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Analysis of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase L1 in Postmortem Serum and Cerebrospinal Fluid in Traumatic Cerebral Deaths

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ABSTRACT

Objective: There is a growing body of research aimed at identifying biological markers that could indicate traumatic cerebral deaths such as traumatic brain damage in the postmortem period. In the event of astrocytic and neuronal injury, glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) are released into cerebrospinal fluid and blood. In the postmortem identification of traumatic brain injury, the present research explores the ability of GFAP and UCH-L1.

Methods: Cerebrospinal fluid and blood samples were obtained from medicolegal autopsies, 17 cases with severe head trauma, 9 cases with the non-lethal head trauma group and 18 control cases. UCH-L1 and GFAP levels in postmortem cerebrospinal fluid and serum were determined from an enzyme-linked immunosorbent assay (ELISA).

Results: GFAP level in cerebrospinal fluid and serum was 2.68±0.67 ng/ml and 0.79±0.92 ng/ml in the lethal head trauma group, 2.74±0.64 ng/ml and 1.05±0.68 ng/ml the non-lethal head trauma group and 2.49±0.55 ng/ml and 1.05±0.89 ng/ml in the control group, respectively. UCH-L1 level in cerebrospinal fluid and serum was 3.02±0.68 ng/ml and 2.69±0.77 ng/ml in the lethal head trauma group, 3.34±0.70 ng/ml and 2.59±0.65 ng/ml the non-lethal head trauma group and 3.28±0.33 ng/ml and 2.74±0.34 ng/ml in the control group, respectively. Elevated cerebrospinal fluid and serum UCH-L1 and GFAP levels were observed in all cases, although absence of statistically significant difference between the trauma and control groups ($p>0.05$).

Conclusion: Further studies are needed to assess whether postmortem serum and CSF GFAP and UCH-L1 concentrations increase regardless of the cause of death.

Keywords: Traumatic brain injury, glial fibrillary acidic protein, ubiquitin C-terminal hydrolase L1, autopsy

1. INTRODUCTION

Traumatic brain injuries (TBI) are considered among common causes of mortality and morbidity. The majority of cases are associated with falls and traffic accidents (1). Deaths from traumatic injuries to the head, occurring particularly during traffic accidents and falls, hold an important place in the practice of forensic medicine (1). The primary tissue damage sustained during a head trauma may cause brain contusion, laceration, intracranial hematoma and skull fracture. A diffuse axonal injury can also occur as a result of the stretching and rupture of brain tissue and vessels following rapid acceleration-deceleration. Ischemia and hypoxia, which may not result directly from the trauma, brain edema, increased intracranial pressure and cellular changes caused by posttraumatic inflammatory processes, can lead to secondary damage (2,3). The effectiveness of various biomarkers has been investigated in the detection of TBI that occurs in patients after sustaining a head trauma. The identification of a biomarker that can indicate brain damage has been challenging due to the multitude of enzymes and proteins that are released into circulation, the complex structure of the brain and the diversity of the cells affected by trauma (4). Studies have identified such biomarkers as glial fibrillary acidic protein (GFAP) for astrocytic injuries; Alpha-II spectrin, c-TAU and phosphorylated neurofilaments (p-NF) for axonal injuries; and neuron-specific enolase (NSE) and ubiquitin c-terminal hydrolase isozyme L1 (UCH-L1) for neuronal injuries (5). These biomarkers can be detected in both blood and cerebrospinal fluid (CSF) following a traumatic brain injury (6). Recent studies have evaluated biomarkers of brain injury and their ability to identify traumatic brain injury in the postmortem period (3,7,8).

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GFAP is the main protein in the astroglial cytoskeleton. Under physiological conditions, GFAP is typically not detectable in the plasma of healthy individuals (9,10). GFAP levels have been reported to be detectable in the CSF and serum within the first hour, particularly in patients with serious to extreme TBI, as well as increased levels in ischaemic cell death and in ischaemic and hypoxic conditions resulting in necrosis (11,12).

The ubiquitin C-terminal hydrolase L1 enzyme is involved in the marking of both ubiquitin precursors and ubiquitinated proteins. UCH-L1 is specifically expressed at high levels in the neurons, and is estimated to account for 1–2% of the soluble proteins in the brain (13,14,15). It has been suggested, due to its abundance in neurons, that UCH-L1 could be used in clinical practice as a neuron-specific biomarker of traumatic brain injury. UCH-L1 levels in cerebrospinal fluid and serum starts increasing shortly after an injury, as does GFAP (4,16). The mechanisms by which biomarkers such as GFAP and UCH-L1 are released into the bloodstream remain unclear, although it has been proposed that cerebrospinal and interstitial fluid exchange, also known as the glymphatic system, and blood-brain barrier disturbance may be due to this (17,18,19). The blood UCH-L1 levels are also low in healthy subjects (4,20). In clinical trials, Diaz-Arrastia et al accepted the upper limit of normal for serum UCHL1 as 0.244 ng / ml (4).

Previous postmortem studies have demonstrated that GFAP can be found in the postmortem brain samples of both humans and gnawers (21,22). Recent studies have reported postmortem GFAP measurements in CSF and serum (7,8), and postmortem UCH-L1 measurements in CSF (23). However no postmortem measurements of UCH-L1 in the serum have been previously reported. The objective of this research is to carry out a postmortem review of the levels of UCHL-1 and GFAP in human serum and cerebrospinal fluid by means of an enzyme-linked immunosorbent assay (ELISA) and to determine the potential of these biologic markers as indicators of postmortem traumatic brain injury. These biomarkers were selected because UCHL-1 and GFAP measured different molecular events and began to increase shortly after injury.

2. METHODS

2.1. Subjects

This project was conducted after obtaining the approval of the Non-interventional Clinical Trials Ethics Committee with the number 60116787-020 / 81511. A total of 44 cases that underwent a medicolegal autopsy in the department of forensic medicine were included in this cross – sectional study. There were 17 cases in the lethal head trauma group, 9 cases in the non-lethal head trauma group, and 18 cases in the control group. In all cases, deaths had occurred at the scene. None of the 44 cases received cardiopulmonary resuscitation and were not hospitalized. Since lethal head trauma and non-lethal head trauma cases died at the scene, they were evaluated according to the investigation records and pathological findings during autopsy and were estimated to be acute death with a short survival time. The control cases were evaluated as acute death since they consisted of sudden cardiac deaths such as acute myocardial infarction. None of the cases had a history of neurodegenerative disease.

2.2. Collection and Storage of Samples

CSF and blood samples were obtained within 24 h of death in the routine forensic autopsies. A 5-ml blood sample obtained from the femoral vein by puncture and centrifuged at 3000 rpm for 15 minutes. A 3–4 ml CSF sample was collected using suboccipital puncture from the same cases and centrifuged at 4000 rpm for 10 minutes to separate it from the blood cells. Before taking the samples, the skin was decontaminated with a 90% ethanol solution. Hemolyzed samples were excluded. Centrifugation process was done according to Teunissen et al (2009) protocol standardization (24). Blood and CSF samples were directly stored at – 80°C freeze in Eppendorf tubes to protect the sample quality and minimize the impact of putrefaction after sample collection and centrifugation process. Later, samples were shipped on dry ice.

2.3. Human GFAP and UCH-L1 ELISA

The GFAP levels in CSF and serum samples were analyzed using a human GFAP ELISA kit (YL Biont Human glial fibrillary acidic protein (GFAP) ELISA Kit; Catalog number: YLA1905HU); and the UCH-L1 levels were determined using a human UCH-L1 ELISA kit (YL Biont Human Ubiquitin Carboxyl Terminal Hydrolase L1 (UCH-L1) ELISA Kit; Catalog number: YLA0790HU). The calibration range was reported to be 0.05 ng/ml→15 ng/ml and the sensitivity was 0.026 ng/ml for GFAP and the calibration range was reported to be 0.1 ng/ml→38 ng/ml and the sensitivity was 0.05 ng/ml for UCH-L1. The intra-assay precision was <8% and inter-assay precision was <10%. The tests were performed using a sandwich-based ELISA method, and all procedures were performed as per the manufacturer's protocol.

2.4. Human GFAP/UCH-L1 ELISA Test Protocol

The GFAP and UCH-L1 levels in the CSF and serum samples were determined using the ELISA kit protocols. Sufficient microwell strips were prepared for the standards, blinds and the number of samples to be tested, and each sample was studied in duplicate in standard, blind and control wells. The microwell strips were washed twice with 400 µl of Wash Buffer per well and the fluid remaining in the wells after washing was withdrawn. The Wash Buffer sat in the wells for 10–15 sec before being withdrawn. The standards were prepared as per the kit protocol. A 100-µl Sample Diluent solution was added to the wells spared for the blinds and a 50-µl Sample Diluent solution was added into the wells spared for the samples. A 50-µl sample was added to the relevant wells, and a 50-µl Biotin-Conjugate solution was added to all wells. The plate was covered with an adhesive film and incubated at room temperature for 2 hours. The adhesive film was removed and the wells were emptied and washed. A 100-µl Streptavidin-HRP solution was added to

all wells. The plate was covered with an adhesive film and incubated at room temperature for 1 hour. The adhesive film was removed and the wells were emptied and washed. A 100-µl TMB Substrate Solution was added into all wells. The strips were incubated at room temperature for 10 minutes. A 100-µl Stop Solution was added to all wells. The absorbance of each well was read at a primary wavelength of 450 nm using a spectrophotometer.

2.5. Statistical Analysis

Continuous variables were expressed in number and percent as mean ± standard deviation (SD), median (minimum-maximum values) and categorical variables. The Shapiro-Wilk Test was used to verify the normality of the distribution of data. The Kruskal-Wallis Variance Analysis was used to compare independent groups if parametric test conditions were not met. The Spearman correlation analysis was used to evaluate the relationships between continuous variables. The Chi-square analysis was used to investigate the discrepancies between categorical variables. The data was analyzed using the SPSS 25.0 software package. In all analyses, a p value less than 0.05 was considered statistically significant.

3. RESULTS

Of the 44 cases, 33 were male and 11 were female, with a mean age of 46.32±15.02 years (Median: 45, Min: 18–Max: 72). Of the cases with a lethal head trauma, eleven had sustained a motor vehicle crash and six had sustained falls. Their injuries included fractures to cranial bones, subarachnoid hemorrhages, subdural hemorrhages and brain contusions. Of the non-lethal head trauma cases, seven had sustained a motor vehicle crash and two had sustained falls, and these cases had suffered only abrasions and lacerations to the scalp. Death of the nine cases was attributed to chest and abdominal traumas. The cause of death was sudden cardiac death in cases in the control group, none of which had sustained a head trauma. In the control group, the causes of death were acute myocardial infarction in 15 cases, hypertrophic cardiomyopathy in 1 case and heart failure in 2 cases. Demographic data for all cases included in the study were shown in table 1.

The mean GFAP level in CSF was 2.68±0.67 ng/ml (range 1.91 – 4.41) in the lethal head trauma group, 2.74±0.64 ng/ml (range 2.05 – 3.89) in the non-lethal head trauma group, and 2.49±0.55 ng/ml (range 1.64 – 3.82) in the control cases. No statistically significant difference between the groups was observed (p=0.447) (Figure 1A).

The mean GFAP level in the serum samples was 0.79±0.92 ng/ml (range 0.06-4.02) in the lethal head trauma group, 1.05±0.68 ng/ml (range 0.05 – 3.88) in the non-lethal head trauma group and 1.05±0.89 ng/ml (range 0.36 – 2.61) in the control cases. No statistically significant difference between the groups was observed (p=0.279) (Figure 1B).

Table 1. *Demographic and pathological characteristics of all cases*

	All of cases (n= 44)	Lethal head trauma group (n= 17)	Non-lethal head trauma group (n= 9)	Control group (n= 18)
Sex				
Female	11	2	2	7
Male	33	15	7	11
Mean age, yrs (SD)	46.32±15.02	41.41±16.55	51.22±15.66	48.5±12.48
Postmortem interval, h (SD)	10.77±6.05	8.7±3.6	11.55±7.47	12.33±6.87
Mechanism of injury				
Motor vehicle crash	18	11	7	-
Fall	8	6	2	-
Cause of death				
Macroscopic cerebral hemorrhage	17	17	-	-
Macroscopic brain contusion	9	9	-	-
Fractures to cranial bones	11	11	-	-
Hemotorax	9	2	7	-
Macroscopic lung contusion	7	3	4	-
Intraabdominal hemorrhage	4	1	3	-
Intraabdominal solid organ lacerations	4	1	3	-
Acute myocardial infarction	15	-	-	15
Hypertrophic cardiomyopathy	1			1
Heart failure	2	-	-	2

The mean UCH-L1 level in CSF was 3.02±0.68 ng/ml (range 1.04 – 3.91) in the lethal head trauma group, 3.34±0.70 ng/ml (range 2.36 – 4.75) in the non-lethal head trauma group and 3.28±0.33 ng/ml (range 2.28 – 3.76) in the control cases. No statistically significant difference between the groups was observed (p=0.428) (Figure 2A).

The mean UCH-L1 level in serum was 2.69±0.77 ng/ml (range 1.32 – 4.80) in the lethal head trauma group, 2.59±0.65 ng/ml (range 1.85 – 4.11) in the non-lethal head trauma group and 2.74±0.34 ng/ml (range 2.27 – 3.48) in the control cases. No statistically significant difference between the groups was observed (p=0.545) (Figure 2B).

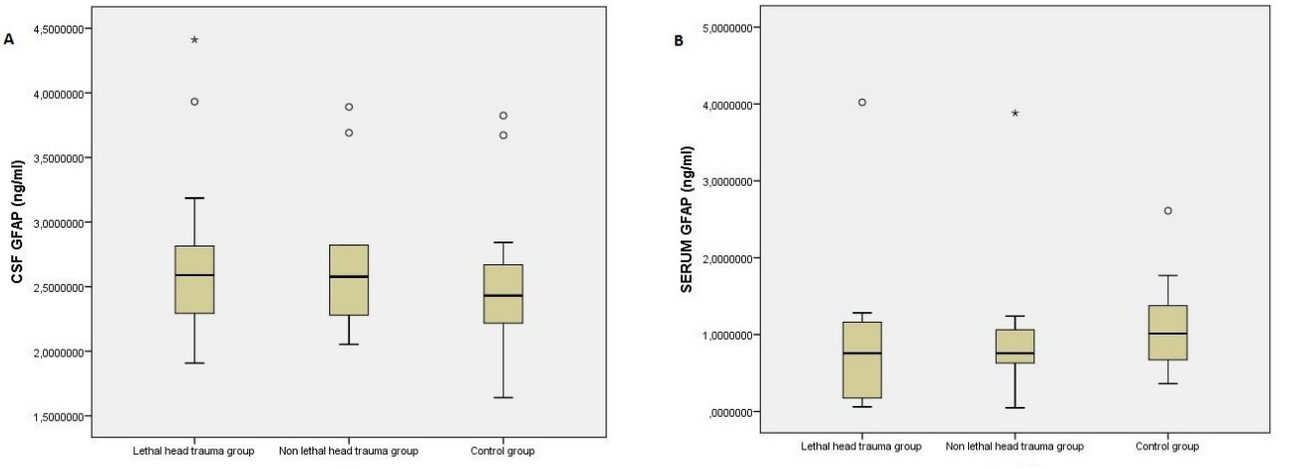

Figure 1. *A; GFAP concentrations in cerebrospinal fluid in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups (Kruskal Wallis test, p>0.05). B; GFAP concentrations in serum in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups (Kruskal Wallis test, p>0.05).*

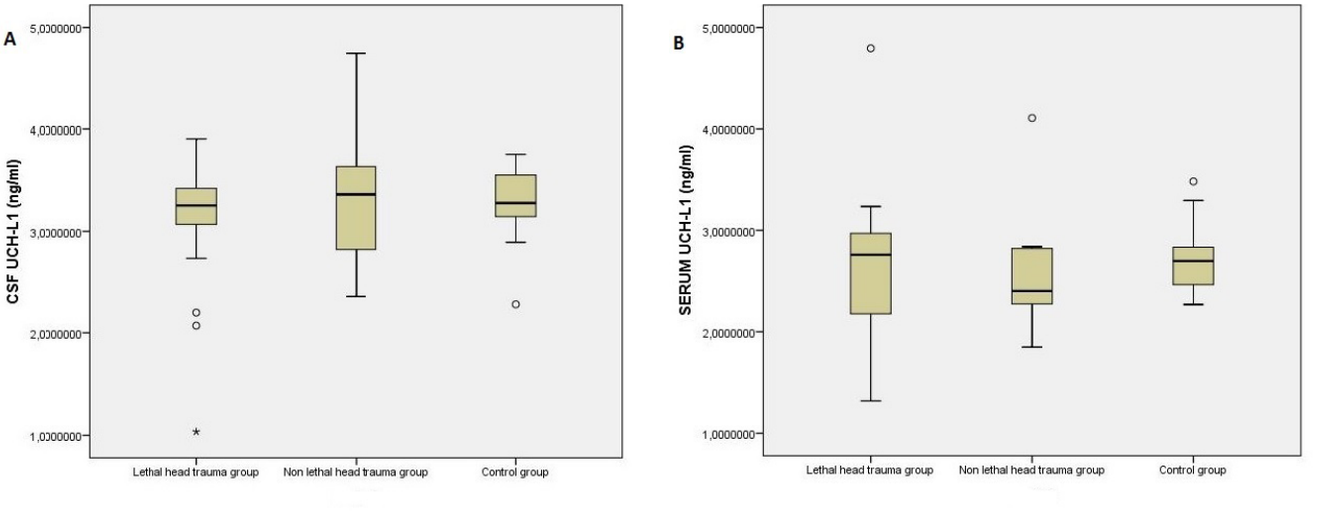

Figure 2. *A; UCH-L1 concentrations in cerebrospinal fluid in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups (Kruskal Wallis test, p>0.05). B; UCH-L1 concentrations in serum in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups.*

When the changes within each group are examined; there was no statistically significant difference between CSF and serum UCH-L1 concentrations in the lethal head trauma group (p> 0.05); CSF UCHL-1 concentrations were statistically significantly higher than serum UCH-L1 concentrations in the non-lethal head trauma group and the control group (p <0.05). The GFAP levels in CSF than serum was higher significantly in all groups was statistically significant (p <0.05) (Table 2).

We didn't observe correlation between CSF GFAP, serum GFAP, CSF UCH-L1, serum UCH-L1 levels and postmortem interval (Spearman's correlation coefficient r<0.20; p>0.05).

Table 2. *Serum and CSF UCH-L1 and GFAP concentrations*

		Mean	Standart Deviation	P value
Lethal head trauma group	CSF UCH-L1	3.02	0.68	0.176
	Serum UCH-L1	2.69	0.77	
	CSF GFAP	2.68	0,67	<0.001*
	Serum GFAP	0.79	0,92	
Non-lethal head trauma group	CSF UCH-L1	3.34	0.70	0.029*
	Serum UCH-L1	2.59	0.65	
	CSF GFAP	2.74	0.64	0.008*
	Serum GFAP	1.05	0.68	
Control group	CSF UCH-L1	3.28	0.33	<0.001*
	Serum UCH-L1	2.74	0.34	
	CSF GFAP	2.49	0.55	<0.001*
	Serum GFAP	1.05	0.89	

*GFAP: Glial fibrillary acidic protein; UCH-L1: Ubiquitin c-terminal hydrolase isozyme L1; CSF: Cerebrospinal fluid. *p<0.05 statistically significant*

4. DISCUSSION

In this study evaluating the potential of biological markers, such as GFAP and UCH-L1, in the prediction of traumatic brain injury in the postmortem period in patients with head trauma, GFAP and UCH-L1 levels could be measured by ELISA in the postmortem CSF and serum samples. It was found in the present study that CSF and serum GFAP and UCH-L1 concentrations are increased both in cases with lethal head trauma and in those who died of non-cerebral causes; however, the discrepancy was not statistically relevant between the groups. These results suggest that the changes in postmortem CSF and serum GFAP and UCH-L1 concentrations are independent of the underlying neurological disorder.

There have been only a few studies in literature evaluating postmortem GFAP concentrations in CSF and serum (7,8). In the study by Olzack et al (2018) the mean GFAP concentration in the CSF was found to be 2346.75±1312.33 pg/ml in head trauma cases and 201.21±66.65 pg/ml in control cases, showing a significantly higher concentrations in the head trauma cases. On the other hand, Breitling et al (2018) evaluated postmortem serum GFAP concentrations and found no statistically significant difference between deaths due to primary cerebral causes and non-cerebral deaths in terms of GFAP concentrations (8). Similar to the findings of Breitling et al (2018), no significant difference was identified in the present study CSF and serum GFAP concentrations between cases who died of head trauma and deaths related with non-cerebral causes. It was hypothesized in the present study that GFAP and UCH-L1 levels will be elevated particularly in severe traumatic brain injuries, and that these markers could be useful in the postmortem diagnosis of traumatic brain injury. The present results reveal, however, that postmortem GFAP and UCH-L1 levels were high regardless of the cause of death, suggesting that other mechanisms could exist that are responsible for this increase. Breitling et al (2018) suggested that increases in postmortem GFAP concentrations in non-cerebral deaths could be attributable to perimortem pathophysiological events that trigger GFAP release (8). Clinical studies report that hypoxia and ischemia may lead to an increase in GFAP concentrations in the CSF and serum by causing a breakdown of astroglial cells and a disturbance of the blood-brain barrier (25,26). In patients who have suffered non-traumatic out-of-hospital cardiac arrest, GFAP levels have been shown to be high (25). An increase in GFAP levels due to hypoxia has also been reported in the patients with neonatal hypoxic ischemic encephalopathy (26). In this study, as the control group consisted of cases of acute cardiac death (such as acute myocardial infarction) that did not receive cardiopulmonary resuscitation and were not hospitalized, an increase in these markers may be due to cardiac death-induced hypoxia.

As a neuron-specific cytoplasmic enzyme, UCH-L1 has been researched as a marker of neuronal injury in the clinical trials of TBI and brain ischemia (4,16,27). It has been reported that UCH-L1 becomes detectable within a couple of hours of trauma (28). The mechanisms by which UCH-L1 is transported from the brain compartments into the circulatory system are yet to be clearly understood, although it has been suggested that it is released into the circulatory system due to neuronal damage and increased permeability of blood-brain barrier (27,29). In the present study, postmortem UCH-L1 concentrations in CSF and serum were found to be increased both in cases with lethal head trauma and in those who died of non-cerebral causes. Other stress factors in the perimortality phase and under hypoxic and ischemic conditions may be affecting UCH-L1 secretion and concentrations, independently of neurological disorders. Clinical studies have indicated increased UCH-L1 concentrations resulting from hypoxic brain injury and disruption of the blood-brain barrier in pediatric patients that survived cardiac arrest, and in patients in whom cardiac arrest was induced for the repair of an aortic aneurysm (30,31). In a postmortem study, Piette et al (2011) reported that a relationship could exist between ubiquitin immunoreactivity in locus coeruleus and the duration of agony (32).

The relatively low number of cases can be considered a limitation of the present study. Since the cases have a short survival time, biomarker release due to mechanical cell trauma may not have been realized at level to distinguish it from other causes of death. The fact that it is high in acute myocardial infarction may be due to the fact that the process of agony is accompanied by a certain extent of cerebral hypoxia. We believe further research is needed with a larger sample in this topic. Different from other studies, however, the simultaneous investigation of the biomarkers of trauma both in the blood and cerebrospinal fluid is one of the strengths of the present study.

5. CONCLUSIONS

In this study postmortem serum and CSF UCH-L1, and GFAP levels, were high in deaths resulting from both traumatic cerebral and non-cerebral causes. Since there are studies in the literature that report different results in this topic, it is thought that other studies to be performed by classifying them according to survival time after trauma are needed. In addition, immunohistochemical studies may be useful to see the effect of hypoxic and agonal processes on biomarker release.

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Conflicts of interest

The authors declare that they have no competing interests.

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