Wernicke-Korsakoff syndrome

Wernicke-Korsakoff syndrome (WKS) is a spectrum of disease resulting from thiamine deficiency, usually related to alcohol abuse [1].

Wernicke's encephalopathy was originally described by German neurologist Karl Wernicke in 1881 as a classic triad of symptoms (mental confusion, ataxia and ophthalmoplegia).

Korsakoff's syndrome is the late manifestation of the condition, where Wernicke's encephalopathy has not been adequately treated [2].

Epidemiology [2] [3]

- Alcohol-related brain damage may contribute to between 10% and 24% of all cases of dementia.
- The incidence of the Korsakoff's syndrome has been reported to be rising in recent years.
- The average global prevalence of Korsakoff's syndrome varies from 0-2% but is higher in the homeless, older individuals living alone or in isolation, and psychiatric inpatients.
- The prevalence does not reflect the alcohol consumption per capita. In France, where wine drinking is commonplace, it is 0.4% whereas in Australia it is 3%.

Pathogenesis

Chronic alcohol consumption can result in thiamine deficiency by causing:

- Inadequate nutritional thiamine intake.
- Decreased absorption of thiamine from the gastrointestinal tract.
- Impaired thiamine utilisation in the cells.

People differ in their susceptibility to thiamine deficiency, however, and different brain regions also may be more sensitive or less sensitive to this condition. Thiamine is a cofactor required by three enzymes in pathways of carbohydrate metabolism:

- A reduction in thiamine can interfere with numerous cellular functions.
- MRI studies suggest that alcohol-related neuronal loss mainly affects thalamus, hypothalamus, and mammillary bodies [2].
- No change is found in basal ganglia, nucleus basalis, or serotonergic raphe nuclei.

Many of these regions, which are normal in those with uncomplicated alcohol dependency, are damaged in people with WKS.

Chronic subdural haematoma has been documented as a cause of WKS; the symptoms persisted after resolution of the haematoma as a result of organic atrophic changes of both the frontal and temporal lobes due to long-term compression [4].

It has also been reported following nutritional stress - eg, laparotomy for small bowel obstruction, followed by total parenteral nutrition for one month, bariatric surgery or rapid weight-loss [5]. Follow-up of thiamine status for at least six months after bariatric surgery is recommended [6].

Other chronic conditions that may cause a thiamine deficiency include AIDS, hyperemesis gravidarum, thyrotoxicosis, cancers that have spread throughout the body, long-term dialysis and congestive heart failure (when treated with long-term diuretic therapy).

Presentation

Any patient with alcohol misuse who presents with confusion, nausea and vomiting, fatigue, weakness or apathy should be considered at high risk of Wernicke's encephalopathy and treated appropriately. Unexplained hypotension or hypothermia should also heighten suspicion [3].

Symptoms

- Vision changes:
    - Double vision.
    - Eye movement abnormalities.
    - Eyelid drooping.
- Loss of muscle co-ordination:
    - Unsteady, unco-ordinated walking.
- Loss of memory, which can be profound.
- Inability to form new memories.
- Hallucinations.

Signs

The patient is usually mentally alert with vocabulary, comprehension, motor skills, social habits and naming ability maintained.

- Examination of the nervous system may show polyneuropathy.
- Reflexes may be decreased (or of abnormal intensity), or abnormal reflexes may be present.
- Gait and co-ordination are abnormal on testing.
- Muscles may be weak and may show atrophy.
- Eyes show abnormalities of movement - nystagmus, bilateral lateral rectus palsy and conjugate gaze palsy.
- Blood pressure and body temperature may be low.
- Pulse may be rapid.
- The person may appear cachectic.

In addition there are the following cognitive features.

Confabulation

- Falsification of memory in clear consciousness - very characteristic of the syndrome.
- Can answer questions promptly with inaccurate and sometimes bizarre answers.

Memory loss

- Anterograde amnesia is the main feature of the syndrome. This is loss of memory for events occurring after the onset of the disorder.
- Inability to learn and repeat simple pieces of information or learn new tasks.
- Often disorientated in time and place.

Retrograde amnesia

- Loss of memory for events before onset of the disorder.
- Some memory of distant events may be preserved.
- Telescoping of events is characteristic - eg, the patient says something happened recently when it took place many years ago.

Encephalopathy

At least two of the four following criteria should be present to diagnose encephalopathy[6].

- Dietary deficiencies.
- Oculomotor abnormalities.
- Cerebellar dysfunction.
- Either an altered mental state or mild memory impairment.

Subclinical episodes can occur.

Differential diagnosis

- Drug misuse
- Alcoholic ketoacidosis
- Delirium tremens

- Dementia
- Chronic hypoxia
- Closed head injury
- Hepatic encephalopathy
- Post-ictal state
- Cerebrovascular disease
- Brain tumour

Investigations

Diagnosis is based mainly on the history and physical examination, and if the condition is suspected, treatment should not be delayed whilst waiting for test results.

- FBC, particularly looking at the MCV.
- U&Es (to exclude hypernatraemia, hypercalcaemia, and uraemia).
- LFTs.
- Glucose.
- Blood arterial gases (to rule out hypercarbia and hypoxia).
- Cholesterol.
- Serum thiamine levels (vitamin B1) levels may be low.
- Pyruvate is elevated.
- Red cell transketolase activity is decreased in thiamine deficiency, but not usually necessary to diagnose the condition.
- Lumbar puncture may be needed to exclude nonfocal CNS infections.

If the history is significant for chronic (long-term) alcohol misuse, serum or urine alcohol levels may be elevated.

Imaging

CT head scan may be useful in the acute phase, but is less sensitive than MRI. Diffusion-weighted imaging (an enhanced view based on local water diffusion properties) can improve MRI sensitivity [7].

Other procedures

Electroencephalography (EEG) may be required to rule out convulsive or non-convulsive status epilepticus.

Associated diseases

- Peripheral neuropathy.
- Paraesthesia.
- Malnutrition.
- Liver disease.
- Delirium tremens (around 10%).
- Beriberi (about 5%).

Management [3]

- A multidisciplinary service tailored to the needs of individual patients, including the management of alcohol misuse.
- Assessment and re-assessment of memory and intellectual impairment in the intermediate term.
- Flexible services ranging from specialised residential home care to domiciliary support should be available.
- Occupational therapy assessments of daily living and neuropsychological assessments of current cognitive function can help to determine whether the patient can go home and, if so, the nature and degree of help and supervision needed.
- The Mental Capacity Act and, on occasions, the Mental Health Act may have to be considered in the early stages of the syndrome.

General principles

Management depends on the underlying cause. In most cases, the aetiological factor is alcohol misuse, aggravated by poor diet. These need to be addressed. Treat as a medical emergency if symptoms are acute. Patients presenting with altered mental state or pre-coma may need oxygen and intravenous rehydration. Comatose patients may require intubation to maintain airway patency.

Pharmacological

- Thiamine orally (IM or IV may be used in secondary care) plus vitamin B complex or multivitamins, which should be given indefinitely. Treatment with thiamine is often started under specialist care, although when deficiency is suspected, it should be started in primary care.
- Offer oral thiamine to harmful or dependent drinkers if either of the following applies[8]:
    - They are malnourished (or have a poor diet); prescribe oral thiamine 50 mg per day (as a single dose) for as long as malnutrition may be present.
    - They have decompensated liver disease.
- A Cochrane review found there was insufficient evidence from randomised controlled clinical trials to guide clinicians in the dose, frequency, route or duration of thiamine treatment of WKS due to alcohol misuse[9]. However, the British National Formulary recommends 25-100 mg orally daily for mild thiamine deficiency and 200-300 mg orally daily for severe deficiency[10].

- Although potentially serious allergic adverse reactions may (rarely) occur during, or shortly after, parenteral administration, the Medicines and Healthcare products Regulatory Agency (MHRA)/Commission on Human Medicines have recommended that [10]:
    - This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of WKS where treatment with thiamine is essential.
    - IV administration should be by infusion over 30 minutes.
    - Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.

Complications

A percentage of patients with Wernicke's encephalopathy develop Korsakoff's syndrome. Only 20% of such patients recover completely, and a significant number require long-term care.

The development of Korsakoff's syndrome may depend in part on the degree of alcohol-related neurotoxicity that occurs before thiamine prevention is instituted, but other dietary deficiencies and the direct neurotoxic effect of alcohol may play a part [1].

- Korsakoff's syndrome can develop in untreated or undertreated Wernicke's encephalopathy.
- Symptoms of alcohol withdrawal syndrome (tremors, hallucinations, convulsions) can complicate the picture.
- Recurrences of encephalopathy can occur in patients who continue to drink alcohol and fail to maintain their thiamine intake, and in non-alcohol-dependent people with persisting thiamine deficiency due to non-compliance or untreated secondary disease.
- Congestive heart failure may be a complication.
- Vertical nystagmus may resolve slowly, but fine horizontal nystagmus may persist indefinitely. Most other ocular symptoms resolve rapidly.

- Ataxia may persist and cause a slow shuffling gait.
- Global confusion state may be slow to resolve, and there may be persisting learning difficulties and memory impairment.

Prognosis[3]

Wernicke's encephalopathy is a medical emergency. Untreated, it leads to death in up to 20% of cases, or to the Korsakoff's syndrome in 85% of survivors. Up to 25% of the Korsakoff group will require long-term institutionalisation.

Prevention

- Alcohol avoidance.
- Patients with significant alcohol dependency should be given thiamine supplementation.
- Identifying which patients are at risk is not always easy but retrospective studies suggest that homeless patients with inadequate social support are at greatest risk.
- Identification of individuals at risk of alcohol-related brain disorder, institution of care plans and adequate follow-up arrangements for such individuals may be as important as thiamine replacement[11].

Further reading

- NDR (Nutrition and Diet Resources) UK
- Nasir S, Abou Areda M, Ma EL, et al; Non-alcoholic Wernicke's encephalopathy: toxic ingestion or an honest mis-steak? J Community Hosp Intern Med Perspect. 2021 Jan 26;11(1):147-151. doi: 10.1080/20009666.2020.1843236.
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