OMEGA-3 FATTY ACIDS FOR NEUROTRAUMA

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WHY ARE WE INTERESTED IN CLINICAL TRANSLATION IN NEUROTRAUMA?

Level One Trauma Centre
Royal London Hospital - >2,000 trauma patients/year
Neurotrauma in a context of polytrauma

Intervention in the “golden hour”
PRESENTATION OF TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) is the leading cause of morbidity and mortality worldwide under the age of 45.
THE IMPACT OF TBI

• In Europe:
  • 2.5 million people suffer a TBI each year
  • 1 million are admitted to hospital
  • 75,000 will die
• TBI is the leading cause of death and disability in young adults.
• The incidence in elderly patients is increasing.
• TBI can strike us all, but males are about twice as likely as females to experience a TBI.
• In younger patients Road Traffic Accidents are the most frequent cause of injury; in older patients falls.
• Moderate and severe head injury (respectively) are associated with a 2.3 and 4.5 times increased risk of Alzheimer’s disease.

Having suffered a TBI, annual mortality remains increased up to seven fold for at least 13 years.
In the US, the annual burden of TBI has been estimated at over $ 70 billion.

In patients with severe TBI, the life time cost per case is estimated at over $ 400,000, with disability and lost productivity cost outweighing medical and rehabilitation costs by a factor of 4.
HUMAN TBI IS VERY HETEROGENEOUS

What regime of treatment for what type of brain injury?
THE PATIENT CARE PATH IN TBI

WHEN WOULD OMEGA-3 BE ADMINISTERED?

(Maas et al 2017)
SECONDARY INJURY PATHWAYS IN TBI

- Trauma affects neurons and non-neuronal cells and triggers a cascade of processes which continue for years after the primary injury event.

(Load and Faden 2010)
TBI AS A CHRONIC CONDITION
PERSISTENT NEUROINFLAMMATION SIGNAL

Inflammation after Trauma: Microglial Activation and Traumatic Brain Injury

Anil F. Ramladhansingh, MRCP,1 David J. Brooks, MD, DSc,1 Richard J. Greenwood, FRCP,2 Subrata K. Bose, PhD,3 Federico E. Turkheimer, PhD,1 Kiri M. Kinnunen, PhD,4 Steve Gentleman, PhD,1 Rolf A. Heckmann, PhD,1,5 Karen Gunanayagam, BSc,1 Giorgio Gelosa, MD,1 and David J. Sharp, MRCP, PhD1

Imaging of the translocator protein (TSPO) reveals neuroinflammatory changes more than a decade after injury
**CHRONIC CONSEQUENCES OF TBI**

**THE TERTIARY INJURY**

(Wilson et al., 2017)

Function
- Disability or limitations to activity\(^1\)
- Limitations to societal participation (e.g., employment)\(^1\)
- Cognitive deficits\(^2,9\)
- Emotional problems\(^10\)
- Behavioural change\(^11\)

Disease
- Mild cognitive impairment\(^10,12\)
- Neurodegenerative diseases
  - Alzheimer’s disease or dementia\(^13,14\)
  - Parkinson’s disease or parkinsonism\(^15,16\)
  - Dementia with Lewy bodies\(^16,17\)
  - Frontotemporal dementia\(^17\)
  - Amyotrophic lateral sclerosis\(^18,18\)
  - Chronic traumatic encephalopathy\(^13,19\)
- Post-traumatic epilepsy\(^20,21\)
- Stroke\(^22,23\)
- Neuroendocrine disorders\(^24,25\)
- Psychiatric illness\(^26,26\)

Mortality
- Mortality of any cause or reduced life expectancy\(^22,28\)

Chronic traumatic encephalopathy
PRIORITIES FOR TBI RESEARCH

- Neuroprotection in the acute phase
- Develop biomarkers predictive of severity and of response to treatment
- Regeneration and restoration of circuitry
- Prevent complications (e.g. post-traumatic stress disorder, personality changes, secondary epilepsy)
THE TRANSLATIONAL PATH FROM PRECLINICAL RESEARCH TO THE CLINIC

$2.5-3 billion; 10-15 years
DOCOSAHEXAENOIC ACID HAS MULTIPLE CELLULAR TARGETS AND ACTIVE METABOLITES

- **Targets**: ion channels (dual pore mechano-activated background potassium channels - TREK-1), voltage-gated sodium channels, retinoid receptors (RXR), peroxisome proliferator receptors (PPAR), GPCRs...

- **Active metabolites** (resolvins, protectins...)

(Michael-Titus and Priestley, 2013)
EXPERIMENTAL EVIDENCE OF EFFICACY OF OMEGA-3 FATTY ACIDS IN NEUROLOGICAL INJURY MODELS

Original Article

Docosahexaenoic Acid (DHA) Provides Neuroprotection in Traumatic Brain Injury Models via Activating Nrf2-ARE Signaling

Xiaojuan Jing, Hongjian Pu, Xiaoming Hua, Zhishuo Wei, Dandan Hong, Jun Chen, and Yejie Shi

A combination of intravenous and dietary docosahexaenoic acid significantly improves outcome after spinal cord injury


Omega-3 polyunsaturated fatty acid supplementation improves neurologic recovery and attenuates white matter injury after experimental traumatic brain injury

Hongan Pu, Yanling Guo, Wenting Zhang, Lanting Huang, Guohua Wang, Anthony K. Lou, Ji Zhang, Pengyue Zhang, Rehara K. Leak, Yun Wang, Jun Chen, and Yanqin Gao

Neuroprotective after Cerebral Hypoxic-Ischemic Injury
SO, SHOULD OMEGA-3 FATTY ACIDS BE IN THE NEUROTRAUMA CLINIC NOW?
Very Early Administration of Progesterone for Acute Traumatic Brain Injury

CONCLUSIONS
This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI. (Funded by the National Institute of Neurological Disorders and Stroke and others; PROTECT III ClinicalTrials.gov number, NCT00622900.)

Figure 2: Efficacy Analysis with the Use of a Sliding Dichotomy Approach. In the sliding dichotomy approach, the GOS was dichotomized with analysis, but the split for dichotomy was differentiated according to the baseline prognostic risk. Prognostic groups (based on worst, intermediate, and best prognostic) were defined by baseline prognostic factors that included age, Glasgow Coma Scale motor score (≤ 2 vs. 3 vs. 4 vs. 5 or 6), scores range from 1 to 6, with lower scores indicating reduced motor response), pupillary response (bilateral response vs. unilateral response, no reactive pupils, or not testable), presence or absence of hypoxemia, presence or absence of hypotension, Marshall’s classification (I vs. II vs. III vs. IV vs. V or VI), and presence or absence of traumatic subarachnoid hemorrhage. The Marshall classification is based on a review of CT scans; scores range from 1 to 6, with a score of 6 or higher indicating visible pathologic changes or worse. The arrow indicates the split for sliding dichotomy differentiated according to prognostic risk. Values were based on a Cochran–Mantel–Haenszel chi-square test with adjustment for geographic region (Asia, Europe, North America, and South America).
MILD TBI – CONCUSSION
FIRST STEPS TOWARDS THERAPEUTIC USE
CONCUSSION CHANGES BRAIN CONNECTIVITY

Connectivity evaluated using functional infrared spectroscopy

(Hocke et al., 2018)

PPCS = persistent post-concussion symptoms
OMEGA-3 FATTY ACIDS AND NEUROPLASTICITY
THE RESTORATION OF CONNECTIVITY POST-NEUROTRAUMA

Dietary Omega-3 Fatty Acids Modulate Large-Scale Systems Organization in the Rhesus Macaque Brain

David S. Grayson,1,2 Christopher D. Kroenke,1,2,1 Martha Neurri,1,4 and Damien A. Fair2,3,5
1Center for Neurocognition, University of California, Davis, California 95616; 2Department of Behavioral Neurocognition, Advanced Imaging Research Center, UC Davis, Davis, California, USA; 3Department of Psychology, Oregon Health and Science University, Portland, Oregon 97239; and 4Division of Neurocognition, Oregon National Primate Research Center, Beaverton, Oregon 97005.

Motor Recovery at 6 Months After Admission Is Related to Structural and Functional Reorganization of the Spine and Brain in Patients With Spinal Cord Injury

Jingming Hou,1 Zimin Xiang,2,3 Rubing Yan,1 Ming Zhao,4 Yongtao Wu,1 Jianfeng Zhong,2 Lei Guo,2 Haitao Li,3 Jian Wang,3 Jixiang Wu,1 Tiansheng Sun,2,5 and Hongliang Liu1,6

Disruption of the axonal cytoskeleton post-injury
Release of Neurofilament L reflects the neuronal damage
DHA ONLY OR DHA PLUS ...?
PHOSPHOLIPIDS DECREASE IN TBI
SIMILAR OBSERVATIONS IN EXPERIMENTAL AND HUMAN TBI
Administration of Docosahexaenoic Acid, Uridine and Choline Increases Levels of Synaptic Membranes and Dendritic Spines in Rodent Brain

Richard J. Wurtman\textsuperscript{a} · Mehmet Cansev\textsuperscript{a, b} · Toshimasa Sakamoto\textsuperscript{a} · Ismail H. Ulus\textsuperscript{a, b}
The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer’s Disease: A Randomised Controlled Study

Hanneke de Waal¹, Cornelis J. Stam², Marieke M. Lansbergen³, Rico L. Wieggers³, Patrick J. G. H. Kamphuis³, Philip Scheltens¹, Fernando Maestú⁴, Elisabeth C. W. van Straaten²,³

Table 1
Nutritional composition of Fortasyn™ Connect, the nutrient combination in Souvenaid

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per daily dose³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eicosapentaenoic acid, mg</td>
<td>300</td>
</tr>
<tr>
<td>Docosahexaenoic acid, mg</td>
<td>1200</td>
</tr>
<tr>
<td>Phospholipids, mg</td>
<td>106</td>
</tr>
<tr>
<td>Choline, mg</td>
<td>400</td>
</tr>
<tr>
<td>Uridine monophosphate, mg</td>
<td>625</td>
</tr>
<tr>
<td>Vitamin E (alpha-tocopherol equivalents), mg</td>
<td>40</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>80</td>
</tr>
<tr>
<td>Selenium, μg</td>
<td>60</td>
</tr>
<tr>
<td>Vitamin B12, μg</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin B6, mg</td>
<td>1</td>
</tr>
<tr>
<td>Folic acid, μg</td>
<td>400</td>
</tr>
</tbody>
</table>

Souvenaid (125 mL [125 kcal] daily dose) contains Fortasyn Connect. Souvenaid is a registered trademark of Nutricia N.V. Fortasyn is a trademark of Nutricia N.V.
TBI AND DEMENTIA

SPECIALISED NUTRITION CONTAINING OMEGA-3 FATTY ACIDS AS PROPHYLAXIS

Summary

Background: Nutrition is an important modifiable risk factor in Alzheimer's disease. Previous trials of the multienriched Fortasyn Complete showed benefits in mild Alzheimer's disease dementia. LipiDiDiet investigated the effects of Fortasyn Complete on cognition and related measures in prodromal Alzheimer's disease. Here, we report the 24-month results of the trial.

Figure: Cumulative Incidence of Dementia by Traumatic Brain Injury (TBI) Severity

(Thau-Zuchman et al., 2018)
NEXT STEPS FOR OMEGA-3
FATTY ACIDS IN TBI
LOOKING INTO THE FUTURE

• TBI is increasingly recognised as a public health issue with massive impact

• There have been significant advances in the characterization of omega-3 fatty acids as neuroactive substances with unique structural and signalling roles

• There is increasing evidence of therapeutic potential of omega-3 fatty acids from the acute to the chronic phase post-trauma

• There are promising steps towards generation of clinically relevant data in pilot studies