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STUDY OF FERRITIN LEVELS AS MARKER OF MORBIDITY IN DENGUE FEVER WITH THROMBOCYTOPENIA

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Abstract

BACKGROUND: Dengue virus (DENV) is a flavivirus (a genus of single-stranded non segmented RNA viruses), and is transmitted to human beings by the bite of Aedes mosquitoes. It is an acute infectious viral disease, also known as break bone fever. It is endemic in more than 100 countries. Methods: Prospective observational study.

Results: 51 Dengue positive Patients were included in the present study. Serum ferritin level was measured on 4th or 5th day of illness in these 51 study Patients.

Conclusion: "High serum ferritin level (>500mcg/dl) was associated with more severe form of Dengue infection (Dengue with warning sign and Severe dengue) in our study"

Keywords: Dengue fever, Severe Dengue and Serum Ferritin.

Introduction

Dengue fever is a mosquito borne viral infection caused by RNA virus of Flaviviridae family. Dengue fever is transmitted by multiple species of female mosquitoes of the *Aedes* type, *A. aegypti* being most usual amongst them. The virus has five serotypes namely DENV1, DENV2, DENV3, DENV4 and fifth newly reported serotype. Subsequent infection with a different type increases the risk of severe complications.

Viral E envelope protein binds to a cellular receptor of which exact nature is not known, virus undergoes endocytosis where endosome is acidified to cause conformational change of E protein, exposing a fusion peptide. This peptide facilitates releasing the virion capsid into the cytoplasm where it is uncoated and synthesis of viral RNA occurs.

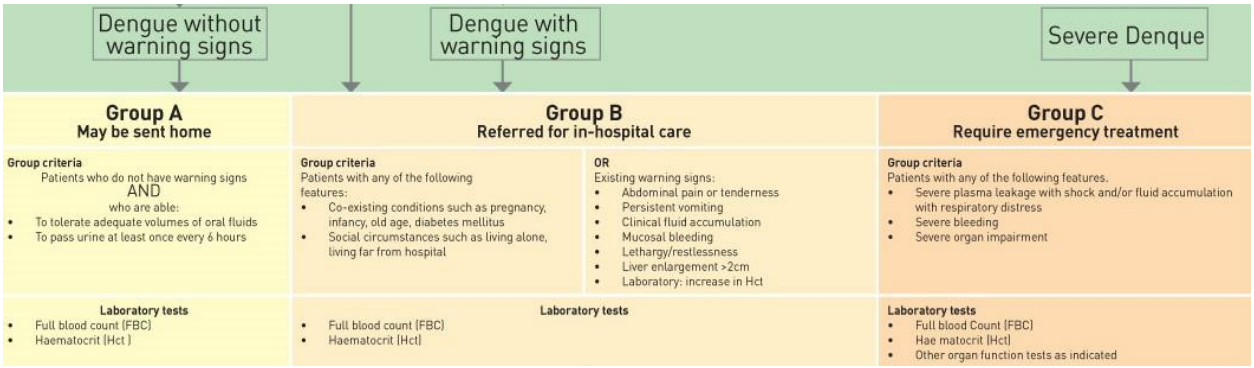
Dengue fever clinically presents in variable forms as painful break bone fever to hemorrhagic fever and may progress on further with severe macrophage activation syndrome causing release of cytokines aptly called as cytokine storm by T-cells and B-cells activation which altered vascular permeability which in turn combined with thrombocytopenia leads to dengue shock syndrome. Intravascular fluid loss due to altered vascular permeability causes hallmark Capillary leak syndrome.

Thrombocytopenia is common and dreaded feature of dengue fever which occur due virus infecting stromal cells of bone marrow which in case of severe infection although rare may progress to pancytopenia

Ferritin is an Iron containing cytosolic globular protein present in almost all eukaryotes; it is used as non toxic form of Iron storage. Iron binds to Apoferritin in circulation to form Ferritin. Its primary function is to act as buffer for iron fluctuations within plasma to extract in excess and provide in deficiencies where it is released in circulation and retains itself in plasma

Ferritin has been also considered as acute phase reactant along with C reactive protein and ceruloplasmin due to inflammation increasing oxidative stress, while Cytokines and interferons are more specific but quite expensive and sparsely available option for same purpose

When it comes to correlation between hyperferritinaemia in dengue fever, viral replication affecting bone marrow causes extensive immune activation, called haemophagocytic lymphohistiocytosis. A study from the Caribbean island Aruba concluded that ferritin can be used as a marker to differentiate between dengue and other febrile illnesses. The presence of hyperferritinemia in dengue patients is indicative for highly active disease resulting in immune activation and coagulatory disturbances. Therefore, patients with hyperferritinemia are recommended to be monitored carefully which according to new classification of dengue fever classified under Group B and above



There are multiple studies which are suggestive of hyperferritinaemia being marker of active dengue fever in which macrophage activation syndrome which further causes haemophagocytic syndrome leading to cytokine storm and further progression of disease causing raised morbidity and mortality

Thus this study aims to study correlation between active dengue fever with Hyperferritinaemia and provide serum Ferritin as marker of dengue fever

STUDY METHODOLOGY-Total 51 Patients were included in our study. This Prospective study was conducted at Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Sangli over a period of 6 months. Approval from IEC has been taken. A positive Rapid dengue test (NS1 Antigen and/or IgM ELISA)patients were included in study. Detailed screening of each patient was done after confirmation, in relation to history, general examination, systemic examination finding. All the investigation like CBC, Dengue (NS1 and/or IgM positive), Serum Ferritin level and other investigations were entered on proforma. Management of each patient was according to the standard protocol of Dengue fever.Serum Ferritin level of all the patients was sent to laboratory on day 4th or 5th of illness. Normal levels were defined as Serum Ferritin level up to 250 mcg/dl. Patients were follow up during their hospital stay for development of symptoms of Dengue fever with warning sign or Severe Dengue or recovery. Serum Ferritin level was measured on 4th or 5th day of illness in these 51 study Patients.In which study Patients divided into 3 groups according to Serum Ferritin level. Group A-Serum Ferritin level 500mcg/dl. Statistical analysis: All the observational findings were recorded and entered into prestructured proform. The whole data was analysed with help of statistician by Chi sq test and p value was said to be significant (<0.05).

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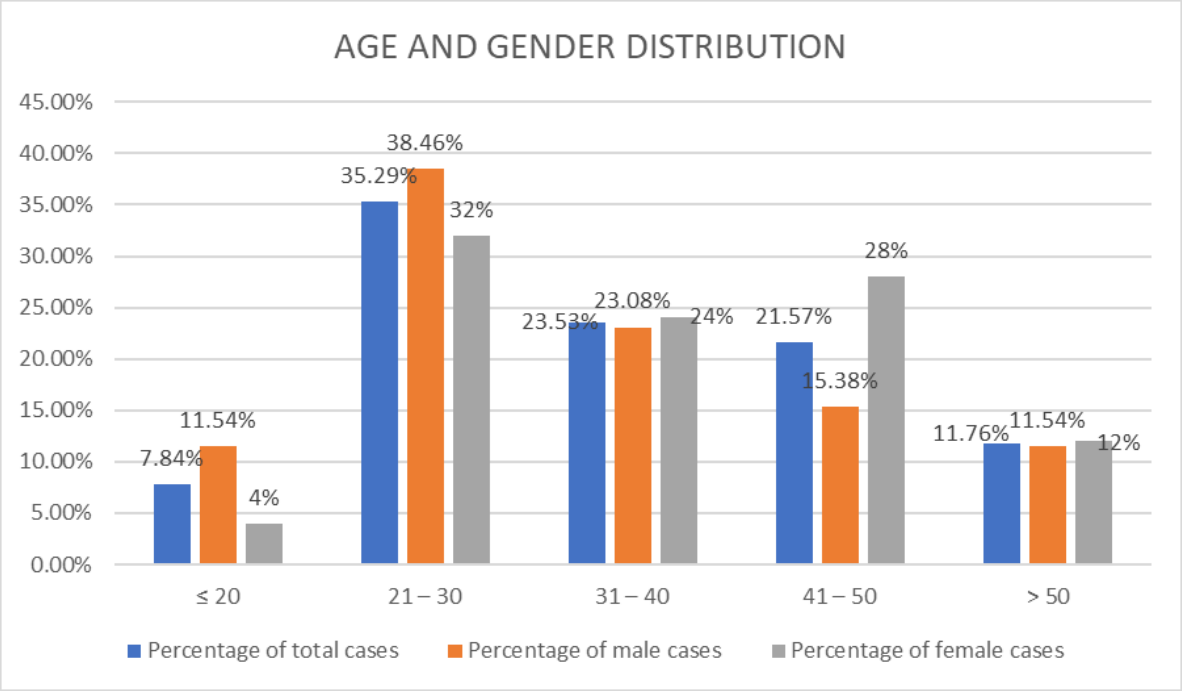
OBSERVATIONS AND RESULTS

Table 1: Age and sex distribution of cases

Age (in years)	Total cases (n=51)	Male (n=26)	Female (n=25)
≤ 20	4 (7.84%)	3 (11.54%)	1 (4%)
21 – 30	18 (35.29%)	10 (38.46%)	8 (32%)
31 – 40	12 (23.53%)	6 (23.08%)	6 (24%)
41 – 50	11 (21.57%)	4 (15.38%)	7 (28%)
> 50	6 (11.76%)	3 (11.54%)	3 (12%)
Total	51 (100%)	26 (50.98%)	25 (49.01%)



In the present study most of the cases i.e. 35.29% cases were seen having age between 21 to 30 years of age followed by 23.53% cases had age from 31 to 40 years of age, 21.57% cases had age from 41 – 50 years of age, 11.76% cases had age more than 50 years of age and 7.84% cases were observed having age less than or equal to 20 years of age. 50.98% cases were male cases and 49.01% were female cases. 38.46% male cases were observed having age from 21 to 30 years of age, 23.08% male case had age from 31 to 40 years of age, 15.38% cases had age between 41 to 50 years of age and 11.54% each male cases were seen having age more than 50 years and less than or equal to 20 years of age. Out of 25 female cases 32% cases were seen having age from 21 to 30 years of age, 28% cases had age from 41 to 50 years of age, 24% cases had age from 31 to 40 years of age, 12% female cases had age more than 50 years of age and 4% female caseshadage less than or equal to 20 years of age.

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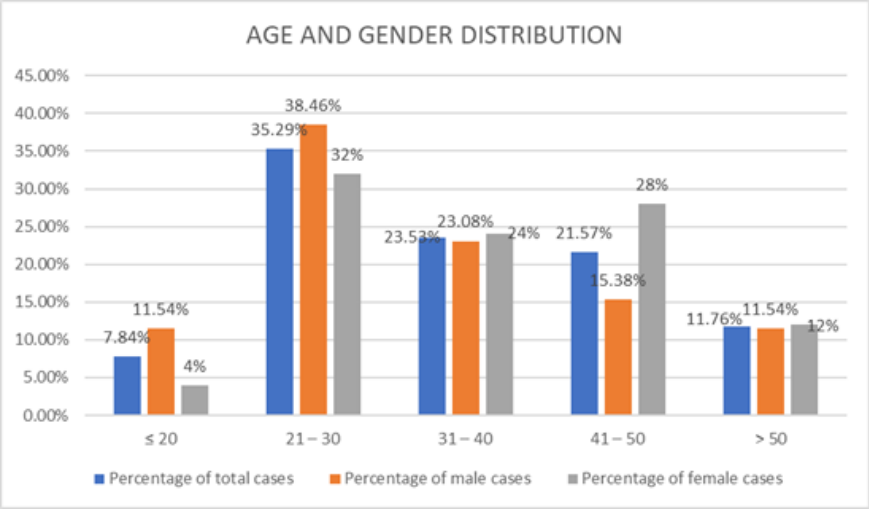

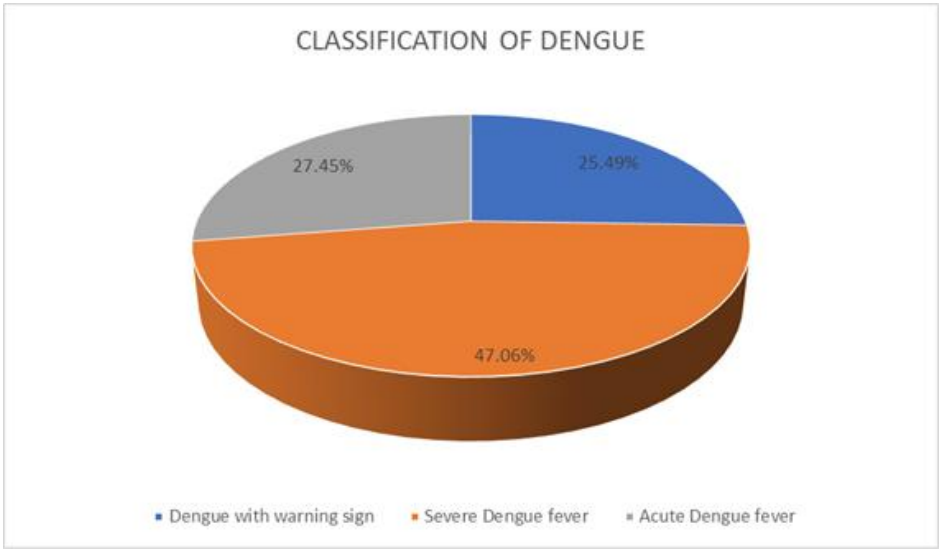

SERUM FERRITIN LEVELS- In the present study severe dengue fever was the most common classification observed in 47.06% cases followed by 27.45% cases with Acute Dengue fever and 25.49% cases with Dengue fever warning sign.

Sr. Ferritin Levels	No of cases (n=51)	Minimum	Maximum	Mean±S.D
Group A (Sr. Ferritin level < 250)	11 (21.57%)	36	242	110.5±57.25
Group B (Sr. Ferritin level 250 - 500)	10 (19.61%)	254	478	337.1±75.35
Group C (Sr. Ferritin level > 500)	30 (58.82%)	530	3645	2599±878.8

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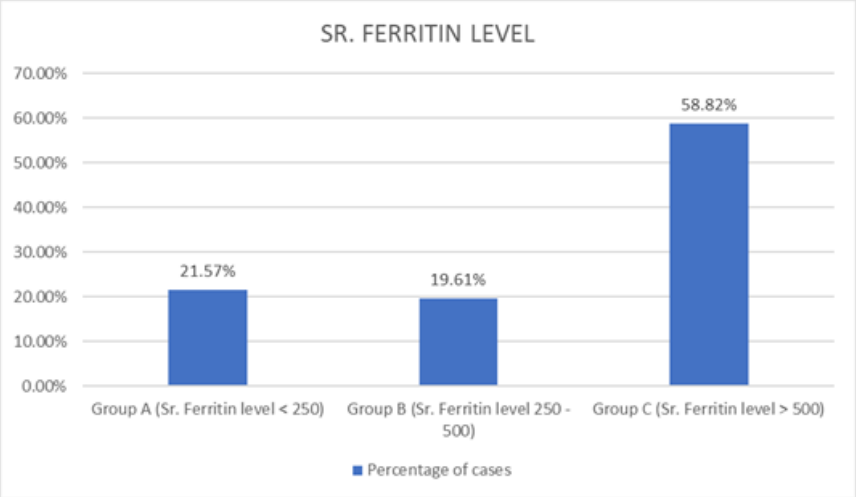
In the present study Most of the cases i.e. 58.82% cases were seen having Sr. ferritin level > 500, 21.57% cases were observed having Sr. Ferritin level < 250 and 19.61% cases had Sr. ferritin level from 250 to 500.



In the present study cases with Severe dengue significant difference was observed in Sr. Ferritin levels. In cases with Acute dengue fever significant difference between Sr. Ferritin level was observed.

Table 4: Comparison of Sr. ferritin level and Severity of Dengue

Serum Ferritin level	Dengue with warning sign	Severe dengue	Acute dengue fever
Group A (Sr. Ferritin level < 250)	1	1	9
Group B (Sr. Ferritin level 250 - 500)	1	4	5
Group C (Sr. Ferritin level > 500)	11	19	0
	-	(P < 0.0001***)	(P < 0.0001***)

Table 5: Platelet Day 1 and Day 3

In the present study statistically no significant difference was observed between the Day 1 platelet count and Day 3 platelet count.

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Platelet_Day1	**98607.84**	**51**	**80041.01**	**11207.98**
	Platelet_Day3	**90725.49**	**51**	**81143.10**	**11362.31**

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In the present study statistically no significant difference was observed between the Day 1 platelet count and Day 3 platelet count.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Platelet_Day1 - Platelet_Day3	**7882.35294**	**28851.79167**	**4040.05893**	**-232.34423**	**15997.05011**	**1.951**	**50**	**.057**

CONCLUSION- present study shows that elevated serum ferritin levels done during early stages of febrile illness (3rd to 7th DAY of ILLNESS) predicts the severity of dengue.

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Dengue fever is a widely prevalent viral infection in the tropical countries. Many patients with dengue fever are known to have severe cytopenias and the mechanism for the same is not known. Macrophage Activation Syndrome (MAS) is a life threatening complication that is known to be triggered by viral infections. This study attempts to examine the possibility of MAS as an underlying cause of cytopenias in dengue fever. Hyperferritinemia which is an important diagnostic criteria for MAS is known to occur in dengue fever also

2] Petchiappan V, Hussain TM, Thangavelu S. Can serum ferritin levels predict the severity of dengue early?: an observational study. Int J Res Med Sci 2019;7:876-81.

Background: Dengue infection is a major public health threat; early recognition is crucial to improve the survival in severe dengue. Although there are various biomarkers to predict the severity of dengue, they are not routinely used in clinical practice for prognostication. We analyzed whether serum Ferritin can be used to predict the severity at an earlier stage. Methods: A hospital based prospective observational study was done involving 119 dengue cases diagnosed by positive NS1 antigen or dengue specific serology (capture ELISA). Serum ferritin was measured in all at the time of diagnosis. Clinical and platelet count monitoring was done daily; classified as severe and non-severe according to 2009 WHO criteria. Results: Out of 119, 5 developed severe dengue; patients with severe dengue had significantly lower median platelet count

3] Roy Chaudhuri S, Bhattacharya S, Chakraborty M, Bhattacharjee K. Serum ferritin: a backstage weapon in diagnosis of dengue fever. Interdisciplinary perspectives on infectious diseases. 2017;2017.

Aims. This retrospective study evaluates ferritin as a surrogate marker for dengue infection (NS1 and IgM negative stage) as opposed to other febrile illnesses of infective or inflammatory etiology (OFI). Methodology. Data of all patients admitted to medical ward and medical ITU during the dengue outbreak were collected. Patients admitted between 5 and 10 days of febrile illness without a diagnosis were included. Patients with NS1 positivity (Days 2–8) and/or positive IgM for dengue (Days 6–10) were considered to be dengue cases and those with other confirmed diagnoses were considered in the OFI group. Ferritin, CRP, TC of WBC, platelet count, SGOT, SGPT, and albumin levels were analysed for both groups. Results. We examined 30 cases of clinically and serologically confirmed dengue fever and 22 cases of OFI. Ferritin level in dengue cohort was significantly higher than the OFI group (). The best cut-off for ferritin level to differentiate dengue from OFI was found to be 1291. The sensitivity at this cut-off is 82.6% and the specificity at this cut-off

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is 100%. Conclusion. Ferritin may serve as a significant marker for differentiating between dengue fever and OFI, in absence of a positive NS1 antigen or a positive IgM antibody for dengue.

4] Mitra S, Bhattacharyya R. Hemophagocytic syndrome in severe dengue fever: a rare presentation. Indian Journal of Hematology and Blood Transfusion. 2014 Sep 1;30(1):97-100.

We describe a 2-year old boy developing virus-associated hemophagocytic syndrome in severe dengue fever. The condition was diagnosed according to the established criteria of the International Histiocyte Society. There was uneventful recovery with corticosteroid therapy. Secondary hemophagocytosis in children can mimic severe sepsis, systemic inflammatory response syndrome, or multi organ dysfunction syndrome and lead to diagnostic difficulties. This report adds to the limited pediatric cases of dengue related hemophagocytic syndrome reported in literature; and underlines the importance of prompt diagnosis and appropriate treatment of this rare but serious complication.

5] Koshy M, Mishra AK, Agrawal B, Kurup AR, Hansdak SG. Dengue fever complicated by hemophagocytosis. Oxford medical case reports. 2016 Jun 1;2016(6):121-4.

Dengue fever, caused by a mosquito-borne virus of the Flaviviridae family, is endemic to India and can present with a wide range of clinical manifestations. The disease presentation can range from a self-limiting febrile illness to life-threatening shock [1, 2]. In recent years, there has been an increase in reports of atypical manifestations, some of which may be severe [3, 4].

Hemophagocytic syndrome is an aggressive disease characterized by excessive immune activation. It can occur in the setting of autoimmune disease, hematological malignancy and infections [5]. Many infections are known to cause hemophagocytosis, and this is often mistaken for sepsis and multiorgan dysfunction and carries a high mortality [6]. Infection by dengue virus is being recognized as a trigger in the recent years [7].

We describe the case of a 29-year-old man who had dengue hemorrhagic fever complicated by the development of hemophagocytosis. This report adds to the limited adult cases of dengue-associated hemophagocytic syndrome described in the literature

6] Valero N, Mosquera J, Torres M, Duran A, Velastegui M, Reyes J, Fernandez M, Fernandez G, Veliz T. Increased serum ferritin and interleukin-18 levels in children with dengue. Brazilian Journal of Microbiology. 2019:1-8.

Activated monocytes/macrophages that produce a cytokine storm play an important role in the pathogenesis of dengue. Interleukin-18 (IL-18) is a proinflammatory cytokine produced by monocyte/macrophages that is increased during dengue. Ferritin is an acute-phase reactant and expressed by cells of the reticulo-endothelial system in response to infection by dengue virus. The aims of this study were to analyze the simultaneous expression of both IL-18 and ferritins in children infected by diverse serotypes of dengue virus (DENV) and determine their association with dengue severity. In this regard, children with dengue (n = 25) and healthy controls with similar age and sex (n = 20) were analyzed for circulating ferritin and cytokines. Monocytes were isolated by Hystopaque gradient and co-cultured with DENV-2. IL-18 and ferritin contents in blood, and IL-18 in culture supernatants were determined by ELISA. Increased levels of ferritin and IL-18 ($p < 0.0001$) were observed in dengue patients, not associated to NS1expression or type of infection (primary or secondary). Highest values of both molecules ($p < 0.001$) were observed in dengue with warning signs and severe dengue. Differential effect on IL-18/ferritin production was observed associated to viral serotype infection. There were no correlations between ferritin vs. IL-18 production, ferritin vs. NS1 status, and IL-18 vs. NS1 status. Viral-infected monocyte cultures showed increased production of IL-18 ($p < 0.001$). In conclusion, increased circulating ferritin and IL-18 are expressed in children infected by different serotypes of DENV associated with dengue severity.

7] van de Weg CA, Huits RM, Pannuti CS, Brouns RM, van den Berg RW, van den Ham HJ, Martina BE, Osterhaus AD, Netea MG, Meijers JC, van Gorp EC. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. PLoS neglected tropical diseases. 2014 Oct 9;8(10):e3214.

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Altogether, we provide evidence that ferritin can be used as a clinical marker to discriminate between dengue and other febrile illnesses. The occurrence of hyperferritinaemia in dengue virus infected patients is indicative for highly active disease resulting in immune activation and coagulation disturbances. Therefore, we recommend that patients with hyperferritinaemia are monitore.

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