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Clinical Paper

Tau proteins in serum predict neurological outcome after hypoxic brain injury from cardiac arrest: Results of a pilot study☆

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ABSTRACT

Objective: To conduct a pilot study to evaluate the prognostic potential of serum tau protein measurements to predict neurological outcome 6 months following resuscitation from cardiac arrest.
Methods: In this retrospective observational study, we employed a new ultra sensitive digital immunoassay technology to examine serial serum samples from 25 cardiac arrest patients to examine tau release into serum as a result of brain hypoxia, and probe for its significance predicting six-month neurological outcome. Serial blood samples were obtained from resuscitated cardiac arrest survivors during their first five days in an intensive care unit, and serum total tau was measured. Cerebral function assessments were made using Cerebral Performance Categorization (CPC) at discharge from the ICU and six months later. Tau data were analyzed in the context of 6-month CPC scores.
Results: Tau elevations ranged from modest (<10 pg/mL) to very high (hundreds of pg/mL), and exhibited unexpected bi-modal kinetics in some patients. Early tau elevations appeared within 24 h of cardiac arrest, and delayed elevations appeared after 24–48 h. In patients with delayed elevations, areas under the curves of tau concentration vs. hours since cardiac arrest were highly predictive of 6-month outcome ($P < 0.0005$).
Conclusion: High-sensitivity serum tau measurements combined with an understanding of tau release kinetics could have utility for hypoxic brain injury assessment and prediction of cerebral function outcome.

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1. Introduction

Objectively measuring severity of brain injury remains a significant unmet clinical need. While clinical rating scales such as the Glasgow Coma Scale (GCS) are useful for grading injury severity, and neuroimaging techniques are useful for identifying the nature and location of the injury, they have limited ability to predict short and long-term outcome. Specific serum biomarkers could expedite diagnosis in sedated or unconscious patients prior to neuroimaging, as well as stratify brain injury for targeted intervention. The potential usefulness of blood biomarkers for brain injury assessment, including in some studies, hypoxic brain injury, has been extensively studied in the past 10 years. These biomarkers include S-100B,[1] neuron-specific enolase, NSE,[2] glial fibrillary acidic protein, GFAP,[3] myelin basic protein, MBP,[4] and tau protein,[5] among others.[6] In severe brain injury, all have shown varying degrees of correlation to clinical and outcome measures depending on the study. In hypoxic brain injury, S-100B and NSE exhibited a positive association with neurological outcome in a pediatric cohort following cardiac arrest.[7] S-100B was subsequently found to be superior to NSE, GFAP and brain derived neurotrophic factor (BDNF) for predicting outcome from hypoxic injury during cardiac arrest.[8] A limitation of S-100B, however, is that it is not specific for neuronal injury, reducing its utility in cases of multiple trauma and less than severe brain injury.[9]

A much less studied serum biomarker for brain injury assessment has been tau protein. Tau (MW 48–67 kDa depending on isoform) is a microtubule stabilizing protein primarily localized in central nervous system neurons, but also expressed at low levels in astrocytes and oligodendrocytes.[10,11] Tau elevation is observed in the cerebrospinal fluid (CSF) of patients with neurodegenerative disease[12] and severe head injuries,[13] suggesting its extracellular release during neuronal damage and a role as a biomarker with specificity for brain injury. Potential movement of elevated CSF tau across the blood brain barrier presents a possibility that measurements of tau in blood could provide a convenient peripheral window into brain/CSF status.[14] However, studies of tau in serum have been hampered by its low abundance (typically low pg/mL), and there are relatively few reports evaluating the usefulness of this biomarker for brain injury assessment. Ost and colleagues found that CSF tau correlated with outcome in 39 severe traumatic brain injury patients, but serum tau was immeasurable in the same patients.[15] In contrast, other groups have successfully measured serum tau in at least a proportion of patients and found significant associations between tau elevation and poor outcome in severe TBI.[5,16] Liliang and colleagues reported serum tau levels ranging from undetectable to 1882 pg/mL that were significantly associated with poor six-month outcome in 34 severe TBI patients ($P < 0.001$).[5] Contrasting results between groups may be due to the different sensitivities of the immunoassay methods used, as well as differences in timing of blood sampling. Currently there is little understanding of the time-dependence of tau appearance in serum following brain injury. A more sensitive method capable of precise serum/plasma tau measurements in all patients is needed to properly evaluate the clinical relevance of serum tau for brain injury assessment.

Recently an ultra-sensitive digital assay technology has become available for tau measurements.[17,18] We employed this technology in a retrospective observational pilot study of blood samples from 25 cardiac arrest patients to examine the time-dependence of tau appearance in serum, and to evaluate its prognostic significance for 6-month neurological outcome.

2. Methods

2.1. Study design and setting

The study was performed at the intensive care unit (ICU) at Uppsala University Hospital, Sweden. Unconscious patients with cardiac arrest were resuscitated with restoration of spontaneous circulation (ROSC). Hypothermia treatment to a body temperature of 32–34 °C for 24 h, ventilation, and pharmacologic support were administered immediately after resuscitation as described.[8] Patients were defined as comatose if they were (i) not awake, (ii) not following any commands, and (iii) not responding to any stimuli. All patients received an arterial line in the radial or femoral artery for blood sampling. Serial blood samples were collected, starting as soon as possible in the emergency phase and continuing at 1, 2, 6, 12, 18, 24, 36, 48, 72, 96, and 108 h after cardiac arrest. Serum aliquots were frozen at −70 °C until tau analysis.

Patient outcome was assessed using the Glasgow–Pittsburgh cerebral performance category (CPC) scale at discharge from the intensive care unit and 6 months later.[19] The CPC scale ranges from 1 to 5, with 1 representing mildest possible neurological deficit (patient is able to return to work), and 4–5 representing the most severe deficit (vegetative) and death. A CPC of 1 or 2 was considered a good outcome ($n = 10$) and a CPC score of 3–5 a poor outcome ($n = 15$), as described.[8] For patients who died after discharge from the ICU, the better of the two scores was used, as recommended by the Utstein templates.[20]

2.2. Tau measurements

Serum samples were measured in triplicate with a novel immunoassay for total tau using digital array technology.[17] Limit of detection of the assay is 0.02 pg/mL, which is over 1000-fold more sensitive than conventional immunoassays (generally 30–60 pg/mL). The assay utilizes the Tau5 monoclonal for capture (Covance), and HT7 and BT2 monoclonal for detection (Pierce/Thermo). This combination of antibodies reacts with both normal and phosphorylated tau with epitopes in the mid-region of the molecule, making the assay specific for all tau isoforms.

2.3. Analyses

Tau elevation profiles were analyzed for area-under-the-curve (AUC) and receiver operating characteristics (ROC) with GraphPad Prism (v5.0d). AUC was evaluated during the first 24-h and over the full time course (to 108 h), assuming a baseline of zero. Four of the 25 patients died 24–48 h after admission, and data analysis for these patients were limited to the first 24 h. AUCs of delayed tau elevation peaks were evaluated with a baseline corresponding to the lowest tau concentration prior to elevation. Because the AUC data were non-Gaussian, the Mann–Whitney test was used for comparison of patients dichotomized by clinical outcome. AUC's were estimated by the trapeziod rule. Logistic regression modeling was used to generate ROC curves, and analyses included area, standard error, 95% confidence interval (CI), and P value. 95% CI's for ROC curves were calculated by Prism by a nonparametric method that makes no assumptions about the distributions of test results in the patient and control groups.[21]

3. Results

Eight Caucasian women and 17 Caucasian men, ranging in age from 25 to 85 years (mean 62 years) in cardiac arrest were resuscitated.[8] The patients exhibited systolic blood pressure

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