NEURON-SPECIFIC ENOLASE: An Introduction

Written by Jenny Chu
Presented by Philippa Holdaway
Wellington SCL
“In a dark place we find ourselves, and a little more knowledge lights our way.”

- Yoda  (George Lucas)
OVERVIEW

- What is NSE?
- NSE and Neuroendocrine Tumours
- NSE levels and OOHCA
- Issues w/ establishing appropriate thresholds
- Future Avenues of Research?
WHAT IS NSE?
WHAT IS NSE?

- Isoform of the enzyme enolase
- Involved in glycolysis
- Biological half-life = 24 hours
WHAT IS NSE?

- **NSE IS VERY ORGAN-SPECIFIC.** Located in:
  - **Neurons**
    - Specialised cells making up nervous system. Highly metabolically active.
  - **Neuroendocrine cells**
    - Receive neuronal input and in response release message molecules into blood
  - **RBCs and Platelets** = pre-analytical interference

- When these cells are injured e.g. traumatic brain injury:
  - NSE leaks out of the cell = Higher NSE levels measured in serum
APPLICATIONS
NSE AS A TUMOUR MARKER

- Neuroendocrine cells synthesise NSE.

- Tumours derived of neuroendocrine cells retain the ability to produce NSE
  - Malignant proliferation of neuroendocrine cells leads to increased NSE levels in serum.

- Valuable for diagnosis, staging, and treatment of neuroendocrine tumours (NETS) e.g. small cell lung cancer (correlates with tumour burden, number of metastatic sites, recurrences and response to treatment)
OTHER PROPOSED USES

• Neuronal:
  • Traumatic Brain Injury
  • Creutzfeldt-Jakob disease
  • Neurodegenerative diseases? – Dubious on this point
  • Stroke
  • Neuronal damage secondary to other disease states e.g. sepsis, metastatic cancer (e.g. breast cancer study)
  • **Severe hypoxic ischaemic encephalopathy**

• Other neuroendocrine malignancies:
  • Pheochromocytoma (cells of adrenal medulla)
NSE: POST CARDIAC ARREST
SUDDEN CARDIAC ARREST

• Leading cause of mortality, and neurologic disability in survivors.

• Cardiac arrest > cerebral blood flow stops > hypoxic ischaemic brain injury
  • Range from mild cognitive deficits to persistent vegetative state.

• Current prognostic variables
  • EEG, Somatosensory-evoked potentials (SSEP), imaging techniques (CT, MRI), Glasgow outcome score
TIME COURSE OF NSE

But when is the right time to measure?

- **Schoerkhuber et al. (1999)** determined NSE concentration measured 72-hours post-ROSC (*return of spontaneous circulation*) = best predictor of neurological outcome. Found significant differences in serial NSE measurements in those with poor vs. Good outcome.

- **Vondrakova et al. (2017):** ‘The highest associations of NSE with outcomes were observed on day 4 and day 3 after cardiac arrest.’ Significant association with prognosis was also found for changes in NSE at different time points.
TIME COURSE OF NSE

• But production and secretion of NSE is a dynamic process!

• Could be more value in assessing NSE changes over time (serial measurements).
TIME COURSE OF NSE

Figure 2. Difference in the time course of NSE levels within 72 hours after ROSC between patients with a good neurological outcome (n=12) and those with a poor neurological outcome (n=14).

Results of a Multi-Centre Study on 1053 Patients. Kaspar et al.

- Suggested NSE equal to or >90 ug/L as a threshold that reliably predicts poor prognosis

- NSE equal to or <17 ug/L reliably predicted good prognosis.

NSE MEASUREMENT

- **Roche Immunoassay**
  - Sandwich electrochemiluminescence
  - Fully automated (18 min)
  - Must be measured with serum indices.
  - Measuring range: 0.05 - 370 ug/L

Non-invasive, rapid, not limited by sedation, easy to interpret
CARDIAC ARREST

CASE 1:

- 51 y/o male admitted to ICU, post-OOHCA, collapsed at home. CPR performed on the scene. ROSC after 31 minutes.

- Serum NSE level 57.4 ug/L (Above High Normal)

- Taken off life support following discussions with family.
CASE 2:
- 53 y/o male admitted to ICU, post-OOHC, collapsed at the gym. AED used on the scene. ROSC after 20 - 25 minutes.
- Serum NSE level 50.3 ug/L *(Above High Normal)*
- Failure to wake after 72 hours. Patient was extubated and referred to palliative care. Deceased.
CARDIAC ARREST

CASE 3:

- 28 year-old male, collapsed at home

- Assisted by paramedics crew who performed CPR & 2x shocks before achieving ROSC 20 mins post-CA

- **Day 1-2**: variable neurology, biting, thrashing
- **Day 4**: significant neurological improvement. GCS: E4V1M6 (all 4 limbs). Head CT normal.

**NSE = 20.7 ug/L** *(ref. < 17.1 ug/L)*
CASE 3 cont’d

- **Day 10**: patient discharged. Diagnosed with Brugada Syndrome

**Brugada Syndrome** – genetic disorder where electrical activity of the heart is abnormal. Increases risk of abnormal heart rhythms and sudden cardiac death.

> No cure. Implantable Cardioverter Defibrillator can be used in higher risk patients.
AN ETHICAL DILEMMA
AN ETHICAL DILEMMA

To prevent falsely suggesting a poor prognosis in these patients:

• Thresholds must be set in a manner that aims to predict poor prognosis with **high specificity**, at the cost of optimal sensitivity.

• **WSCL ICU Trial Thresholds:**
  • <17.1 ng/mL: suggests good outcome
  • >90 ng/mL: suggestive of poor prognosis
POTENTIAL AREAS TO EXPLORE

- Investigate optimal time of collection and serial measurements
- South Africa – use in penitentiaries
SUMMARY

- NSE levels correlate with disease states involving neuronal/neuroendocrine damage incl. hypoxic ischaemic encephalopathy

- Limitations exist – dynamic process, one measurement = just a snapshot in time! Consider serial measurements?

- Ethics – life support should not be terminated on the basis of a single biomarker level. Consider:
  - Dynamic approach to NSE and…
  - Comprehensive multimodal prognostication protocol
ACKNOWLEDGEMENTS

Max Reed, HoD Biochem WSCL

Dr Carol Siu, Chem Path WSCL

Dr Melissa Yssel, Chem Path WSCL
REFERENCES


REFERENCES CONT’D


REFERENCES CONT’D
