgA against HSP 60 levels (p=0.0496) was found (Table 6).

DISCUSSION

Metals from dental alloys are not a physiological component of a human organism. Undesirable side effects may, therefore, appear in sensitive individuals after dental alloys are placed in their oral cavity (Prochazkova *et al.* 2004). Oral discomfort is often associated with diverse types of allergies and metal intolerance (Wataha 2000) and this fact was confirmed by the results of this study.

Galvanic cells as well as released metal ions may have local and/or general effects on a human organism. This study has shown that the higher the measured galvanic currents values were, the more often the inflammatory affections of the oral mucosa appeared and the higher the risk of this complication was.

Human saliva plays an important defence role in the oral cavity. The oral tissues are under a long-term influence of metal ions, which are released, in low amounts but continuously due to electrochemical corrosion and abrassion from dental alloys (Wataha 2002; Prochazkova *et al.* 2006). Dental metal restorations significantly increase a metal ion concentrations in the saliva (Kucerova *et al.* 2002; Prochazkova *et al.* 2006). The mucosal immune system plays an important role in the defense mechanisms, this study evaluated mucosal defense markers in the saliva.

It is thus necessary to eliminate galvanic cells from the mouth of sensitive individuals. The positive effect of this treatment was confirmed in previous publications of our research group (Prochazkova *et al.* 2004; Prochazkova *et al.* 2006), as well as in this study and our results are in concordance with the previously published article (Lindh *et al.* 2002). After the galvanic cells elimination the patients subjectively experienced an alleviation of their symptoms, as was confirmed by an objective clinical examination and by determining the levels of salivary immune defense markers.

We can conclude that galvanic currents play role in the development of inflammatory affections, lichenoid changes or metallic pigmentations on the oral mucosa and tongue. The higher the galvanic currents values are, the higher the risk of inflammatory and lichenoid lesions is. Lower values of galvanic currents lead frequently to metallic pigmentations.

After the removal of electro active restorations from the oral cavity of the patients with oral discomfort positive changes in the clinical picture were found: within half a year the majority of the patients claimed an improvement of their health, the inflammatory affections on the oral mucosa healed, while lichenoid changes merely diminished. Metallic pigmentations were the only aspect that did not disappear.

The patients with oral discomfort had different levels of immunologic markers in the saliva. Significantly decreased production of IgA1, IgA2, secretory IgA antibodies and lysozyme, analogous to increased

Summarizing table. Levels of IgA1, IgA2, sIgA, lysozyme and antiIgA/HSP 60 in control group without discomfort and galvanism, in group with discomfort and galvanism and in part of group with discomfort and galvanism after electro active restorations removal.

Geometric mean (mg/l)	IgA1	IgA2	sIgA	lysozyme	antiIgA/HSP 60
"no discomfort, no galvanism group"	5506	712	669	6	0.03
"discomfort+galvanism group"	1154	309	266	1.1	0.27
part of "discomfort+galvanism group" after electro active restorations removal	3236	716	381	9.4	0.23

The results show decreased levels of IgA1, IgA2, sIgA and lysozyme and increased level of antiIgA/HSP 60 in "discomfort+galvanism group" as compared to "no discomfort, no galvanism group". After electro active restorations removal, the decreased levels of IgA1, IgA2, sIgA and lysozyme increased to levels similar to "no discomfort, no galvanism group" and increased level of antiIgA/HSP 60 started to decrease.

levels of IgA against HSP 60, played an important role in immune reactions of patients with oral discomfort.

After the removal of electro active restorations from the oral cavity of patients with oral discomfort, a significant increase of IgA2 levels in saliva and increase of IgA1, sIgA and lysozyme levels were observed. A significant decrease of IgA against HSP 60 levels was found at the same time.

The results of this study confirmed the importance of measuring galvanic currents in the patients with symptoms of oral discomfort. Measurements of galvanic phenomena in these patients and a subsequent electro active restorations removal should become a common therapeutic procedure, especially in the patients with inflammatory and lichenoid changes on the oral mucosa and tongue.

Any restoration showing a galvanic current over 5 μA can be described as an electro active restoration. A decision to remove such a restoration is governed by the clinical status of a patient. Restorations showing galvanic currents over 10 μA should always be removed in case of patients with oral discomfort.

ACKNOWLEDGEMENTS

The study was supported by the research projects NT 13087-3 and NT 14164-3 of the Internal Grant Agency, Ministry of Health, Czech Republic and by Research Programme PRVOUK-P28/LF1/6 of Ministry of Education, Youth and Sports, Czech Republic.

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