Trajectory clustering using latent class models for unsupervised TBI biomarker temporal phenotype discovery

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Abstract

Background: TBI biomarkers display population-level time-varying kinetics [1] which may be a rich source of pathobiological information [2]. At an individual level, deviations from stereotypical trajectories may represent different pathological processes or secondary insults. A method for discovering such phenotypes may be useful in individualising treatments in real-time.

Method: Serial blood (12hourly) and CSF (6hourly) samples were obtained from seventeen adult patients with severe TBI (Stockholm ethics committee approval #2009/1112-31). S100B and neuron-specific enolase (NSE) concentrations were measured along with blood:CSF albumin quotient Qa as a measure of blood-brain-barrier (BBB) integrity. S100B and NSE concentrations were log-transformed: Equivalent to the assumption of baseline exponential decay. We used trajectory modeling combining a quadratic mixed effects model with latent group analysis to search for characteristic trajectories in the measured parameter.

Results: For serum S100B, we discovered two phenotypes with fast and slow kinetics. The fast group corresponded with patients with more severe extracranial injury. For serum NSE, again two phenotypes were discovered; a time-decaying group and another with a peak around day 4.

CSF analysis yielded two latent groups for both S100B and NSE: a time-decaying group and another displaying prolonged elevation over several days.

Qa data clustered into three groups: two with fast, slow decay and another with prolonged elevation. The group with prolonged BBB permeability had corresponding poorer outcomes.

Conclusions: Small numbers prevent statistical comparison, but trajectory modeling identified a number of phenotypes with plausible pathobiological significance. In particular the technique revealed a group of patients with secondary serum NSE release and another with sustained BBB permeability. Such groups seem to relate to injury profile and outcome suggesting biological relevance. To our knowledge this is the first use of an unsupervised clustering technique in kinetic phenotype discovery.

References:

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