

Rheumatoid Arthritis among Periodontitis Patients in Baddi Industrial Estate of Himachal Pradesh, India: A Cross Sectional Study

YASH PAUL DEV¹, NITIN KHULLER², PATTHI BASAVARAJ³, SURESH G⁴

ABSTRACT

Aim: To determine whether there is a relationship between periodontal disease and rheumatoid arthritis.

Methods: A total of 1520 (852 - periodontal group; 668 - general group) individuals of 30-70 years age group and residents of Baddi industrial estate in Himachal Pradesh, India, were assessed for the prevalence of rheumatoid arthritis and Periodontal Disease (PD). The prevalence and severity of periodontitis were determined by recording the Community Periodontal Index (CPI) with loss of attachment, based on WHO guidelines (1997). The criteria considered for diagnosis of rheumatoid arthritis were as those given by American Rheumatism Association -1988. Frequency distributions for bivariate analysis and logistic regression for

multivariate analysis were used for assessment of statistical association between variables.

Results: In patients referred for periodontal treatment, the prevalence of rheumatoid arthritis was 4.4%. Females (3.2%) and subjects aged above 50 years (3.5%) showed a significantly higher prevalence in comparison to their counterparts ($p < 0.001$). The odds of rheumatoid arthritis in females were nearly three times ($OR = 2.813$) higher than those in males, which was also statistically significant ($p < 0.05$).

Conclusion: The findings provide evidence of a relationship, suggesting that individuals with moderate to severe periodontal disease are at higher risk of suffering from rheumatoid arthritis and vice versa.

Key words: Dental health, Extra-synovial, Periodontitis, Rheumatoid arthritis

INTRODUCTION

Recent studies have shown that periodontal disease may be related to a number of systemic diseases, including an increased incidence of atherosclerosis, coronary heart disease, myocardial infarction and stroke [1-4]. In addition to the above well documented examples, a number of other chronic conditions of altered connective tissue metabolism, hormone imbalance and altered immune function have likewise been associated with increased risk of periodontal disease [5]. Most of these associations can be explained moderately by excessive production of inflammatory cytokines and other inflammatory mediators caused by periodontitis [6].

Among these, Rheumatoid Arthritis (RA) is of particular interest, since it is a chronic systemic inflammatory disorder characterized by the accumulation and persistence of an inflammatory infiltrate in the synovial membrane, that leads to synovitis and the destruction of the joint architecture. This demonstrates patterns of soft and hard tissue destruction remarkably similar to those prominent in chronic periodontitis. RA occurs worldwide and it affects approximately 1% of the world population in a female/male ratio of 3:1 and has a peak incidence of onset in women in the fourth and fifth decades of life [7,8]. Although the aetiologies of these diseases are distinctly separate, the underlying pathological processes are of sufficient similarity, to warrant consideration of the hypothesis, that individuals at risk of developing rheumatoid arthritis may also be at risk of developing periodontitis, or vice versa [9-12]. In this sense, both conditions are associated with destruction of bone, mediated by inflammatory cytokines such as interleukin-1, tumoural necrosis factor and prostaglandin E2 [13].

Periodontitis may be a risk factor for arthritis development, as it enhances the severity of rheumatoid arthritis [14,15]. Furthermore, reports have emerged, which suggest that reduction of extra-synovial

chronic inflammation, associated with periodontal treatment, may have a beneficial effect on established rheumatoid arthritis [14,16,17].

The literature reports on the relationship between periodontal disease and RA are controversial. The methodologies applied in the studies are as diverse as their results and conclusions. Hence, this study was conducted with objective of ascertaining the correlation between rheumatoid arthritis and periodontal disease in the population of Nalagarh-Baddi in Himachal Pradesh, India.

Null hypothesis: There is no relationship between rheumatoid arthritis and periodontitis.

METHODS

Study Design and Study Population

This cross-sectional study was conducted from December 2011 to February 2012 among 1520 individuals aged 30 to 70 years (both genders), attending Swami Devi Dayal Hospital and Dental College, Panchkula, India. All the eligible subjects who were residents of Baddi industrial estate in Himachal Pradesh formed the study population.

The exclusion criteria were: smoking; diabetes mellitus; individuals who had undergone periodontal treatment (including prophylaxis) and/or antibiotic therapy over the past three months, faulty prosthesis and fillings, systemic diseases and bone disorders like osteoporosis, that required prophylactic antibiotic therapy and females who were pregnant and lactating.

Brief Profile of the Study Area

Baddi is an industrial town in the south western Solan district of Himachal Pradesh, a hilly state of northern India. It is emerging as the pharmaceutical industry capital of India. More than half of India's pharmaceutical production, mainly formulations, would

originate from Himachal Pradesh in few years, as 200 odd medium and large-scale units are coming up in and around Baddi. The number of migrant labourers is on the rise and since there is no provision for accommodation of the workers in majority of the industrial units, they live in slums. Today, there are over 800 medical and pharma companies alone in Baddi, including giants like Cipla and Dabur [18].

Ethical Considerations

Our research was conducted in full accordance with the guidelines of World Medical Association Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of Swami Devi Dayal Hospital and Dental College, Panchkula. Written informed consents were obtained from participants after explaining to them the nature and purpose of research.

METHODOLOGY

Within the study, two groups were identified. The Periodontal Group (PG) was derived from the 852 patients referred for periodontal treatment and the remainder of 668 patients were the General Group (GG), who were referred for general dental treatment (other than referred for periodontal treatment). The prevalence and severity of periodontitis was determined by recording the Community Periodontal Index (CPI) with loss of attachment, based on WHO guidelines (1997) [19].

To determine the prevalence of rheumatoid arthritis, the patients' latest medical-dental reports were evaluated. The criteria for diagnosis of rheumatoid arthritis were as those given by American Rheumatism Association -1988 [7]. The new criteria were as follows: 1) morning stiffness in and around joints, lasting at least 1 hour before maximal improvement; 2) soft tissue swelling (arthritis) of 3 or more joint areas, observed by a physician; 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of rheumatoid factor; and 7) radiographic erosions and/or periarticular osteopaenia in hand and/or wrist joints. Criteria 1 through 4 must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required. This new criteria has demonstrated 91-94% sensitivity and 89% specificity for RA as compared to those in non-RA rheumatic disease control subjects [7].

Preceding the commencement of the study, examiner was standardized and calibrated in the Department of Periodontics by a senior Faculty member, to ensure uniform interpretations, understanding and application of the codes and criteria for the diseases to be observed

and recorded and to ensure consistent examination. The examiner first practised the examination on a group of 10 subjects with wide range of levels of disease condition. The data on periodontal status was entered on a WHO Oral Health Assessment Form (1997). Then, a group of 20 subjects with varying levels of oral diseases were examined on two successive days and the results were compared to know the diagnostic variability. A very good intra examiner agreement (90%) was obtained for assessment of CPI.

STATISTICAL ANALYSIS

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor of SPSS, version 15.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations. The Chi-square test (χ^2) was used to assess the differences in the prevalence of periodontal diseases and rheumatoid arthritis between the groups. Multiple logistic regression was performed for estimating values of Odds Ratio (OR) and the respective 95% Confidence Interval (CI). A p-value of less than 0.05 was considered as indicating statistical significance.

RESULTS

The study sample comprised of 1520 adults, aged 30 to 70 years, with mean age of 45 ± 2.6 years [Table/Fig-1]. Among these, 802 (52.8%) were males and 718 (47.2%) were females. They included 852 (56.1%) subjects from Periodontal Group (PG) and 668 (43.9%) subjects from General Group (GG). Majority of the subjects (36.9%) belonged to the 30-40 years age group and a few (13.9%) were aged over 60 years.

[Table/Fig-2] presents the percentages of persons according to the highest score recorded for each person. Around 22.6% of the

Variables	Periodontal group n (%)	General group n (%)	Total n (%)
Gender			
Male	462 (54.2)	340 (50.9)	802 (52.8)
Female	390 (45.8)	328 (49.1)	718 (47.2)
Age (in years)			
30-40	296 (34.7)	264 (39.5)	560 (36.9)
40-50	240 (28.2)	206 (30.8)	446 (29.3)
50-60	190 (22.3)	112 (16.8)	302 (19.9)
60-70	126 (14.8)	86 (12.9)	212 (13.9)
Total	852 (56.1)	668 (43.9)	1520 (100)

[Table/Fig-1]: Distribution of the study population based on gender and age

Variables	Periodontal group		Total	χ^2 p-value	General group		Total	χ^2 p-value
	Male n (%)	Female n (%)			Male n (%)	Female n (%)		
Community Periodontal Index (CPI)								
Healthy	0	0	0	26.481 0.001*	67 (19.7)	84 (25.6)	151 (22.6%)	3.404 0.638
Bleeding	0	0	0		226 (66.5)	228 (69.5)	454 (68)%	
Calculus	0	0	0		47 (13.8)	16 (4.9)	63 (9.4)%	
Pocket (4-5mm)	302 (65.4)	232 (59.5)	534 (62.7)		0	0	0	
Pocket (6-8mm)	160 (34.6)	158 (40.5)	318 (37.3)		0	0	0	
Loss of attachment								
0-3mm	145 (31.4)	135 (34.6)	280 (32.9)	82.381 0.04*	0	0	0	-
4-5mm	240 (51.9)	202 (51.8)	442 (51.9)		0	0	0	
6-8mm	65 (14.1)	42 (10.8)	107 (12.5)		0	0	0	
9-11 mm	12 (2.6)	11 (2.8)	23 (2.7)		0	0	0	
Total	462 (54.2)	390 (45.8)	852 (100)		340 (50.9)	328 (49.1)	668 (100)	

[Table/Fig-2]: Prevalence of periodontal disease among the study population according to groups and gender (n=1520)
Test applied- chi-square test, * indicates statistical significance at p<0.05

subjects in the general group scored healthy. Bleeding was confined to 68% patients and calculus was recorded among 9.4% patients. Shallow pockets and deep pockets were recorded in 62.7% and 37.3% patients respectively in the periodontal group. According to gender, females were affected by severe periodontal diseases (deep pockets) more than males and the difference observed was statistically significant ($p=0.001$). More than half (51.9%) the study subjects in periodontal group demonstrated the loss of attachment to be 4-5 mm, followed by 0-3 mm in 32.9% population. Between the genders, the loss of attachment was also found to be more in females, which was statistically significant ($p=0.04$).

The overall prevalence of rheumatoid arthritis was 4.4% (37 out of 852) in the PG group. In relation to gender and age groups, females (3.2%) and subjects aged above 50 years (3.5%) showed a higher prevalence in comparison to their counterparts. This observed difference between gender and all the age groups for rheumatoid arthritis was statistically significant [Table/Fig-3].

Variables	Rheumatoid arthritis n (%)	No rheumatoid arthritis n (%)	Total n (%)	χ^2 p-value
Gender				
Male	10 (1.2)	452 (53.0)	462 (54.2)	18.784 0.001*
Female	27 (3.2)	363 (42.6)	390 (45.8)	
Age (in years)				
30-40	1 (0.1)	295 (34.6)	296 (34.7)	12.690 0.001*
40-50	7 (0.8)	233 (27.3)	240 (28.2)	
50-60	19 (2.2)	171 (20.1)	190 (22.3)	
60-70	10 (1.3)	116 (13.6)	126 (14.8)	
Total	37 (4.4)	815 (95.6)	852 (100)	

[Table/Fig-3]: Distribution of rheumatoid arthritis in the periodontal group based on gender and age

Test applied- chi-square test, * indicates statistical significance at $p<0.05$

We estimated the odds ratios and their 95% confidence intervals for variables affecting rheumatoid arthritis in our study population [Table/Fig-4]. The odds of rheumatoid arthritis in adults aged over 50 years were nearly 1.4 times higher than those in adults aged less than 50 years. In females, the odds were nearly three times ($OR=2.813$) higher than those in males. These observations were also statistically significant.

Variables	Category	Odds Ratio	95% Confidence Interval
Age in years	≤ 50	1.386*	0.913-1.541
	> 50		
Sex	Male	2.813*	0.854-1.475
	Female		

[Table/Fig-4]: Estimates of multiple logistic regressions for variables affecting rheumatoid arthritis

* Indicates statistical significance at $p\leq 0.05$

DISCUSSION

The relationship between rheumatoid arthritis (RA) and the progression of inflammatory conditions elsewhere in the body, such as chronic Periodontitis (CP), is controversial. The host defence response to foreign material is generally considered to be a protective process, whereby innate and acquired mechanisms are activated to dilute, destroy or negate damaging agents and to initiate tissue repair. This response involves the co-ordinated activation of numerous biologic pathways of inflammation, resolution and repair, all of which may be observed in the chronically inflamed periodontium. If all are appropriately regulated, then tissue repair ensues; however, if all are not appropriately controlled, the inflammatory response becomes chronic and persistent, leading to further tissue destruction and progression of disease. It is this lack of control (dysregulation) that is thought to contribute to the pathogenesis of other chronic inflammatory diseases such as rheumatoid arthritis.

In the present study, it was reported that the individuals referred for periodontal treatment had a higher prevalence of rheumatoid arthritis (4.4%). This is a very high prevalence as compared to the 1% prevalence reported in the normal population [7]. This finding was consistent with other reports on the association of RA and periodontitis and its severity [20,21]. The increased prevalence of rheumatoid arthritis in the periodontitis group in the present study suggests a possible link between the manifestations of these two chronic inflammatory diseases. Patients with PD have a higher prevalence of RA than patients without PD [22]. De Pablo and colleagues [23], using data from the Third National Health and Nutrition Examination Survey (NHANES III), showed a significant association between RA and PD in the US population. In patients with RA, a significant correlation between teeth loss and alveolar bone loss was found, and this may well represent various aspects of periodontal health [24].

To date, only a few studies have examined the extent of the association between RA and periodontal disease and amongst these studies, the results have been conflicting (Kasser et al. 1997, Tolo et al. 1990) [25,26]. The lack of uniformity in classifying the various forms of periodontal disease and rheumatoid arthritis in these studies has made it difficult to compare the above studies.

Indeed, there are remarkable similarities in the pathogenesis of these two conditions at both the cellular and molecular levels. Cytokines are believed to play a pivotal role in both periodontal tissue destruction and destruction of joints in rheumatoid arthritis. The most important of these cytokines are TNF and IL-1. Both are probably produced by macrophages that are activated by T-cells. TNF and IL-1, in turn, stimulate synovial cells and periodontal ligament cells to proliferate and produce various mediators of inflammation and MMPs, that contribute to cartilage destruction in joints and alveolar bone destruction in periodontium. Thus, a chain of events is set up, that leads to progressive damage [27-29]. Most of these associations can also be explained in part by the excessive production of pro-inflammatory cytokines and other inflammatory mediators, among which prostaglandin E2 (PGE2), Tumour Necrosis Factor (TNF) α , and interleukin (IL-6) appear to dominate [6,30].

In the present study, the prevalence of rheumatoid arthritis increased with increasing age in both the periodontal and general practice patients. Many were affected by lifestyle factors such as obesity and lack of physical activity. Persistent inflammation leads to joint destruction, but the disease can be controlled with drugs. The incidence may be on the decline, but the increase in the number of older people in some regions makes it difficult to estimate future prevalence. This is in agreement with findings of other studies which have reported that the prevalence of systemic diseases in these populations increases with increasing age [31,32].

Periodontal pocket measurements and attachment loss are used to assess periodontal disease, but they cannot accurately measure inflammation or predict future outcomes. According to Kao et al., much of the focus of dentists and dental hygienists is on periodontal pocket depth. They caution that we should also measure clinical attachment level (CAL), the presence and prevalence of gingival inflammation and radiographic evidence of alveolar bone loss [33]. If we believe that decreasing the oral inflammatory load can support oral and systemic health, we must be able to accurately assess risk and disease and be able to detect changes in the inflammatory process. It is likely that in the future, periodontal disease may be added to the list of factors that are used to assess patients risk profiles and in addition, treatment of periodontal disease may become a standard part of the therapy for patients with the systemic diseases like coronary heart disease, stroke, diabetes and other diseases.

The main limitation of the present study was its cross-sectional nature, which posed problems in relation to hypothesis testing, since data on risk factors and outcome were assessed at the same time. Further investigation into this relationship is necessary, to shed

some light on the workings of the inflammatory cells that destroy the bone in both diseases. In particular, longitudinal studies are needed to elucidate the temporal relationship between PD and RA, in order to derive firm conclusions. In addition, as our sample represented only one resident area- the Nalagarh-Baddi industrial estate in Himachal Pradesh, the generalizability of the findings obtained is questionable.

CONCLUSION

The findings of the present study indicate that moderate to severe periodontitis is an independent risk factor for rheumatoid arthritis. Patients referred for periodontal practices have a higher prevalence of rheumatoid arthritis as compared to the general practice population. In general, it seems that patients referred for periodontal care are less healthy than their counterparts in the general dental population.

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REFERENCES

- Offenbacher S, Katz VL, Fertik GS. Periodontal infection as a risk factor for pre-term low birth weight. *J Periodontol*. 1996; 67: 1103-13.
- DeStefano F, Anda RF, Kahn S, Williamson D, Russel C. Dental disease and risk of coronary heart disease and mortality. *BMJ*. 1993; 306: 688-91.
- Beck JD, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol*. 1996; 67: 1123-37.
- Haraszthy V, Zambon J, Trevisan M, Shah R, Zeid M, Genco R. Identification of pathogens in atheromatous plaques. *J Dent Res*. 1998; 67: 1123-37.
- Bartold PM. Connective tissues of the periodontium. Research and clinical implications. *Australian Dental Journal*. 1991; 136: 255-61.
- Nilsson M, Kopp S. Gingivitis and periodontitis are related to repeated high levels of circulating tumor necrosis factor-alpha in patients with rheumatoid arthritis. *J Periodontol*. 2008; 79: 1689-96.
- Arnett F, Edworthy S, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988; 31: 315-24.
- Harris ED Jr. Clinical features of rheumatoid arthritis. In: Textbook of Rheumatology, eds. Kelly, W. N., Harris, E. D. and Sledge, C. B., 5th edition, 1997; 898. Philadelphia: WB Saunders.
- Moen K, Brun JG, Madland TM, Tynning T, Jonsson R, Ig G and A antibody responses to B. forsythus and P. intermedia in arthritis patients. *Clin Diagn Lab Immunol*. 2003; 10: 1043-50.
- Ogrendik M, Kokino S, Ozdemir F, Bird PS, Hamlet S. Serum antibodies to oral anaerobic bacteria in patients with rheumatoid arthritis. *Medscape General Medicine*. 2005; 7: 1-7.
- Bozkurt FY, Yetkin AZ, Berker E, Akkus S. Anti-inflammatory cytokines in gingival crevicular fluid in patients with periodontitis and rheumatoid arthritis: a preliminary report. *Cytokine*. 2006; 35: 180-85.
- Marotte H, Farge P, Gaudin P, Alexandre C, Mougin B, Miossec P. The association between periodontal disease and joint destruction in rheumatoid arthritis extends the link between the HLA-DR shared epitope and severity of bone destruction. *Ann Rheum Dis*. 2006; 65: 905-09.
- Bartold PM, Marshall RI, Haynes DR. Periodontitis and Rheumatoid Arthritis: A Review. *J Periodontol*. 2005; 76: 2066-74.
- Ribeiro J, Leão A, Novaes AB. Periodontal infection as a possible severity factor for rheumatoid arthritis. *J Clinical Periodontol*. 2005; 32: 412-16.
- Havemose-Poulsen A, Westergaard J, Stoltze K, Skjødt H, Danneskiold-Samsøe B, Loch H, et al. Periodontal and hematological characteristics associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. *J Periodontol*. 2006; 77: 280-88.
- Al-Katma MK, Bissada NF, Bordeaux JM, Sue J, Askaari AD. Control of periodontal infection reduces severity of active rheumatoid arthritis. *J Clin Rheumatol*. 2007; 13: 134-37.
- Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *J Periodontol*. 2009; 80: 535-40.
- Baddi, Available at <http://en.wikipedia.org/wiki/Baddi> [Accessed on 12th January 2013].
- World Health Organization. Oral Health Surveys, Basic methods. Fourth edition, World Health Organization, Geneva, 1997.
- Mercado FB, Marshall RI, Klestov AC, Bartold PM. Is there a relationship between rheumatoid arthritis and periodontal disease? *J Clinical Periodontol*. 2000; 27: 267-72.
- Mercado FB, Marshall RI, Klestov AC, Bartold PM. Relationship between rheumatoid arthritis and periodontitis. *J Periodontol*. 2001; 72: 779-87.
- Georgiou TO, Marshall RI, Bartold PM. Prevalence of systemic diseases in Brisbane general and periodontal practice patients. *Aust Dent J*. 2004; 49: 177-84.
- De Pablo P, Dietrich T, Mc Alindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *J Rheumatol*. 2008; 35: 70-76.
- Lagervall M, Jansson L, Bergström J. Systemic disorders in patients with periodontal disease. *J Clin Periodontol*. 2003; 30: 293-99.
- Kasser UR, Gleissner C, Dehne F, Michel A, Willershausen-Zönnchen B, Bolten WW. Risk for periodontal disease in patients with longstanding rheumatoid arthritis. *Arthritis Rheum*. 1997; 40: 2248-51.
- Tolo K, Jorkend L. Serum antibodies and loss of periodontal bone in patients with rheumatoid arthritis. *J Clin Periodontol*. 1990; 17: 288-91.
- Offenbacher S, Heasman P, Collins J. Modulation of host PGE2 secretion as determinant of periodontal disease expression. *J Periodontol*. 1993; 1: 432-44.
- Kornman KS, Crane A, Wang HY, Di Giovine FS, Newman MG, Pirk FW, et al. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol*. 1997; 24: 72-77.
- Reynolds J, Meikle M. Mechanisms of connective tissue destruction. Importance of the balance of MMPs and inhibitors in tissue destruction and implication for human periodontitis and its treatment. *Periodontol*. 2000 1997; 14: 144-57.
- Abou-Raya S, Abou-Raya A, Naim A, Abuelkheir H. Rheumatoid arthritis, periodontal disease and coronary artery disease. *Clin Rheumatol*. 2007; 27: 421-27.
- Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ*. 2003; 81: 646-56.
- Reginster JY. The prevalence and burden of arthritis. *Rheumatology*. (Oxford) 2002; 41 Supp 1: 3-6. Review.
- Kao RT, Lee S, Harpenau L. Clinical challenges in diagnosing and monitoring periodontal inflammation. *Journal of the California Dental Association*. 2010; 38: 263-68.

PARTICULARS OF CONTRIBUTORS:

- Professor and Head, Department of Periodontics, Swami Devi Dayal Hospital and Dental College.
- Associate Professor, Department of Periodontics, Swami Devi Dayal Hospital and Dental College.
- Professor and Head, Department of Public Health Dentistry, DJ College of Dental Science and Research.
- Professor and Head, Department of Oral Pathology and Microbiology, Vishnu Dental College and Hospital.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Yash Paul Dev,
Professor and Head, Department of Periodontics, Swami Devi Dayal Hospital and Dental College, Barwala, Panchkula, India.
Phone: +91-9001341988; E-mail: yashpauldev@yahoo.com

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