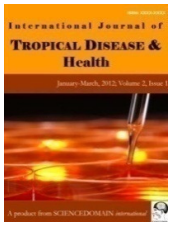

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Does Co-Suffering by Ischemic Heart Disease and Tuberculosis Exist in Community Endemic for These Diseases?

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Aims: Tuberculosis (TB) has been thought associated with developing atherosclerosis, a hallmark of ischemic heart disease (IHD) pathology. Animal studies and human autopsy & case studies have shown association of TB with atherosclerosis. There is paucity of data showing co-suffering by TB and IHD. The objective of the study was to explore the co-suffering by IHD and TB in community endemic for these diseases.
Study Design: Retrospective secondary data analysis.
Place and Duration of Study: Mahatma Gandhi Hospital, Jodhpur, Rajasthan, India between January 2011 and December 2011.
Methodology: Retrospective secondary data analysis done for patients admitted with IHD at tertiary hospital in Jodhpur, Rajasthan, India; a setting endemic for TB and IHD both.
Results: Study revealed 1.6% of total admitted cases of IHD were co-suffering with TB. Majority of these (68.2%) reported history of TB diagnosis and/or treatment. About one third (31.8%) cases were co-suffering with current diagnosis and/or treatment for TB. Cases co-suffering by TB & IHD were on average 7 years elder than cases of IHD. This difference in age was statistically significant

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(p=0.05).
Conclusion: The study demonstrated that co-suffering by IHD and TB does exist in setting endemic for both these diseases. Patients older than 53 yrs (Mean age 65.63 yr - 2 SD 12.47 yr) age presenting with clinical features suggestive of IHD should be explored for the history or current status of TB. Studies on co-suffering by these are needed among patients attending peripheral health centres for validation.

Keywords: Tuberculosis; ischemic heart disease; co-suffering; elder; age; community study; India.

ABBREVIATIONS

ATT: Anti Tubercular Therapy; ICD: International classification of diseases; IHD: Ischemic heart disease; HSP: Heat shock protein; TB: Tuberculosis; NCD: Non-communicable disease; ID: Infectious Disease; LMICs: Low- & Middle-income countries; CABG: Coronary artery bypass graft; AMI: Acute myocardial infarction; LAMA: Left hospital Against Medical Advise.

1. INTRODUCTION

The convergence of non-communicable diseases (NCDs) and infectious diseases (IDs) in low- and middle-income countries (LMICs) presents new challenges in policy and research. Most LMICs have significant dual disease burdens of NCDs such as cardiovascular disease, diabetes and cancer, and IDs including tuberculosis (TB), HIV/AIDS and parasitic diseases. A combined strategy is needed in surveillance and disease control; yet, experts, institutions and policies that support prevention and control of these two overarching disease categories have limited interaction and alignment [1].

TB has been thought to be associated with low degree of atheroscerosis. An autopsy study involving 17500 subjects from five European towns were conducted. Subjects were divided in to three groups, first group - subjects who diagnosed with TB as principal disease, second group- subjects who diagnosed with other chronic lung disease (excluding TB) as principal disease and third group – subject diagnosed with other chronic lung disease (excluding TB) as NOT the principal disease e.g. Cor pulmonale. Objective of the study was to estimate and compare the prevalence of atherosclerosis in these groups. Study revealed higher prevalence of complicated and calcified aortic lesions in TB subjects in comparison to low atherosclerosis group (excluding TB). However subjects with mild atherosclerosis were more prevalent in the low atherosclerosis group. The same pattern was found for the coronary arteries, where the prevalence of stenosis was considerably higher in men with TB than low atherosclerosis group. The differences were statistically significant for complicated and calcified aortic lesions in men, and less frequently in coronary artery also. Subjects with TB in all decades had more extensive aortic and coronary lesions of all kinds (except fatty streak) than the low atherosclerosis group. These differences were always highly significant in men; in women, however, they were significant only in the case of fibrous plaques and raised aortic lesions [2].

Follow-up study in humans has shown that serum titres of antibody against mycobacterial Heat Shock Protein (HSP65) increases significantly in subjects with progressive carotid artery atherosclerosis. This association was turned out to be independent of age, sex and other risk factors on multiple linear regression analysis [3]. Involvement of Heat Shock Protein65 in atherosclerosis has also been proved in experimental study on C57BL/6J mice. In comparison to mice immunized with phosphate-buffered saline or non-immunized, mice immunized with HSP-65 showed significantly enhanced atherosclerosis and even more in mice immunized with *Mycobacterium tuberculosis* bacteria; all three groups fed high cholesterol diet. However mice that were fed a Chow diet did not develop early fatty streak in their aortas regardless to the immunization protocol applied [4]. Another study also reported formation of atheromatous plaques in mice vaccinated with recombinant HSP65 and HSP65 rich *M. tuberculosis* bacteria. These investigators also attempted to detect *M. tuberculosis* complex DNA using IS6110 specific primers in atherosclerotic plaque samples of patients of coronary artery bypass graft (CABG) surgery. However none of the samples showed *M. tuberculosis* DNA in polymerase chain reaction [5].

In another animal study, two groups of rabbits were immunized with BCG vaccine and saline separately. After 8 weeks on 0.25-1% cholesterol diet, rabbits immunized with BCG showed significantly higher percentage of aortic area covered with atherosclerotic plaque than other group (p=0.05) [6]. There is considerable amount of data supporting the hypotheses that HSP65 can be involved in the progression of atherosclerosis [7].

Rare cases of tuberculous myocarditis have been reported from western countries [8,9]. *M. tuberculosis* associated cases of acute myocardial infarction (AMI) [10,11], pericarditis [12,13,14,15]; myopericarditis [16] and osteomyelitis of sternum [17] have also been reported from many parts of the world.

Although there is ample data suggesting involvement of TB in cardiovascular diseases, epidemiological studies reflecting community scenario of these two diseases are scarcely available. One such study on prevalence of coronary heart disease, as synonymously called ischemic heart disease (IHD), in patients with pulmonary TB in Russia revealed diagnosis of coronary heart disease in 8.4% patients [18].

We could not trace the prevalence of TB among diagnosed cases of IHD. Epidemiological study on co-suffering by these two diseases is scarcely available in settings endemic particularly for these two diseases. India is high TB burden country [19] with growing prevalence of IHD [20]. This study was undertaken in Jodhpur district of Rajasthan state of India; a country facing dual disease burden by IHD & TB. The research question framed was; Do cases of IHD admitted in hospital report co-suffering by TB? If yes, the sub-question framed was; what way the cases of co-suffering by IHD & TB differ from cases of IHD without TB?

2. METHODOLOGY

Retrospective secondary data analysis was performed on the data collected under coronary artery disease (CAD) study [21]. Study was evaluated for ethical clearance by the institutional ethics committee of Desert Medicine Research Centre. In brief, secondary data of CAD as synonymously called as IHD patients admitted in in-door department of Mahatma Gandhi Hospital, Jodhpur, Rajasthan, India during 2000 to 2002 was retrieved on data extraction form. All IHD patients diagnosed and admitted consecutively during period from January 2000 to December 2002 in the hospital and with medical records available were included in this study. All patients diagnosed with IHD, were segregated as per assigned international classification of diseases IXth revision (ICD IX) code [22]. ICD IX code *410* was assigned to acute myocardial infarction (AMI) group of patients, whereas code *413* was assigned to angina group of patients. All consecutively admitted patients diagnosed as IHD and coded as ICD IX codes during study period constituted our study sample.

Patient's general characteristics (such as *age*, *gender*, *religion*, *residence*, *occupation*), *time since onset of symptoms*, *date of admission*, *diagnosis*, disease history, ICD IX code, treatment advised (*heparin indicated*, *enzyme indicated*), treatment given (*Streptokinase given*), type of treatment outcome [*discharge* of patient from hospital, patient left hospital against medical advise (*LAMA*), & *death* of patient] *date of treatment outcome*, etc were extracted from hospital physician's prescription slips, medical records and recorded on 'Data extraction form'.

Collected data was depersonalized & entered in Epi-info version 3.5.3. Entered data was checked for missing values, double entries, extreme values and corrected with hard data before undertaking statistical analysis.

2.1 Data Analysis

We defined co-suffering by IHD & TB in a patient if he/she was diagnosed with IHD and TB status. The presence of TB status was defined based on either of the two criterion (1) if there was reported history of prior diagnosis of TB and/or anti-tuberculous therapy (ATT) (2) the patient was found suffering with TB and/or taking ATT, as per the history taken by the treating physician, diagnostic reports, diagnosis made and treatment prescriptions found available. Patients were divided in to two groups based on their diagnosis viz. (Group I) IHD with TB status & (Group II) IHD without TB status. Two new variables viz. *employment status* and *hospital stays in days* were created using data of original variables. There were 13 types of *occupation* categories mentioned in patient's records; the similar type of *occupation* categories were grouped to form 4 categories of *employment status* variable. The variable *hospital stays in days* for every patient was estimated by subtracting date of admission from date of discharge.

The quantitative and qualitative variables so obtained with respect to the two groups of patients were compared. Univariate analysis was performed to evaluate statistically significant difference if any between two groups. Chi-square (χ^2) test and student's unpaired 't' test were computed for qualitative and quantitative variables respectively. p=0.05 was considered significant for all statistical analysis.

3. RESULTS AND DISCUSSION

A total of 1412 patients were admitted during the study period. Out of these, 22 patients did not possess information on either few or all variables viz. *religion, date of admission*, *date of treatment outcome,* and *time since onset of symptoms.* These patients were skipped from the analysis. Finally 1390 patient's record with all relevant information was analyzed. Twenty two (1.6%) of 1390 patients were diagnosed as suffering of IHD with TB status (Group I). Remaining 1368 patients were diagnosed as suffering of IHD without TB status (Group II). As per the ICD codes, out of the total 1390 IHD cases, 1314 (94.5%) cases received the ICD code *410*, which included 22 Group I and 1292 Group II cases. On the other hand 76 (5.5%) cases received the ICD code *413*, which belonged to Group II only (Table 1).

Table 2 depicts the distribution of Group I cases. The majority (68.2%) of Group I cases reported history of either TB diagnosis and/or ATT. One third (31.8%) cases were diagnosed to be suffering with TB and/or receiving ATT beside IHD.

Table 3 compares the variables of cases of Group I with cases of Group II. Analysis revealed that both groups were similar as far as the qualitative variables are concerned. None of the qualitative variables viz. *ICD code*, *gender*, *heparin indicated*, *enzyme indicated*, *religion*, *streptokinase given*, *treatment outcome, residence* and *time since onset* could achieve statistical significance value (p=0.05) for the difference. However out of the two quantitative variables viz. *age in years* and *hospital stays in days* analyzed in Table 3, variable *age in years* could achieve the level of statistical significance. The mean *age in years* was 65.63 years in Group I cases; where as it was 58.28 years in Group II cases. The cases in Group I were on average 7 years elder than the cases in Group II. Patients in both the groups stayed in hospital for similar length of duration, as the difference was not statistically significant.

Group I and Group II cases were also compared within the similar ICD codes. As there was not any Group I case with ICD code *413*, we could not compare Group I and Group II having ICD code *413*. Cases with ICD code 410 were having Group I and Group II cases, so these were compared. The results of the univariate analysis computed upon these cases are depicted in Table 4.

Analysis in Table 4 also revealed that Group I and Group II cases were similar as far as the qualitative variables are concerned. However the quantitative variable *age in years* again could achieve the level of statistical significance. The mean *age in years* was 65.63 years in Group I cases; where as it was 58.24 years in Group II cases. The cases in Group I were again found about 7 years elder on average than the cases in Group II.

The details on the clinical presentation, diagnosis and past history of the cases co-suffering by IHD & TB status (Group I) are given as APPENDIX Additional File – 'A'.

Most LMICs, India one among them, are facing dual disease burden of NCDs including IHD and IDs including TB. Combined strategy is needed in surveillance and disease control of these two overarching disease categories; yet, experts, institutions and programme policies have limited interaction and alignment [1]. India is having high disease burden not only of TB [19] but also of IHD [20].

Studies have reported association of TB with atherosclerosis, a hallmark of IHD pathology among human [2,3] and animals [4-7]. Case studies reporting association of *M. tuberculosis* with myocarditis [8,9], AMI [10,11], pericarditis [12-15]; myopericarditis [16] and osteomyelitis of sternum [17] have also been reported from different parts of the world.

In spite of available data from animal studies and human autopsy & case studies suggesting involvement of TB in cardiovascular diseases, there is scarcity of epidemiological studies reflecting community scenario of TB & IHD. An epidemiology study in Russia documented the 8.4% prevalence of IHD among patients of pulmonary TB [18]. We could not trace the prevalence of TB (diagnosed either with current diagnosis, treatment or by past diagnosis, treatment) among diagnosed cases of IHD. Epidemiological study on co-suffering by these two diseases is scarcely available in settings endemic particularly for these two diseases.

Table 1. IHD patients with their ICD codes and TB status (n=1390)

TB status	Admitted IHD patients (n=1390)		Total [n (%)]
	Diagnosed with ICD code *410* [n (%)]	Diagnosed with ICD code *413* [n (%)]	
With TB status (Group I)	22(1.6)	0(0.0)	22(1.6)
Without TB status (Group II)	1292(92.9)	76(5.5)	1368(98.4)
Total	1314(94.5)	76(5.5)	1390(100)

Table 2. Distribution of cases of IHD (code 410) with TB status (Group I) with respect to occurrence of TB (n=22)

Occurrence of TB		Total [n (%)]
Reported history [n (%)]*	Currently diagnosed [n (%)]#	
15(68.2)	7(31.8)$	22(100)

* *Included IHD patients who reported history of TB diagnosis and/or ATT*

\# *included IHD patients who have been diagnosed as currently suffering with TB and/or receiving ATT*

$ *One case diagnosed as having concurrent tubercular pleural effusion also reported history of anti tubercular therapy*

Table 3. Cases of IHD with TB status (Group I) and without TB status (Group II) and their Variables

Variable	IHD cases with TB status (n=22) [Group I]	IHD cases without TB status (n=1368) [Group II]	p value
ICD Code [n (%)]	ICD code *410*= 22 (100) ICD code *413*=0 (0)	Code *410* = 1292 (94.4) Code *413* = 76 (5.6)	0.62*
Gender [n (%)]	Male=14 (63.6) Female=8 (36.4)	Male = 1017 (74.3) Female = 351 (25.7)	0.25
Heparin Indicated [n (%)]	NO=22 (100) YES=0 (0)	NO=1352 (98.8) Yes = 16 (1.2)	1.00*
Enzyme indicated [n (%)]	NO=21 (95.5) Yes=1 (4.5)	NO = 1291 (94.4) Yes = 77 (5.6)	1.00*
Religion [n (%)]	Hindu=20 (90.9) Other=2 (9.1)	Hindu = 1140 (83.3) Other = 228 (16.6)	0.56*
Streptokinase given [n (%)]	NO=20 (90.9) Yes=2(9.1)	NO = 1096 (80.1) Yes = 272 (19.9)	0.28*
Time since onset [n (%)]	<24 hrs=11 (50) 1-3 days=6 (27.3) 4-7 days=1 (4.5) >week=4 (18.2)	<24 hrs = 709 (51.8) 1-3 days = 367 (26.8) 4-7 days = 147 (10.7) > week = 145 (10.6)	0.61#
Treatment outcome [n (%)]	Discharge=20 (90.9) LAMA=1 (4.5) Death=1 (4.5)	Discharge = 1125 (82.2) LAMA = 41 (3) Death = 202 (14.8)	0.22#
Employment status [n (%)]	Un-employed = 4 (18.2) Self-employed = 16 (72.7) Govt. service = 1 (4.5) Retired from Job = 1 (4.5)	Un-employed = 372 (27.2) Self-employed=672 (49.1) Govt. service = 156 (11.4) Retired from Job = 168 (12.3)	0.50#
Residence$ [n (%)]	Rural = 8 (36.4) Urban = 14 (63.6)	Rural = 436 (32.1) Urban = 924 (67.9)	0.66
Age in years (Mean ± SD)	65.63±12.47	58.28±13.15	**0.009**
Hospital stays in Days (Mean ± SD)	6.68±3.27	6.17±3.82	0.5337

Table 4. Cases of ICD code *410* with TB status (Group I) and without TB status (Group II) and their variables

Variable	ICD code *410* cases with TB status (n=22)	ICD code *410* cases without TB status (n=1292)	p value
Gender [n (%)]	Male=14 (63.6) Female=8 (36.4)	Male=968 (74.9) Female=324 (25.1)	0.22
Heparin Indicated [n (%)]	NO=22 (100) Yes=0 (0.0)	NO=1276 (98.8) Yes=16 (1.2)	1.00*
Enzyme indicated [n (%)]	NO=21 (95.5) Yes=1 (4.5)	NO=1215 (94.0) Yes=77 (6.0)	1.00*
Religion [n (%)]	Hindu=20 (90.9) Other=2 (9.1)	Hindu=1077 (83.3) Other=215 (16.7)	0.56*
Streptokinase given [n (%)]	NO=20 (90.9) Yes=2(9.1)	NO=1020 (78.9) Yes=272 (21.1)	0.28*
Time since onset [n (%)]	<24 hrs=11 (50) 1-3 days=6 (27.3) 4-7 days=1 (4.5) >week=4 (18.2)	<24 hrs=677 (52.4) 1-3 days=355 (27.5) 4-7 days=132 (10.2) >week=128 (9.9)	0.53#
Treatment outcome [n (%)]	Discharge=20 (90.9) LAMA=1 (4.5) Death=1 (4.5)	Discharge=1054 (81.6) LAMA=38 (2.9) Death=200 (15.5)	0.19#
Residence [n (%)]	Rural = 8 (36.4) Urban = 14 (63.6)	Rural=417 (32.5) Urban=867 (67.5)	0.69
Employment status [n (%)]	Un-employed = 4 Self-employed = 16 Govt. service = 1 Retired from Job = 1	Un-employed = 321 Self-employed = 660 Govt. service = 152 Retired from Job =159	0.41#
Age in years (Mean ± SD)	65.63±12.47	58.24±13.22	**0.009**
Hospital stays in days (Mean ± SD)	6.68±3.27	6.17±3.82	0.53

Our study demonstrated that in setting endemic for both IHD as well as TB, the cases co-suffering with IHD and TB do exist. The proportion of cases co-suffering with IHD and TB was 1.6%. The majority of these (68.2%) had history of either TB diagnosis or ATT; however nearly one third of these cases (31.8%) were having disease co-burden by IHD as well as TB. These 31.8% cases were diagnosed to be currently having IHD with either TB and/or ATT.

This study finding is an issue of discussion with respect to two different endemic diseases i.e. IHD, which is a NCD and TB, which is an ID. These two diseases with different etiologies affected same set of patients in this study. These two diseases occur in two different socio-economic status population groups. Tuberculosis is known to occur in low socioeconomic strata [23-26]; whereas IHD in affluent section of society [27]. The convergence of these two different diseases can be believed to occur because of two hypotheses. First hypothesis is that the cases of TB are developing IHD which got detected in our study as major proportion of cases (68.2%) co-suffering with IHD and TB. The second hypothesis is there is fast socio-economic and lifestyle related changes taking place putting TB susceptible population at risk of IHD too. Our study detected occurrence of disease co-burden by these two diseases in 31.8% of cases co-suffering with these. Although the proportion reported of cases co-suffering by IHD & TB is only 1.6%, it can be because of tip of iceberg phenomenon. Since this study was conducted at a tertiary care centre, there can be large proportion of such cases seeking health care from peripheral health institutions.

Detection of such cases at peripheral health institutions is essential for guiding adequate treatment and improving prognosis. There are clinical features beside characteristic signs & symptoms, shared by these two diseases. Chest pain and dyspnea are the symptoms with which cases of TB [28-30] and IHD [31] can present at

health centers. Such cases can escape from diagnostic work out.

Our study tried to find out the patient related factors associated with cases co-suffering with IHD & TB status. We found that cases co-suffering with IHD & TB status were on an average 7 years elder than the cases of IHD. The mean age of cases co-suffering with IHD & TB status was 65.6 yrs whereas that of cases of IHD was 58.3 yrs only. This difference in mean age of Group I and Group II patients persisted even among patients with ICD IX code *410* (Table 4). Here also cases co-suffering with ICD code *410* & TB status were on an average 7 years elder than the cases of ICD code *410*.

4. CONCLUSION

Elderly patients particularly older than 53 yrs (Mean age 65.63 yr - 2 SD 12.47 yr) age presenting with clinical features suggestive of IHD should be explored for the history or current status of TB. Cases co-suffering with IHD and TB do exist in endemic countries so they should be suspected among patients elder than 53 yrs if present with suggestive symptoms. Epidemiological studies on co-suffering by TB and IHD among patients attending peripheral health centres are needed in setting endemic for these two diseases for validating these findings.

CONSENT

Not applicable.

ETHICAL APPROVAL

Institutional ethics committee of Desert Medicine Research Centre approved the study.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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APPENDIX

Additional File – 'A'

Clinical details of patients of ischemic heart disease with tuberculosis (n=22) [Group I]

Patient's ID	Clinical presentation	Diagnosis	Past disease history
A	Chest heaviness, perspiration	Left ventricular dysfunction, right bundle branch block	Anterior wall myocardial infarction, anti tubercular therapy, pleural effusion, tuberculosis
B	Breathlessness, fever, palpitation	Pleural effusion, follow up case of diabetes, hypertension, IHD	Anti tubercular therapy, diabetes, hypertension, ischemic heart disease
C	Chest pain, nausea	Acute anteroseptal myocardial infarction	Anti tubercular therapy, chest pain, pulmonary tuberculosis
D	Breathlessness, chest pain, convulsion, disorientation, fever, pain in back, staring eye	Acute inferior wall myocardial infarction, diabetes	Anti tubercular therapy, diabetes, tubercular meningitis
E	Breathlessness, chest pain, ghabrahat	Ischemic heart disease, left bundle branch block	Anti tubercular therapy, ischemic heart disease, koch's lung, left bundle branch block
F	Altered sensorium, fever	Pyrexia	Diabetes, ischemic heart disease, koch's chest
G	Loose motion, shortness of breath, vomiting	Left ventricular failure	Hypertension, ischemic heart disease, koch's chest
H	haemoptysis	Acute hypertension, Ischemic heart disease, parkinsonism	Hypertension, ischemic heart disease, koch's chest, multiple infarction syndrome
I	Chest pain, perspiration, shortness of breath	Unstable angina, pyrexia	Hypertension, ischemic heart disease, tubercular abdomen
J	Fever, ghabrahat	Acute anterior wall myocardial infarction	Hypertension, ischemic heart disease, tuberculosis
K	Chest pain, ghabrahat	Unstable angina	Hypertension, koch's chest
L	Breathlessness	Acute anterior wall myocardial infarction	Pulmonary tuberculosis
M	Breathlessness, chest pain, ghabrahat, pain in back & shoulder, weakness	Acute inferior wall myocardial infarction, complete heart block	Tuberculosis
N	Chest pain, vomiting	Acute anterior wall myocardial infarction	Chest tuberculosis
O	Chest pain	Acute anterior wall myocardial infarction, adrenal crisis, cardiogenic shock, koch's chest	Nill
P	Pain in back & chest	Acute anterior wall myocardial infarction, diabetes, koch's chest	Inferior wall myocardial infarction
Q	Chest pain, cough with sputum, fever, nausea, shortness of breath, vomiting	Acute anterior wall myocardial infarction, koch's chest	Nill
R	Chest pain, nausea	Acute anterior wall myocardial infarction, pulmonary tuberculosis	Nill
S	Breathlessness, chest pain	Acute anterior wall myocardial infarction, tubercular pleural effusion	Nill

T	Chest pain, fever, vomiting	Diabetes, koch's chest	old antero-septal myocardial infarction, pleural effusion
U	Headache, vertigo	Follow up case of chronic obstructive pulmonary disease, diabetes, hypertension, ischemic heart disease, tuberculosis	Chronic obstructive pulmonary disease, diabetes, hypertension, ischemic heart disease, tuberculosis
V	Chest pain, ghabrahat, sweating	Right bundle branch block, recurrent ventricular tachycardia, tubercular pleural effusion	Anti tubercular therapy, ischemic heart disease, pleural effusion

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