Eponyms in medicine revisited

Wernicke–Korsakoff syndrome

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Wernicke’s disease and Korsakoff’s psychosis have been recognised since the end of the last century. The former is characterised by nystagmus, ataxia of gait, conjugate gaze palsy and mental confusion. These symptoms usually have an abrupt onset, occurring more often in combination. Wernicke’s disease is associated with nutritional deficiency, especially due to alcoholism.

Korsakoff’s psychosis is a mental disorder in which retentive memory is hugely impaired in an otherwise responsive patient. This disorder is also associated with alcoholism and malnutrition.

A symptom complex comprising both a defect in learning and memory and the manifestations of Wernicke’s disease is appropriately designated as the Wernicke–Korsakoff syndrome.

Historical features

The first description of the disease by Carl Wernicke in 1881 was of an illness of sudden onset with paralysis of eye movements, ataxia of gait and mental confusion. He observed it in three patients, two alcoholics and a patient with persistent vomiting after the ingestion of sulphuric acid, who presented with progressive stupor and coma, progressing to death. Wernicke described punctate haemorrhages affecting grey matter around the third and fourth ventricles and aqueduct of Sylvius and designated the pathology ‘polioencephalitis hemorrhagica superioris’.

In 1852, Magnus Huss mentioned a disturbance of memory in alcoholics, elucidated between 1887 and 1891 by the Russian psychiatrist SS Korsakoff, who considered that the polyneuropathy and the memory of disorder represented ‘two facets of the same disease’, which was designated psychosis polyneuritica (box 1).

The postulation that a single cause was responsible for both Wernicke’s disease and Korsakoff’s psychosis was first made by Murawieff in 1897.1

Epidemiology

Data on prevalence of Wernicke–Korsakoff syndrome have come mainly from necropsy studies (box 2).2-8 A pilot study of 31 consecutive alcohol-related deaths over an eight-month period revealed Wernicke’s encephalopathy in 17 cases. Analysis of the clinical records revealed that a disturbance of mental state was the commonest finding and neurological signs were present in only two of the 17 cases, showing that Wernicke’s encephalopathy may easily be overlooked as a cause of deterioration in mental state.9

A clinical diagnosis of Wernicke’s encephalopathy, Korsakoff’s psychosis or the Wernicke–Korsakoff syndrome is still being missed; for example, it was made in only 20% of the 131 cases in a necropsy study.10 The pathology may be overlooked due to the rigid traditional diagnostic criteria and to the subclinical forms of Wernicke’s encephalopathy which, following repeated episodes, can give rise to the pathological damage typical of the Wernicke–Korsakoff complex.11,12

Clinical features

The clinical triad described by Wernicke is composed of ophthalmoplegia, ataxia and disturbance of consciousness and mental state.13 The ocular abnormalities consist of nystagmus (horizontal and vertical), weakness or paralysis of external rectus muscles with impairment of conjugate gaze, accompanied by diplopia and internal strabismus. In advanced stages of the disease, miosis and nonreacting pupils can occur. Retinal haemorrhages occur occasionally, but papilloedema is rare.14

The ataxia is of stance and gait and, in the acute stage of the disease, can hinder walking or standing without support. Lesser degrees of the disorder can present with a slow walk and wide-based stance.

Summary

Alcohol abuse is one of the most serious problems in public health and the Wernicke–Korsakoff syndrome is one of the gravest consequences of alcoholism. The pathology is often undiagnosed in its less evident presentations, therefore an accurate diagnostic approach is a critical step in treatment planning. Treatment is based on restoration of thiamine, although this is insufficient to prevent the psychological decline of a great number of patients. The cognitive impact of the pathology is derived from the interaction of alcoholic neurotoxicity, thiamine deficiency and personal susceptibility. In this article, the literature concerning Wernicke-Korsakoff syndrome is reviewed.

Keywords: Wernicke-Korsakoff syndrome, amnestic disorders, alcoholism, thiamine deficiency

Wernicke–Korsakoff syndrome: original description

Carl Wernicke (1881)

- abrupt onset of paralysis of eye movements, ataxia of gait and mental confusion
- first designated as ‘polioencephalitis haemorrhagica superioris’
- punctate haemorrhages affecting grey matter around third and fourth ventricles and aqueduct of Sylvius.

SS Korsakoff (1887–1891)

- amnestic syndrome and polyneuropathy
- designated as ‘psychosis polyneuritica’
- two facets of the same disease

Box 1

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Accepted 7 February 1996
The disturbances of mental state and consciousness occur mostly as a global confusional state, in which the patient is apathetic, inattentive and with minimal spontaneous speech. The disturbances of consciousness and of mental state occur in all but 10% of patients. With prompt thiamine intake, the patient recovers alertness and some mental performance. Others, a minor proportion, show signs of alcohol withdrawal, with agitation, hallucinations, confusion and autonomic overactivity. Although stupor and coma are rare, a group of patients can have these initial manifestations of Wernicke’s disease, leading to death if untreated.

The characteristic Korsakoff amnestic state is marked by a permanent gap in memory, where the core disorder is a defect in learning (anterograde amnesia) and loss of memory (retrograde amnesia). Immediate memory is preserved, but short-term memory is impaired. The learning defect can render the patients incapable of all but the most habitual tasks. The disturbance is due to defective encoding at the time of original learning rather than exclusively to a defect in the retrieval mechanism. Long-term memory appears to be maintained through multifocal networks, rather than a specific anatomical spot, since a patient with severe lesions in areas thought to be specific for the Wernicke–Korsakoff syndrome proved to have excellent long-term memory.

Besides memory impairment, involving mostly free recall tasks of both verbal and nonverbal material, Korsakoff patients were inferior to non-Korsakoff alcoholics on tests sensitive to frontal lobe function, suggesting hypofrontality.

Confabulation is considered a hallmark of Korsakoff’s psychosis. In the early stages of the disease, confusion is profound and confabulation is evident and significant; in the convalescent phase, the patient recalls fragments of the past in a distorted manner. The statement that confabulation is a patient’s device to diminish embarrassment caused by a gap of memory is controversial.

Mild peripheral neuropathy is commonly associated with Wernicke–Korsakoff disease. Cardiovascular dysfunctions occur, usually as tachycardia, postural hypotension and electrocardiographic abnormalities, that resolve after thiamine administration. In the chronic stage of the disease, patients can show impaired capacity to discriminate between odours.

Korsakoff’s psychosis may occur as a feature of third ventricle tumours, infarction or surgical restoration of temporal lobes, or as a sequela of herpes simplex encephalitis. The Wernicke–Korsakoff syndrome associated with thiamine deficiency has been described in patients on dialysis, with acquired immunodeficiency syndrome, in hyperemesis gravidarum and following gastroplasty for management of obesity.

Neuropsychology

Several models have been proposed to account for the neuropsychological deficits. In the right hemisphere hypothesis, the psychological processes for which the right hemisphere appears dominant, such as perceptual–motor and visual–spatial skills are distinguished sensitive to the neurotoxic effects of alcohol. In the frontal lobe dysfunction hypothesis, abstraction and problem-solving deficits were credited to effects of alcohol on the frontal lobes. However, the current neurobiological hypothesis advocates a milder generalised brain dysfunction to explain the nonspecific and highly variable pattern of cognitive impairment.

Using the Wisconsin card sorting test and memory tests in Korsakoff patients, non-Korsakoff amnestic patients, patients with frontal lobe resection, and controls, it was found that memory impairment alone cannot account for the problem-solving difficulties of Korsakoff patients.

Investigations

Computed tomography (CT) and magnetic resonance imaging (MRI) evaluations of Wernicke’s encephalopathy revealed lesions in the medial portions of the thalami and midbrain, dilatation of the third ventricle and atrophy of mammillary bodies. Brain CT measurements revealed wider third ventricle and more dilated lateral ventricles in Korsakoff patients than in matched non-Korsakoff alcoholics, the widening of the interhemispheric fissures between the frontal lobes being particularly marked.

Brain shrinkage is detectable in a high proportion of alcoholic patients, with ventricular enlargement and widening of fissures and sulci over the hemispheres. Current drinking history seems to play a role in the pathology, since CT scans from members of Alcoholics Anonymous were closer to those of normal controls than to those of current alcoholics, although a degree of dilatation was found in certain cases.
Neurochemistry

Absorption of thiamine is impaired by both malnutrition and alcohol, which explains why its intake is reduced in alcoholics. The situation is often made worse by liver disease that leads to reduced body stores and impaired metabolism of thiamine. Liver dysfunction may also enhance the toxic effect of alcohol on the brain, possibly through imbalance in amino acid metabolism.

Personal susceptibility to the Wernicke–Korsakoff syndrome may be related to individual differences in thiamine enzyme systems. Different levels of affinity were found between thiamine pyrophosphate, which acts as coenzyme, and transketolase, an enzyme concerned with brain glucose metabolism. Nevertheless, there is little evidence to support the hypothesis of an inborn transketolase abnormality in Wernicke–Korsakoff patients, suggesting that extragenetic factors may explain the differences between these patients and matched normal controls. In an enzymatic and immunochemical study with fibroblasts of patients with Wernicke–Korsakoff syndrome, transketolase was found to be catalytically defective but immunochemically normal.

It is remarkable that about a third of subjects seem to be resistant to the development of the pathology, despite substantial alcohol abuse, suggesting that vulnerability to the Wernicke–Korsakoff syndrome is highly variable.

Physiological features

There is evidence of a relationship between the cognitive deficit and decreased hemispheric blood flow, with an association between regional abnormalities and specific cognitive impairment. The cerebral vascular transit time of patients with Alzheimer-type dementia and Korsakoff's psychosis was increased.

Reduced cerebral blood flow was found in chronic alcoholism, which recovered with thiamine and abstinence, and throughout cortical and subcortical structures of patients with Korsakoff's psychosis.

Pathology

Microscopic changes in the mamillary bodies are by far the most common finding in necropsy studies. The diagnosis of Wernicke–Korsakoff syndrome will be missed in about 25% of cases if brains are not examined microscopically, although macroscopic changes of the mamillary bodies have been documented during life in cases of Wernicke–Korsakoff syndrome by MRI.

In an attempt to evaluate the impact of a 'moderate' alcohol intake on the brain, several brain measures of 'moderate' drinkers (30–80 g of alcohol/day), alcoholics (more than 80 g of alcohol/day), alcoholics with cirrhosis, alcoholics with Wernicke's encephalopathy and a control group (teetotal or less than 20 g/day) were investigated. Although the difference in various brain measures between the moderate drinkers and the control group was not statistically significant, this autopsy study revealed a consistent trend in the measures suggesting loss of cerebral tissue, as evidenced by reduced cerebral weight, increased ventricular volume and pericerebral space, the main loss being in white matter.

White matter is composed of approximately 70% water, 20% lipids and 10% protein, and most of the latter two elements is combined to form membranes (myelin in particular). Demyelinating lesions show an increase in water content and a decrease in lipid content, thus reversing the pattern seen during maturation of the brain. The pattern of change in water and lipid content of the cerebral white matter of alcoholic patients is similar to the ageing pattern and to demyelinating lesions in the above-mentioned study. Rats exposed to alcohol for five months had significant reduction of branching of the dendritic areas in the hippocampus, which reverted after two months of abstinence.

Clinical and neuroradiological studies have shown that clinical deficits and brain shrinkage are reversible in a proportion of alcoholics, mainly young ones, following a prolonged period of abstinence. There may be two different pathological changes in white matter: an irreversible component due to neuronal death, similar to the pattern seen in Wallerian degeneration and a reversible lesion, characterised by subtle structural change, difficult to identify by histological examination.

In 131 cases of Wernicke's encephalopathy diagnosed at autopsy, most of them alcoholics, only 26 patients were diagnosed during life, raising the possibility that thiamine-dependent brain damage may exist in many alcoholics before it is suspected. The hypothesis of cumulative cerebral damage could help to explain why memory is so notoriously affected in many alcoholics and why Korsakoff syndrome does not respond well to thiamine.
Treatment

Treatment of Wernicke–Korsakoff syndrome should be started immediately with the administration of thiamine, since its use prevents the progression of the disease and reverses the brain abnormalities that have not resulted in fixed structural changes.1

Patients should be hospitalised and be given 50–100 mg of thiamine intravenously for several days3,19 because intestinal absorption is usually impaired in alcoholics.37 Hypomagnesaemia can compromise the treatment response and replacement therapy should be considered. The thiamine solution should be fresh, since it can be inactivated by heat.39 In spite of the risk of intestinal absorption impairment, maintenance treatment with oral dosages of 50 to 10 mg of thiamine three or four times daily for several months should be instituted. The patients should resume a balanced diet.

Recovery from ataxia after thiamine treatment can be incomplete, suggesting an irreversible (neuropathological) damage besides the reversible (biochemical) pattern of the disease.51

In attempts to assess the neurochemical aspects of the pathology, improvements in function have been reported with clonidine52,53 and fluvoxamine,54 suggesting dysfunction in noradrenergic and serotonergic systems, respectively.

Wernicke–Korsakoff syndrome complicates treatment of alcoholism. Alcoholics in cognitive decline respond poorly to psychotherapy and educational efforts, However, longitudinal studies of psychometrics show continuous improvement of mental state during periods of abstinance, but evidence of neuronal damage should be taken into account when planning treatment.55

Prognosis

The mortality rate is high, ranging from 10 to 20%, mainly due to pulmonary infection, septicemia, decompensated liver disease, and an irreversible stage of thiamine deficiency.1,19 The prompt institution of treatment can modify the prognosis of the Wernicke–Korsakoff syndrome. The ophthalmooplegia begins to improve within hours to days and nystagmus, ataxia and confusion within days to weeks.19 In about 60% of patients a residual nystagmus or ataxia may remain.1,19

Once established, the Korsakoff syndrome has a poor prognosis, leaving about 80% of patients with a chronic memory disorder. Evidence suggests that patients are capable of learning simple repetitive tasks involving procedural memory. The amnestic symptoms recover slowly and incompletely and the maximum degree of recovery may take a year or so.1 However significant recovery of cognitive function can occur, depending on factors such as age and continuous abstinence3 and cannot be predicted accurately during the acute stages of the illness. Interestingly, once recovered, the Korsakoff patient seldom demands alcohol, but will drink it if it is offered.

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The Editorial Board meeting of the Postgraduate Medical Journal, held in London on 25 September 1995.
Wernicke-Korsakoff syndrome.

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doi: 10.1136/pgmj.73.855.27

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