Serum Tau is predictive of 6-month neurological outcome following cardiac arrest

J.D. Randall,1 H. Zetterberg,2 E. Mortberg,3 S. Rautonen,1 P. Patil,1 E. Ferrell,1 D. Foumier,1 C. Kan,1 T. Campbell,1 A. Hruka,2 B. Plak1, K. Mihmelen,1 T. Pischl,3 D. Duffy,5 K. Blennow6 and D. Wilson2

1Quanterix Corporation, Cambridge, MA; 2Department of Surgical Sciences, Anaesthesia and Intensive Care, Uppsala University, Uppsala, Sweden; 3Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Molndal, Sweden.

Background

Tau, a microtubule associated protein, plays an important role in the assembly of tubulin monomers into microtubules and maintaining the cytoskeleton and axonal transport. The presence of tau in cerebrospinal fluid (CSF), serum or plasma is thought to represent neuronal damage from physical trauma or apoptotic death of neurons. During ischemic injury from cardiac arrest, cell death could occur from the initial hypoxic insult as well as an apoptotic cascade resulting in delayed neuronal death. The measurement of tau in CSF has been well documented, but the presence and measurement of tau in human blood components has been difficult due to inadequate sensitivity of current assay methods. A direct link between acute oxygen deprivation and the appearance of tau in human peripheral blood has not been previously described. We employed a new technology Single Molecule Arrays, SiMoA® capable of ultraselective protein measurements to look for changes in serum tau in patients following cardiac arrest and resuscitation, and to correlate these changes to 6-month neurological outcome.

Method

28 unselected patients with cardiac arrest were resuscitated with restoration of spontaneous circulation (ROSC). Serial blood samples were collected within 6h after cardiac arrest, and continued at intervals from 1-108h. Inclusion criteria included age, systolic BP, obtaining after ROSC, and a Glasgow Coma Scale. 17 Patient outcome was assessed in concordance with the Glasgow-Philadelphia cerebral performance category (CPC) scale as discharge from the intensive care unit and 6 months later. Serum aliquots were frozen until assay. Samples were measured in triplicate by SiMoA® Tau assay, which has a limit of detection of 0.05 pg/mL.

Results

Hypoxia induced changes in serum Tau

Time dependent elevations of serum tau were observed in all patients. Tau appearance as estimated by area-under-the-curve (AUC) was found to be significantly associated with neurological outcome (p<0.01). A many patients with poor neurological outcome, tau appeared in one or both of two major elevation peaks, the first occurring hours after cardiac arrest, and the second appearing days later. The magnitude of the second peak appeared to be of somewhat greater significance for long-term outcome than the first.

Conclusion

These data are the first to directly measure the effects of oxygen deprivation on the appearance of tau in human peripheral blood. The kinetics profile could be related to acute initial hypoxic injury followed by apoptotic neuronal death and/or damage associated with central swelling. Serum tau elevation was found to reflect a strong association with 6-month neurological outcome.