ALCOHOL WITHDRAWAL:
UNDERSTANDING THE
PATHOPHYSIOLOGY OF WERNICKE’S
ENCEPHALOPATHY

Allan D. Thomson

Molecular Psychiatry Laboratory, Dpt. of Mental Health Sciences, University College London (UK); National Addiction Centre, Institute of Psychiatry, London (UK)
WERNICKE-KORSAKOFF SYNDROME

- Poor diet ± alcohol
- Thiamine deficiency
- WERNICKE’S ENCEPHALOPATHY
- Korsakoff Psychosis
Left untreated, thiamine deficit can cause severe brain damage resulting in death or progression to the chronic phase - Korsakoff’s Psychosis - characterised by:

- Short term memory deficit
- Confabulation
- Apathy

The acute phase - Wernicke’s Encephalopathy - is characterised by the classical triad of symptoms:

- Oculo-motor abnormalities
- Cerebellar dysfunction or ataxia
- Confusion
a) Ophthalmoplegia before treatment

b) Ophthalmoplegia after treatment with thiamine IV
YOU CAN’T TRUST THE TRIAD

97 cases WE (94 misuse alcohol) diagnosed PM
64 patients not diagnosed clinically

(Harper et al., 1986)
How common is Wernicke Korsakoff Syndrome

- 26,691 postmortems general hospitals
- 1.4% cases indicative WE

- In alcoholics neuropathological lesions WE
- 12.5%

- 35% WE + cerebellar degeneration (thiamine dependent)

- 80% cases not diagnosed prior to postmortem

(Harper et al., 2003)
Outcome of Wernicke's Encephalopathy

- **20%** Die
- **70%** i.e. (85% of 80%) Korsakoff's Psychosis
  - 50% of these require long-term care
- **10%** Recover

Adapted from Victor et al., 1989
THE AMNESIC SYNDROMES

“An abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient.”

VICTOR, COLLINS and ADAMS, 1971
DEFINITIONS OF MEMORY DISORDER:

• **Anterograde amnesia (A.A.)** = impairment in new learning i.e. in recall and recognition memory for episodes and facts arising after the onset of an illness or injury.

• **Retrograde amnesia (R.A.)** = loss of memory for episodes or facts which occurred before the onset of an illness or injury.
KORSAKOFF'S PSYCHOSIS

ADAPTATION to every new situation requires the acquisition of new information and its integration with past experience.

FAILURE TO MAKE NEW MEMORIES RENDERS THE PATIENT HELPLESS IN SOCIETY AND CAPABLE OF PERFORMING ONLY THE MOST HABITUAL ROUTINES.
21 September 2010

Dementia cost ‘to top 1% of GDP’

The costs associated with dementia will amount to more than 1% of the world's gross domestic product this year at $604bn (£388bn), a report says.
PREVALENCE OF SERIOUS ALCOHOL MISUSE IN UK

150,000 Hospital admissions per year (Strategy Unit 2003)
15-22,000 Deaths per year (Strategy Unit 2003)
78,000 Admissions to NHS hospitals mental or behavioural disorder associated with alcohol misuse (Strategy Unit 2003)
23,000 Admitted with acute intoxication (Strategy Unit 2003)
30,000 Episodes for alcohol dependence syndrome
1/3 all A & E attendances (Strategy Unit 2003: Royal College Physicians 2001)
20% General hospital admissions have alcohol problems (Strategy Unit)
Peak age for alcohol related deaths men and women 1991 was 70 years and in 2000 is 55-70 years (Strategy Unit 2003)

Thomson AD & Marshall EJ Alcohol & Alcoholism, 159-167, 2006
It was recently estimated that, at any given time, there are more than 3 million people in the UK who are either malnourished or at risk of malnutrition.

93% are living in the community, including 2–3% of whom are in sheltered housing, with 5% in care homes and 2% in hospital.6

The number of malnourished people leaving NHS hospitals in England has risen by 85% over the past 10 years.

Recently the UK government admitted that nearly 140,000 patients left hospital in 2006–7 suffering from malnourishment

Malnourished people leaving NHS hospitals in England increased by 85% in ten years

Up to 70% of malnourished patients undiagnosed

Around 70-80% patients enter and leave hospital without correction of the malnutrition
THE LETHAL COMBINATION: THIAMINE DEFICIENCY PLUS ALCOHOL

DIETARY DEFICIENCY ALONE

WERNICK’S ENCEPHALOPATHY DUE TO DIETARY DEFICIENCY ALONE CAN BE CURED WITH RELATIVELY SMALL DOSES OF ORAL THIAMINE AND RARELY LEADS TO KS

THIAMINE DEFICIENCY AND ALCOHOL

WERNICK’S ENCEPHALOPATHY IN ASSOCIATION WITH ALCOHOL MISUSE MAY REQUIRE UP TO 1 GRAM OF THIAMINE INTRAVENOUSLY IN THE FIRST 24 HOURS AND 56% - 84% CAN DEVELOP KS WITH SMALLER IV DOSES
It is important to realise that when an individual begins to drink heavily and to develop the first signs of thiamine deficiency they are starting on a lethal downward spiral of destruction.

They will gradually accumulate more and more damage to different bodily functions which will interfere with thiamine utilisation and combine to make their recovery ultimately impossible.

If you understand what is happening you can reverse this process.

If you miss the opportunity to help them they may become permanently brain damaged.

*Your patient your call*
PATHOPHYSIOLOGY OF WERNICKE’S ENCEPHALOPATHY

Genetic predisposition to damage

Inadequate thiamine (vitamin B1) intake

Thiamine Transport problems – gut, blood brain barrier, neurone

Increased demands for thiamine – DT’s, detoxification NDM receptor

Alcohol intake – neurotoxicity, damage to apoenzymes – increased metabolic demands

Organ damage – liver storage, reduced thiamine phosphorylation

Magnesium deficiency

Predisposing diseases

Inadequate treatment
THIAMINE

Daily requirement 1-2mg
men 1.4; women 1.0

Body stores are small.
Liver: 3-4 mg. Total body ?30 mg

Depletion soon reflected in reduced circulating levels and reduced stores
Liver controls 11.5 pg/µg
Severely fatty liver 1.6 pg/µg

Dietary sources of vitamin B1 include whole grains, brewer's yeast, organ meats, lean pork, seeds/nuts and legumes.
OTHER FACTORS AFFECTING THIAMINE ABSORPTION AND UTILIZATION

FOLATE DEFICIENCY
Deficiency of folic acid and thiamine depletion itself can cause malabsorption of thiamine from the gastrointestinal tract.

THIAMINE TRANSPORT/PHOSPHORYLATION
The effectiveness of the various transport systems, and the subsequent phosphorylation required for thiamine to become the co-enzyme, may contribute to how well an individual copes with thiamine deficiency or responds to therapy.

ETHANOL
- Accelerates cerebellar metabolism of thiamine (LaForenza et al., 1990)
- Inhibits thiamine pyrophosphokinase
- Inhibits the renal tubular reabsorption of filtered thiamine is exacerbated by furosamide therapy (Hoffman and Goldfrank, 1989)

MAGNESIUM
Magnesium is required as a cofactor for many thiamine dependent enzymes and deficiency of this metal may also induce clinical signs of thiamine deficiency.

OTHER FACTORS AFFECTING BIOAVAILABILITY OR METABOLISM THIAMINE
- Gastrointestinal carcinoma
- AIDS, Anorexia and Anorexia nervosa,
- Multiple organ failure,
- Rapid parenteral carbohydrate loading
Thiamine diphosphate acts as a co-factor for a number of thiamine-dependent enzymes. Thiamine deficiency leads to a reduction in the activity of these enzymes, and this further leads to alterations in mitochondrial activity, impairment of oxidative metabolism, decreased energy status and eventually selective neuronal death. (Hazell AS, Butterworth RF. Update of Cell Damage Mechanisms in Thiamine Deficiency: Focus on Oxidative Stress, Excitotoxicity and Inflammation. Alcohol Alcohol 2009; 44(2): 141-7.

The pathophysiological changes inherent to WE are initially reversible with administration of parenteral thiamine. Without adequate treatment these changes become permanent. (Sechi GP, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007; 6:442–455.)
Relationship between the dose of radioactive thiamine given orally and the cumulative 72h urine radioactivity. 200 mg of non-radioactive thiamine hydrochloride was given intravenously with each oral dose.
The radioactivity in the serum and urine after administration of 5.0mg of radioactive thiamine orally to 3 healthy subjects with and without prior administration of ethanol (1.5gm per kilogram); 200mg of nonradioactive thiamine was given intravenously along with the oral dose.
The radioactivity in the serum and urine after administration of 5.0 mg. of radioactive thiamine orally to 12 malnourished alcoholic patients before and after treatment; 200 mg. of nonradioactive thiamine was given intravenously along with the radioactive thiamine.
THIAMINE HYDROCHLORIDE MALABSORPTION IN MAN

M Malnutrition Malabsorption

A Alcohol (1/3) Malabsorption

M + A Increases Malabsorption
Oral dose absorption of thiamine is greatly reduced in malnourished and/or chronic alcohol misusers. Prompt restoration of thiamine levels is essential to prevent neurological sequelae.

SLC19 GENE FAMILY

SCL19A1 Regulates folate influx plus mono- & pyrophosphate derivatives of thiamine

SCL19A2 High affinity thiamine transporter

SCL19A3 Low affinity thiamine transporter
Mitochondria

TCA CYCLE

Isocitrate
α-Ketoglutarate

Succinate

α-KGDHC

Thiamine transporters

- SLC19A2
- SLC19A3

Adapted from Singleton and Martin, 2001
## UCL PROJECT- Candidate Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>WKS NSW</th>
<th>WKS UK</th>
<th>UK Alcoholics</th>
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<tbody>
<tr>
<td><strong>SLC19A2</strong></td>
<td>Mutation screening: 3’ UTR base pair change</td>
<td>In progress</td>
<td>In progress</td>
</tr>
<tr>
<td>(Guerrini et al., 2005)</td>
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<tr>
<td><strong>SLC19A3</strong></td>
<td>Mutation screening: intron 1 Indel</td>
<td>No association</td>
<td>No association</td>
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<tr>
<td>(Guerrini et al., in preparation)</td>
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<tr>
<td><strong>OGDH (E1K)</strong></td>
<td>Mutation screening: no genetic variants</td>
<td>No association</td>
<td></td>
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<tr>
<td><strong>Transketolase</strong></td>
<td>2D-Proteomics studies (Alexander-Kaufman et al., 2006-2007)</td>
<td>No association</td>
<td>In progress</td>
</tr>
<tr>
<td>(Guerrini et al., in preparation)</td>
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FUNCTION NMDAR RECEPTOR
The NMDA-type glutamate receptor (NMDAR) plays an essential role in synaptic plasticity and learning and memory. It is well established that the NMDAR is a major target of alcohol (ethanol) in the brain and has been implicated in ethanol-associated phenotypes such as tolerance, dependence, withdrawal, craving, and relapse.

EFFECTS OF ALCOHOL ON NMDA RECEPTOR
Chronic alcohol exposure blocks NMDA receptor at glutamine site causing an increase in glutamate receptors (UP REGULATION).

Cessation alcohol frees receptors to accept more glutamate.

HYPERACTIVE STATE
Thiamine deficiency causes an increase in glutamate

INCREASES EXCITABILITY
INCREASES THIAMINE REQUIREMENT

Administration of thiamine reduced raised glutamate levels thus reducing excito-toxicity.
How far down the road is your patient?
Clinical evaluation of patients at risk of thiamine deficiency

Patients may present with different combinations of symptoms and signs.

Clinical history

- Weight loss in past year
- Reduced Body Mass Index
- General clinical impression of patient's nutritional status
- High dietary carbohydrate intake
- Recurrent episodes of vomiting in past month
- Co-occurrence of other nutritionally related conditions (polyneuropathy, amblyopia, pellagra, anaemia)

Early signs—symptoms of thiamine deficiency
- Loss of appetite
- Nausea/vomiting
- Fatigue, weakness, apathy
- Giddiness, diplopia
- Insomnia, anxiety, difficulty in concentration
- Memory loss Later signs—symptoms

• Classic triad: oculomotor abnormalities, cerebellar dysfunction (ataxia) and confusion
• Quiet global confusion with disorientation in time/place
• Confabulation/hallucination. Onset of coma.
DOSE OF THIAMINE HYDROCHLORIDE REQUIRED TO TREAT WERNICKE’S ENCEPHALOPATHY

DOSE THIAMINE HYDROCHLORIDE

50 MG THIAMINE ORALLY INADEQUATE

100-250 MG THIAMINE IM/IV – 56%-84% DEVELOP KF

DOSES OF UP TO 1GM OF THIAMINE HYDROCHLORIDE MAY BE REQUIRED INITIALLY TO ACHIEVE A CLINICAL RESPONSE

Nakada, T & Knight, RT 1984

Linbert MC & Oyler, RA 1990

LINGFORD-HUGHES ET AL. J. PSYCHOPHARMACOLOGY, 2004
Diagnosis and treatment of Wernicke’s Encephalopathy

Patients with a history of alcohol misuse with one, or more, of the following otherwise unexplained symptoms:

- Ophthalmoplegia
- Ataxia (not due to intoxication)
- Acute confusion (not due to intoxication)
- Memory disturbance
- Comatose/unconscious
- Unexplained hypotension & hypothermia

A presumptive diagnosis of Wernicke’s Encephalopathy should be made.

Despite the relatively rare occurrence of anaphylactoid reactions administration should take place in surroundings where resuscitation facilities are available.

Treatment of alcoholics with withdrawal related neuropsychiatric symptoms:

Administer a minimum of 500 mg thiamine hydrochloride IV t.d.s. for 3-5 days.

Dilute thiamine with 50-100ml of normal saline and infuse over 30 minutes.

Check Mg++ level.

No Response:

- Discontinue supplementation.
- Unless patient comatose/unconscious or diagnosis WE confirmed by other means.

Response:

250 mg thiamine once daily for 5 days (in patients with ataxia, polyneuritis, memory disturbance - continue treatment for as long as improvement continues).
Hypomagnesemia
(begins treatment for low normal or low serum magnesium)

• Assume an average deficit of 2 mEq/kg magnesium and replace as outlined:23
  • 6 g IV, first 3 h
  • 5 g IV, each of next 12 h
  • 5 g/d, each of next 4 d
• Reduce doses and increase monitoring for renal impairment

Malnutrition

• Multivitamins

Martin Dunitz, London, 2006, 1677-1685
Patients with WE due to thiamine deficiency alone can be successfully treated with small doses of oral thiamine. Patients who develop WE while misusing alcohol require large parenteral doses sometimes as much as 1 gram in 24 hours.

- **POSSIBLE GENETIC PREDISPOSITION TO DAMAGE/DISFUNCTION OF THIAMINE TRANSPORT OR UTILIZATION**
- **GRADUAL REDUCTION OF THIAMINE SUPPLY TO THE TISSUES DUE TO INADEQUATE DIETARY INTAKE, MALABSORPTION (DUE TO DAMAGE CAUSED BY ALCOHOL AND/MALNUTRITION)**
- **IMPAIRED TRANSPORT INTO MANY CELLS INCLUDING NEURONE.**
- **DAMAGE TO APO-ENZYMES, DAMAGE TO NMDR AND OTHER CHANNELS**
- **INCREASED DEMANDS FOR THIAMINE DUE TO REPEATED EPISODES OF ALCOHOL WITHDRAWAL**

Treatment following an acute episode of WE will not only have to supply the increased requirements for thiamine as suggested above but also compensate for any long term damage caused by all of the biochemical/structural changes precipitated by the acute WE event.
CONCLUSIONS (1)

a) There is evidence of unrecognised thiamine deficiency in patients both in the Community and in hospital

b) Patients in general hospitals with WE are not identified in 80% cases before autopsy and die as a result or survive but develop KS due to inadequate treatment.

c) Early signs and symptoms have been identified to aid in the diagnosis

d) The Study of the pathophysiology of WE confirms that multiple factors such as dietary deficiency of thiamine, malabsorption, excessive loss and impaired utilisation all play a part in compromising the individual.

e) These factors operate together to create an inadequate supply of thiamine to the brain and when this becomes critical the brain damage characteristic of WE occurs.

f) Thiamine deficiency and alcohol is a LETHAL COMBINATION
   In contrast to patients who have non-alcoholic WE, whose who have WE in association with alcohol misuse must be treated with large IV doses of thiamine (Pabrinex) sometimes requiring 1 gram in 24 hours.
g) RECOMMENDATIONS have been made for the dose of thiamine required for prophylaxis and treatment of WE but no formal dose-ranging placebo-controlled studies on the use of B-complex vitamins in alcoholics exist. Knowledge of appropriate thiamine dose is based in uncontrolled trials and empirical practice.

h) When the patient presents in the Accident and Emergency department it is important to decide how far along this destructive pathway they are and whether they require IV prophylactic treatment or the full recommended treatment for WE.

i) Correct other brain nutritional deficiencies.

j) Guidelines should be clear, simple, readily available, easy to fill-in and regular audits should take place to ensure that they are appropriately and correctly used.

m) A system for recording treatment clearly and accurately is essential so that everybody knows what treatment the patient has received.

n) Thiamine (Pabrinex in UK) is a cheap, effective and safe drug whereas; inadequate treatment can lead to expensive long term care and/or to litigation. Patients must have an adequate supply of magnesium present.
It is better to give too much thiamine too soon than to give too little too late.
Association between SLC19A3 genetics markers and Wernicke Korsakoff Syndrome

23 SNP markers we selected for genotyping in 109 cases of WKS and 222 psychiatrically screened, ancestrally matched controls (2 markers failed quality control procedures).

Four of the markers showed evidence of association with WKS (P=0.0196-0.0394).

The exons of SLC19A3 will be screened for polymorphisms and/or mutations in the WKS DNA samples.
Special Issue: Alcohol Related Brain Damage


Jonathan Chick and Philippe de Witte
Editorial

E. Jane Marshall, Irene Guerrini and Allan D. Thomson
Introduction: The Seven Ages of Man… or Woman (Shakespeare)

Consuelo Guerrini, Alissa Bazinet and Edward P. Riley
Foetal Alcohol Spectrum Disorders and Alterations in Brain and Behaviour

Fulton T. Crews and Kim Nixon
Mechanisms of Neurodegeneration and Regeneration in Alcoholism

Roberta J. Ward, Frederic Lallemant and Philippe de Witte
Biochemical and Neurotransmitter Changes Implicated in Alcohol-Induced Brain Damage in Chronic or ‘Binge Drinking’ Alcohol Abuse

Clive Harper
The Neuropathology of Alcohol-Related Brain Damage

Alan S. Hazell and Roger F. Butterworth
Update of Cell Damage Mechanisms in Thiamine Deficiency: Focus on Oxidative Stress, Excitotoxicity and Inflammation

Michael Kopelman, Allan D. Thomson, Irene Guerrini, UCL and E. Jane Marshall
The Korsakoff Syndrome: Clinical Aspects, Psychology and Treatment

Edith V. Sullivan and Adolf Pfefferbaum
Neuroimaging of the Wernicke-Korsakoff Syndrome

Irene Guerrini, Allan D. Thomson and Hugh M. Gurling
Molecular Genetics of Alcohol-Related Brain Damage

Izuru Matsumoto
Proteomics Approach in the Study of the Pathophysiology of Alcohol-Related Brain Damage.

Rosanna Mancinelli and Mauro Caccanti
Biomarkers of Alcohol Related Thiamine Deficiency
ALCOHOL AND ALCOHOLISM

The Wernicke-Korsakoff Syndrome (WKS)
THE CLINICAL COLLECTION

Carl Wernicke
(1848–1904)

Sergei Korsakoff
(1851–1900)

International Journal of the Medical Council on Alcohol
Journal of the European Society for Biomedical Research on Alcohol

WERNICKE-KORSAKOFF SYNDROME

THE CLINICAL COLLECTION

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1. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse
   Alcohol & Alcoholism Vol. 33 No. 4 pp 317–326 1998

   Alcohol & Alcoholics Vol. 35 Suppl. 1 pp 2–7 2000

3. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department
   Alcohol & Alcoholics Vol. 37 No. 6 pp 515–521 2002

4. The natural history and pathophysiology of Wernicke's encephalopathy and Korsakoff's psychosis
   Alcohol & Alcoholics Vol. 41 No. 2 pp 151–158 2006

5. The treatment of patients at risk of developing Wernicke's encephalopathy in the community
   Alcohol & Alcoholics Vol. 31 No. 2 pp 159–167 1996

6. Review: Wernicke's encephalopathy revisited: Translation of the case history section of the original manuscript by Carl Wernicke 'Lehrbuch der Gehirnkrankheiten fur Aerzte und Studirende' (1881) with a commentary
   Alcohol & Alcoholics Vol. 42 No. 2 pp 174–179 2008

7. Wernicke's encephalopathy: 'plus ca change, plus c'est la meme chose'
   Alcohol & Alcoholics Vol. 43 No. 2 pp 185–186 2008

The following articles are from Alcohol & Alcoholism Special Issue – ALCOHOL RELATED BRAIN DAMAGE Vol. 44 Issue 2 March–April 2009

8. The Seven Ages of Man… (or Wernicke)

9. The Korsakoff syndrome: clinical aspects, psychology and treatment

10. Molecular genetics of alcohol related brain damage