Korsakoff syndrome

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Synonyms
Alcohol-induced persisting amnestic disorder; Alcohol-induced encephalopathy; Korsakoff psychosis; Korsakoff's disease; Korsakoff's syndrome; Transketolase defect; Wernicke-Korsakoff syndrome

Key points
• The main clinical characteristic of Korsakoff syndrome is a disproportionate impairment in memory in comparison to other cognitive functions.
• Korsakoff syndrome is directly linked to a deficiency of thiamine.
• Korsakoff syndrome is frequently associated with chronic alcohol abuse, but has also been observed in the context of a number of other conditions that cause malnutrition or malabsorption.
• Treatment with thiamine may at least partially reverse the condition.

Historical note and nomenclature
In 1887, Korsakoff wrote the first of a series of papers describing a neurologic syndrome characterized by chronic changes in mental status and memory that often accompanied polyneuropathy. He noted the characteristic problems in new learning (anterograde amnesia) as well as the deficits in remembering past events (retrograde amnesia), and emphasized that these occurred in the context of clear attention and consciousness. He also commented on the fact that patients tended to confabulate, sometimes making up stories or events entirely, but more frequently confusing the temporal context of actually experienced events. A majority of patients who developed this syndrome had a history of chronic alcohol abuse, but Korsakoff also described the syndrome following other disorders such as prolonged vomiting, typhoid fever, and intestinal obstruction. He suggested that the common factor in these disorders might be the presence of a substance toxic to the nervous system.

Six years earlier in 1881, Carl Wernicke had described a neurologic syndrome of acute onset characterized by ataxia, ophthalmoplegia, nystagmus, polyneuropathy in the arms and legs, and a global confusional state. Although Korsakoff did not
make reference to Wernicke's work, he mentioned the presence of several of the same symptoms in his patients. Not until several years later was it realized that the symptoms described by Wernicke and Korsakoff often occur sequentially in the same patients (Gudden 1896). For this reason, the syndrome is also referred to as Wernicke Korsakoff syndrome. Occasionally, the term Korsakoff psychosis is used. In cases of alcoholic origin, the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) classification is alcohol-induced persisting amnestic disorder (American Psychiatric Association 1994).

Clinical manifestations

The principal manifestation of Korsakoff disease is a disproportionate impairment in memory in comparison to other cognitive functions. Most prominent is anterograde amnesia for both verbal and nonverbal information. Even in the face of multiple repetitions, patients are unable to learn new names, faces, or facts, and they forget events that happened shortly before. These deficits are not due to an inability to attend to incoming information, as patients can repeat information in the absence of any delay. However, as soon as any distracting activity is interposed, the information is forgotten. This sensitivity to interference is the principal characteristic of the memory impairment and is thought to be due to a combination of 2 factors: (1) a failure to fully encode all the aspects of incoming information, and (2) a failure of retrieval, stemming from an inability to inhibit competition from irrelevant information (Verfaellie and Cermak 1996). When comparing Korsakoff patients with non-Korsakoff alcoholics, it has been observed that Korsakoff patients present impairments of the different components of working and episodic memory; episodic memory is more significantly impaired in Korsakoff patients than in non-Korsakoff alcoholics. Furthermore, in Korsakoff syndrome a disproportionately large encoding deficit is observed (Pitel et al 2008; 2009). Executive function impairments can also be observed.

Retrograde amnesia is also a typical feature of the disorder, commonly extending back 25 years or more. Memory for autobiographical information as well as knowledge of public events and facts are affected. Regardless of the nature of the information, memories from childhood and early adulthood are remembered better than memories from the recent past. This temporal gradient is markedly steeper than that seen in dementing disorders such as Alzheimer disease (Kopelman 1989; Fama et al 2004). Retrograde and anterograde amnesia co-occur in Korsakoff disease, but the severity of these impairments is poorly correlated, suggesting that they reflect distinct underlying deficits.

Confabulations may also occur, although primarily in the acute (Wernicke) stage of the disorder. Two types of confabulation can be distinguished: provoked or spontaneous (Lorente-Rovira et al 2011). The former is more frequently observed in Korsakoff syndrome. Spontaneous confabulation involves an unprovoked outpouring of unrealistic episodic autobiographical claims (Borsutzky et al 2008; Glowinski et al 2008). These may represent a tendency for patients to fill in gaps in memory when faced with questions they cannot answer. More rarely, patients will spontaneously tell bizarre, unrealistic stories. But in general, patients confabulate in response to questions about experiential (episodic) memory and questions to which the answer is unknown (Van Damme and d'Ydewalle 2010). The presence and persistence of confabulation does not depend on the severity of the memory disorder, suggesting again that different mechanisms are involved. Furthermore, confabulation is not specific to Korsakoff syndrome, but is seen in a variety of patients with lesions in the frontal lobes, basal forebrain, or both. It is thought to be caused by disruption in 1 or more cognitive processes needed for effective reality monitoring, such as temporal discrimination, source monitoring,
and self-initiated memory retrieval (Johnson et al 1997). Impaired performance in
temporal order memory (Downes et al 2002), source memory (Kessels et al
2008), and working memory tasks (van Asselen et al 2005) is also observed.

It is usually accepted that declarative memory (factual knowledge) is
significantly impaired, whereas procedural memory (motor learning) is preserved
(Victor et al 1989). It has been found, however, that Korsakoff patients normally
learn a motor task only when directive feedback is provided, whereas no learning
occurs at all in the absence of this information (Swinnen et al 2005). Directive
feedback information seems in consequence crucial for normal procedural learning
in patients with Korsakoff syndrome. Using the distinction between involuntary
unconscious (or implicit) memory and involuntary conscious (or explicit) memory,
it has been reported that Korsakoff patients exhibit defects only in involuntary
conscious memory (d’Ydewalle and Van Damme 2007). By the same token,
visuoperceptual learning (e.g., recognition of incomplete pictures) may be
preserved in Korsakoff syndrome (Fama et al 2006). Noteworthy, when providing
extra explanations to the patient, encouraging to answer, and allowing additional
processing and responding time, some improvement in memory test performance
is observed (Van Damme and d’Ydewalle 2008).

Of note, regardless of the significant declarative (explicit) memory defect,
patients with Korsakoff syndrome present a normal memory for implicit contextual
information (Oudman et al 2011); implicit contextual memory is usually
understood as the ability to acquire contextual information from one’s
surroundings without conscious awareness.

Although disproportionate deficits in memory are the defining feature of the
disorder, variability in the level of general intellectual functioning is observed.
Many patients perform in the average range on standard IQ tests, but others
demonstrate more widespread cognitive deficits (Jacobson et al 1990a).

The extra-memorial deficits most commonly noted in Korsakoff patients are
deficits in planning, decision making, and problem solving and deficits linked to
impaired frontal executive control (Brand et al 2005). Patients perform poorly on
clinical tests of frontal function such as the Wisconsin Card Sorting test, verbal
fluency, and Trails B (Squire 1982; Jacobson et al 1990). Because the frontal
lobes play an important role in the planning and initiation of systematic memory
search, frontal deficits may contribute to the inability to retrieve premorbidly
acquired information. Visuospatial and visual-perceptual deficits are also observed
on a variety of concept formation tests that require discrimination and
classification of complex visual stimuli (Kopelman 1995). Comparing Korsakoff
and non-Korsakoff alcoholics, it has been found that Korsakoff patients are
impaired on tests of memory, fluency, cognitive flexibility, and perseveration.
Non-Korsakoff alcoholics may show some frontal system deficits as well, but these
are milder (Oscar-Berman et al 2004). Brokate and colleagues investigated a
sample of 17 Korsakoff amnesics, 23 alcoholics without Korsakoff syndrome, and
21 controls with peripheral nerve diseases, matched for intelligence and education
(Brokate et al 2003). Korsakoff amnesics, but not alcoholics, showed marked
memory impairment. They also scored lower in each of the executive tasks, the
alcoholics only in the alternate response task. This task also correlated with the
years of the alcohol dependency. The authors conclude that Korsakoff syndrome is
associated not only with memory impairment but also with a global executive
deficit. The decline in the ability to alternate between different responses would
argue for a restricted neurotoxic effect of alcohol on some frontal lobe areas.

General cognitive decline is especially common in female patients and may
warrant a diagnosis of alcoholic dementia. Cutting defined alcoholic dementia as a
global deterioration of cognitive functions (Cutting 1978). Clinically, the term
Korsakoff syndrome is typically limited to those patients who have a disproportionate disorder of memory, whereas the term alcoholic dementia is used for patients with a more global cognitive impairment (Salmon et al 1993). The nosological distinction between Korsakoff syndrome and alcoholic dementia, however, is highly controversial because the clinical differentiation is imprecise and no distinct neuropathological basis has been established for alcoholic dementia (Victor and Adams 1995). This has led some to conclude that all cognitive disorders secondary to alcoholism can more appropriately be seen as varying along a continuum of severity (Bowden 1990).

Changes in personality are also typical of Korsakoff syndrome. Patients lack insight, are apathetic about ongoing events, and are unconcerned about personal appearance. A lack of interest in alcohol is also striking.

The initial clinical presentation of Korsakoff disease is variable. Although often marked by the acute signs of Wernicke encephalopathy, the disorder can also have an insidious onset, without clinical evidence of an antecedent Wernicke encephalopathy. Furthermore, a minority of patients who present with the acute signs of the Wernicke stage (less than 25%) do not develop Korsakoff syndrome and are left with only minimal cognitive deficits following recovery (Victor et al 1989). Jauhar and Montaldi studied 8 patients with Korsakoff syndrome, only 4 of whom had had a documented Wernicke episode (Jauhar and Montaldi 2000). All subjects showed amnesia without intellectual deterioration. MRI abnormalities were seen in each group to the same extent (atrophy of mammillary bodies, to a lesser extent thalamic and some generalized gyral atrophy). No MRI measure differentiated the groups. Cerebral blood flow showed reduction of flow to the anterior temporal regions bilaterally, extending to the parietal lobes, to the same degree in each group. The authors concluded that patients with an insidious onset of Korsakoff syndrome have the same pathology as those with classical Wernicke-Korsakoff disease.

Clinical vignette

A right-handed white male with a 25-year history of alcohol abuse was hospitalized in April 1986 at age 62 in a state of dehydration and malnutrition. His problems began that April when he was fired from his job, which prompted increased alcohol consumption and poor eating. At the end of May, he was noted by his son to be forgetful, having delusions and hallucinations. During the hospitalization, he was described as confused, disoriented, and agitated. He was given a diagnosis of acute Wernicke encephalopathy and treated with folate and thiamine. He was transferred to a hospital closer to his family in November 1986. During this time he was severely disoriented and was unable to remember the location of his room or the reason for his hospitalization. He often confabulated, stating for instance, that he was in the hospital for an appendectomy. He estimated his age to be 35 years. He was given a diagnosis of alcoholic Korsakoff syndrome.

Neurologic exam in November 1986 revealed end-point nystagmus bilaterally and mild dysmetria on finger-to-nose testing. Rapid alternating movements were performed poorly bilaterally. He had absent ankle jerks and decreased pinprick sensation in his feet consistent with peripheral neuropathy. His gait was mildly ataxic in tandem.

Mental status exam was also abnormal. He was alert but only oriented to person. He did not know the date or the name of the hospital. His immediate span of attention was intact. He recalled 3 of 3 words without distraction after 30 seconds, but 0 of 3 after 5 minutes of intervening activity. He was unable to recall personal
information that occurred in the recent past. He was unable to state the current
president, but correctly stated that Roosevelt was president during World War II.
Repeated neuropsychological evaluations revealed a consistent pattern of
deficits. He demonstrated low average performance on tests of intelligence.
Performance on tests of simple attention was intact. On tests of complex
attention, his performance was slow and characterized by frequent
perseverations. Basic language skills were preserved, although some problems
with confrontation naming were noted. Basic perceptual abilities were intact but
tasks requiring visuospatial integration were performed poorly. His anterograde
amnesia was extremely dense and out of proportion to his other cognitive deficits.
Performance on all measures of new learning was severely impaired. He also
demonstrated extensive retrograde amnesia: he had difficulty recalling
autobiographical events in response to verbal cues. His recall of famous
individuals conformed to the classic Korsakoff pattern, with better recall of remote
versus recent individuals.

Table 1. Korsakoff Patients’ Performance on Standard Neuropsychological
Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Adult Intelligence Scale-Revised Verbal IQ</td>
<td>95</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale-Revised Performance IQ</td>
<td>83</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale-Revised (WAIS-R)</td>
<td></td>
</tr>
<tr>
<td>• Attention</td>
<td>101</td>
</tr>
<tr>
<td>- General</td>
<td>53</td>
</tr>
<tr>
<td>- Delay</td>
<td>52</td>
</tr>
<tr>
<td>California Verbal Learning Test</td>
<td></td>
</tr>
<tr>
<td>• Trial 1-5</td>
<td>3, 2, 2, 3, 3 /16</td>
</tr>
<tr>
<td>- Delayed recall</td>
<td>0</td>
</tr>
<tr>
<td>- Cued recall</td>
<td>0</td>
</tr>
<tr>
<td>- Recognition</td>
<td>12/16 Hits</td>
</tr>
<tr>
<td>- Delayed recall</td>
<td>0</td>
</tr>
<tr>
<td>- Cued recall</td>
<td>0</td>
</tr>
<tr>
<td>- Recognition</td>
<td>24/28 False Alarms</td>
</tr>
<tr>
<td>Famous Faces Recall (20-70s)</td>
<td>4, 4, 2, 1, 1, 0 /8</td>
</tr>
<tr>
<td>Digits Forward, Backwards</td>
<td>6, 5</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>47/60</td>
</tr>
<tr>
<td>Trails B</td>
<td>179 sec, 0 errors</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>20% to 24%</td>
</tr>
<tr>
<td>Benton Facial Recognition</td>
<td>49/54</td>
</tr>
<tr>
<td>Benton Line Orientation</td>
<td>28/30</td>
</tr>
<tr>
<td>Hooper Visual Organization</td>
<td>16/30</td>
</tr>
</tbody>
</table>

The man was admitted to long-term care in 1989 where he remained until his
death in 1992. He remained abstinent. He led a rather isolated existence and was
apathetic with regard to daily activities. He demonstrated limited insight into his
medical condition.

Etiology
Korsakoff syndrome is directly linked to a deficiency of thiamine (vitamin B1). It
is most commonly associated with chronic alcohol abuse, in which case low
dietary intake of thiamine is thought to combine with alcohol-induced impairments
in thiamine absorption and metabolism (Sechi and Serra 2007; Zahr et al 2011).
It has also been suggested that thiamine deficiency produces an age-related
vulnerability to diencephalic amnesia (Pitkin and Savage 2004), and in
consequence, it may not only be the chronic use of alcohol but also the advancing age of the patient. Stacey and Sullivan compared the alcohol and thiamine intakes of 35 alcohol-dependent patients with 49 healthy young undergraduates. The clinical group consumed significantly less thiamine than the healthy group and well below the minimum safe daily intakes (Stacey and Sullivan 2004). However, Korsakoff syndrome has also been described in the context of a number of other disorders that cause malnutrition or malabsorption, including severe dysphagia (Karaïskos et al 2008), anorexia nervosa (Altinyazar et al 2010; Saad et al 2010), persistent vomiting, intravenous feeding, gastrointestinal carcinoma, dialysis, and AIDS. Other conditions such as bowel obstruction (Deb et al 2001-2002), hyperemesis gravidarum (Accetta et al 2002; Yoon et al 2005), and primary CNS lymphoma (Toth et al 2002) have been also mentioned. Korsakoff syndrome following chronic subdural hematoma has been also described (Inagaki et al 2003). Thanks to generally improved standards of nutrition, Korsakoff syndrome of nonalcoholic origin is currently on the decline. Head traumas with bilateral lesions of the limbic circuit may result in a memory disorder alike to the Korsakoff disease but frequently referred as of "Korsakowian syndrome" or "mental syndrome of Korsakoff" (Brion et al 2001). Rahme and associates described a case of acute Korsakoff-like syndrome resulting from the combination of a left anteromedian thalamic infarct and a right hippocampal hemorrhage (Rahme et al 2007).

In Korsakoff syndrome of alcoholic etiology, direct neurotoxic effects of alcohol on cortical association areas have been implicated as well. These may be responsible for the visuo perceptual and problem-solving deficits seen in Korsakoff patients as well as in nonamnesic chronic alcoholics (Butters 1985). However, the relationship between frontal dysfunction and alcohol abuse per se remains controversial because frontal deficits have also been observed in Korsakoff syndrome of nonalcoholic etiology. This suggests that diencephalic lesions, indirectly, may also cause cortical dysfunction. Wijnia and Goossensen hypothesized that the Korsakoff syndrome might illustrate a cognitive dysfunction caused by cerebello-cerebral pathways being disconnected in brain areas that are known to be affected in Wernicke encephalopathy (Wijnia and Goossensen 2010). Vulnerability to Korsakoff syndrome is highly variable. Among alcoholics with extensive drinking histories and malnutrition, only a minority develop the syndrome. Krabbendam and colleagues analyzed MRI brain structure volumes in patients with Korsakoff syndrome, patients with chronic alcoholism, and healthy control subjects (Krabbendam et al 2000). The patients with alcoholism had normal cognitive performance and normal brain structural volumes. The patients with Korsakoff syndrome had performance deficits on tests of memory, visuo perception, and executive functions as well as reduced brain structural volumes. These results suggested that the cognitive deficits cannot be ascribed to mere chronic consumption of alcohol.

A genetic predisposition to impaired thiamine metabolism has been postulated in individuals with Korsakoff syndrome (Guerrini et al 2009). Considerable attention is currently being given to the possibility of abnormalities in the metabolism of transketolase, an enzyme that requires the active form of thiamine, thiamine pyrophosphate, as a cofactor (Martin et al 1995b). A subgroup of patients may be predisposed to more severe brain damage as a consequence of abnormalities in the transketolase protein (Heap et al 2002). It has been further suggested that stress processes play an important early role in the brain damage associated with thiamine deficiency (Todd and Butterworth 1999). A number of inborn errors of metabolism have been described in which clinical improvements can be documented following administration of pharmacological doses of thiamine, such
as thiamine-responsive megaloblastic anemia (Singleton and Martin 2001). Manzardo and Penick proposed that an inherited insensitivity to thiamine can precipitate brain abnormalities early in life that will increase the risk of developing alcoholism and Wernicke-Korsakoff syndrome in adulthood (Manzardo and Penick 2006).

Pathogenesis and pathophysiology
Bilateral, symmetrically placed, punctate lesions in the area of the third ventricle, fourth ventricle, and aqueduct are the hallmarks of Korsakoff syndrome. Lesions in the midbrain and cerebellum are responsible for the neurologic symptoms of the Wernicke stage, whereas lesions in the diencephalon are critical for the amnesia that characterizes Korsakoff syndrome. Bilateral mammillothalamic tracts dysfunction can also lead to Korsakoff syndrome (Yoneoka et al 2004). It has been suggested that the characteristic neuropathology includes neuronal loss, micro-hemorrhages, and gliosis in the paraventricular and peri-aqueductal grey matter. Lesions in the mammillary bodies, the mammillothalamic tract, and the anterior thalamus probably are more important to memory dysfunction than lesions situated in the medial dorsal nucleus of the thalamus (Kopelman et al 2009).

Considerable debate exists regarding the minimal lesion necessary to cause severe amnesia. Based on their extensive analysis, Victor and colleagues suggested that damage to the dorsomedial nucleus of the thalamus is essential in the causation of memory deficits (Victor et al 1989). Others have implicated both the mammillary bodies and thalamus (Butters 1985). There is also disagreement about which portion of the thalamus is critical: the dorsomedial nucleus, or the anterior and midline areas including the preretinal nucleus (Mair et al 1979).

The presence of diencephalic lesions can also be seen in vivo using structural imaging techniques. Shrinkage of the mammillary bodies is visible on MRI, but this is the case for Korsakoff as well as non-Korsakoff alcoholics. Additional volume decrease in the anterior diencephalon, however, appears selectively in Korsakoff patients (Jernigan et al 1991; Shear et al 1996). Volumetric MRI analysis had revealed thalamic and mammillary body atrophy in the Wernicke-Korsakoff patients as well as frontal lobe atrophy with relative sparing of medial temporal lobe structures (Reed et al 2003). Periaqueductal and periventricular gray matter and collicular bodies are also affected (Sullivan and Pfefferbaum 2009). Variable degrees of neocortical involvement are observed, especially in the frontal and parietal areas (Shimamura et al 1988; Jernigan et al 1991). Cortical atrophy is seen in the form of enlarged lateral ventricles and widening of the interhemispheric fissures, Sylvian fissures, and frontal sulci. Frontal atrophy, however, is also present in non-Korsakoff alcoholics (Jacobson and Lishman 1990b; Emsley et al 1996). Using structural MRI volumetric analysis in patients with organic amnesia (Korsakoff syndrome, herpes encephalitis, and focal frontal lesions), Colchester and colleagues demonstrated that patients with Korsakoff syndrome showed decreased thalamic measurements but no significant changes in the medial temporal lobes, whereas patients with herpes encephalitis showed severe medial temporal but not thalamic atrophy (Colchester et al 2001). In the patients with known frontal lobe lesions, quantitative analysis on MRI showed reduced frontal lobe volume but no significant temporal lobe or thalamic atrophy.

Further evidence for cortical dysfunction in Korsakoff syndrome comes from functional imaging studies, which have demonstrated widespread depression of metabolism in major portions of the frontal and parietal lobes as well as in the cingulate (Joyce et al 1994; Paller et al 1997). Aupee and colleagues (Aupee et al 2001) used positron emission tomography in patients with permanent amnesia
Permanent amnesia was associated with hypometabolism in the thalamus, posterior cingulate cortex, and mesial prefrontal cortex (near the anterior cingulate gyrus), bilaterally as well as in the left supramarginal and middle temporal gyri. The individual analysis showed that this group pattern was found in essentially each patient, regardless of the cause of amnesia.

Caulo and colleagues analyzed episodic memory for faces using functional MRI in a subject with Wernicke-Korsakoff syndrome and diencephalic lesions but without medial temporal lobe damage (Caulo et al 2005). Results were compared with 8 controls. Three tasks were used: (1) face encoding; (2) face perception; and (3) face recognition. Activation was found to be greater in the right hemisphere. In controls, both the encoding and recognition tasks activated 2 hippocampal regions (anterior and posterior). In the Wernicke-Korsakoff patient, no hippocampal activation was observed during either encoding or recognition. The authors emphasize that although the damage did not involve the medial temporal lobe, the hippocampal memory encoding was absent. They suggested that anterograde amnesia in Korsakoff syndrome could be the expression of damage to an extended hippocampal system. Noteworthy, Korsakoff patients are impaired in recognizing facial emotional expressions (Montagne et al 2006).

Ataxia and cerebellar signs may be also observed in alcoholics with or without Korsakoff syndrome. Using MRI, it has been observed that alcoholics may have gray but not white matter cerebellar hemisphere volume deficits, whereas Korsakoff patients have deficits in both tissue types. Alcoholics and Korsakoff patients had gray and white matter volume deficits in anterior superior but not posterior inferior vermis. Regional distribution, but not severity of cerebellar volume deficits, is similar in alcoholic individuals whether or not complicated by Korsakoff syndrome and relates to ataxia (Sullivan et al 2000). Ataxia in Korsakoff syndrome has also been associated with elevated cerebellar glucose metabolism (Fellgiebel et al 2004).

The pathogenic mechanism that determines the formation and the distribution of brain lesions is still not fully understood. Thiamine is intimately involved in several enzymatic reactions that are essential for glucose metabolism and neurotransmitter reactions. Animal studies of thiamine deprivation suggest that reductions in thiamine-dependent enzymes trigger a series of metabolic events, including decreased intracellular energy levels, increased histamine release, glutamate accumulation, and ultimately, cell death. Diencephalic areas may be especially vulnerable because of their high energy demand (Langlais 1995). Alternatively, it has been suggested that glutamate accumulates in peripheral tissues and reaches a concentration in the blood at which it passes into cerebral ventricles and contiguous brain areas, thus, preferentially affecting periventricular brain tissues (McEntee 1997).

Although a number of neurotransmitter systems are affected by thiamine deprivation, it remains unclear which neurotransmitters are implicated in Korsakoff amnesia. McEntee and colleagues have argued that monoaminergic disruption may be critical (McEntee et al 1984; McEntee and Mair 1990). They found significant reductions in 3-methoxy-4-hydroxyphenylglycol, the primary metabolite of norepinephrine, in the CSF of Korsakoff patients, and the magnitude of this reduction was correlated with the severity of memory impairment. Administration of the norepinephrine agonist clonidine had a beneficial effect on performance on a small number of anterograde memory tests, but these findings have been difficult to replicate (O’Carroll et al 1993). Serotonin has also been implicated, and modest improvements in memory have been obtained with the administration of the serotonin uptake inhibitor fluvoxamine (Martin et al 1995a).
Finally, because of its known role in memory, the possible contribution of acetylcholine depletion in Korsakoff amnesia has also been addressed. Thiamine deprivation does affect acetylcholine synthesis, and a reduction in neurons in the cholinergic basal forebrain has been described in at least some Korsakoff patients. However, cholinergic dysfunction does not account for the memory disorder, and damage to the cholinergic system is not sufficient to cause a persisting amnesia in Wernicke-Korsakoff syndrome (Nardone et al 2010).

**Epidemiology**

The incidence of Korsakoff syndrome is low, having been estimated at approximately 10 per million of first psychiatric admissions (Centerwall and Criqui 1978). Other statistics, based on hospital admissions as well as general population studies, estimate its occurrence at about .05% (Victor and Laureno 1978). The number of new cases of Korsakoff syndrome appears to be declining thanks to improved nutritional standards. Furthermore, excessive alcohol intake is currently seen more often in the context of polydrug abuse, resulting in a different combination of neurotoxic and behavioral effects.

Several large autopsy studies have found neuropathological changes consistent with a diagnosis of Wernicke encephalopathy or Korsakoff syndrome in 2% to 3% of postmortem examinations (Torvik et al 1982; Harper et al 1986). However, a majority of these cases had not received a clinical diagnosis of Wernicke-Korsakoff syndrome during life. Two factors have been identified that may explain the low rate of concordance between clinical and pathological diagnosis: (1) a proportion of the undiagnosed patients may have more general cognitive decline consistent with alcoholic dementia, and (2) many chronic alcoholics may suffer from repeated subclinical episodes of Wernicke encephalopathy associated with periodic thiamine deficiency. Findings such as these have raised the possibility that the severity and extent of cognitive deficits seen in alcoholics should be conceptualized as falling on a continuum, mediated by the severity of the underlying neuropathology (Bowden 1990).

**Prevention**

Because alcohol abuse is the primary cause of Korsakoff syndrome, moderation of or abstinence from alcohol is an important preventative measure. Additionally, the possibility of thiamine deficiency should be considered carefully in all patients with a history of alcoholism or malnutrition. Substitution with at least 100 mg/day intravenously or intramuscularly is recommended (Heye et al 1994). Effective treatment and prophylaxis may only be achieved by use of parenteral vitamin supplements because oral supplements are not absorbed in significant amounts (Cook 2000). In patients with acute Wernicke encephalopathy, treatment with thiamine is critical in order to prevent the occurrence of fatal midbrain hemorrhages. This should be done prior to administration of glucose-enriched fluids. Given proper vitamin supplementation, the confusional state typically clears and marked improvement in the neurologic symptoms occurs. Paparrigopoulos and colleagues reported a case of complete recovery following aggressive thiamine treatment (600 mg/day orally and 300 mg/day intramuscularly) in a 52-year-old man with a 10-year history of heavy alcohol abuse (Paparrigopoulos et al 2010). Ishibashi and colleagues reported physiological conduction failure with minimal conduction delay due to thiamine deficiency in 3 patients with Wernicke-Korsakoff encephalopathy (Ishibashi et al 2003). The symptoms of neuropathy, however, lessened within 2 weeks after an intravenous thiamine infusion.
However, the cognitive decline and the onset of Korsakoff syndrome can usually not be prevented. It has been emphasized that many population groups worldwide have thiamine deficiency; consequently, they are at risk of developing Wernicke-Korsakoff syndrome. Thiamine supplementation of some staple food products (eg, flour) is an easy and safe measure that potentially can improve the thiamine reserve of different human groups (Harper 2006). It has also been suggested that correct diagnosis and treatment of Wernicke-Korsakoff syndrome will result in a decrease in the rate of maternal deaths (Wedisinghe et al 2011).

**Differential diagnosis**

Persistent global amnesia can occur as a consequence of a number of neurologic disorders, including cerebrovascular accidents, rupture and surgical repair of anterior communicating artery aneurysms, encephalitis, and anoxia. The presentation of the amnesic syndrome may be strikingly similar regardless of etiology; therefore, these neurologic conditions should all be considered in the differential diagnosis. Traumatic brain injury occasionally may result in a selective memory disorder as well. Because patients under the influence of alcohol are prone to head injury from falls and other accidents, it is important to rule out a traumatic etiology.

A difficult differential diagnosis is Alzheimer disease, which may present with relatively isolated memory dysfunction in the early stages of the disease. Obviously, a careful history of alcohol consumption and nutritional status are of primary importance in the differential diagnosis. A history of Wernicke features allows an unequivocal diagnosis of Korsakoff syndrome, but it should be kept in mind that Korsakoff syndrome can occasionally occur without signs of a preceding Wernicke syndrome. Attention to the course of illness is critical because the memory disorder seen in Alzheimer disease is progressive, whereas in Korsakoff syndrome it is stable.

Severe memory disorders can also be seen in the context of more global intellectual deterioration. A diagnosis of alcoholic dementia is warranted if patients demonstrate, in addition to amnesia, severe deficits in conceptual and problem-solving abilities as well as marked impairments on visuospatial and visuoconstructive tasks (Salmon et al 1993). In contrast to the acute onset of Korsakoff syndrome, the global cognitive deficits seen in alcoholic dementia usually develop more gradually.

**Diagnostic workup**

Korsakoff syndrome is a clinical diagnosis that is based on the identification of an amnesic syndrome in the context of a history of alcohol abuse or malnutrition. A diagnosis can be made only when the confusional state associated with Wernicke encephalopathy has sufficiently cleared. All cognitive functions should be thoroughly evaluated in order to characterize the pattern and severity of the memory disorder and to screen for the possibility of general intellectual decline. A diagnosis of Korsakoff syndrome is warranted only when the memory deficits are more prominent than other cognitive disorders in the domains of language, visuoperceptual functioning, problem solving, and judgment.

A complete history should be taken with particular emphasis on alcohol use and nutritional status, evidence of an acute episode of Wernicke encephalitis, and any associated features. Information should also be obtained regarding other medical conditions that may be part of the differential diagnosis (eg, febrile illness, head injury, tumor). A complete physical and neurologic examination is necessary.
Although the acute neurologic signs associated with Wernicke encephalopathy usually recover, up to 60% of Korsakoff patients continue to show ocular and cerebellar signs. A slow, shuffling, wide-based gait and inability to walk tandem are typical. Laboratory testing is routinely performed with special attention to folate and thiamine levels. Computed tomography or MRI is useful in ruling out other causes of global amnesia, such as stroke, tumor, or contusion. The presence of hemorrhagic lesions surrounding the third and fourth ventricle, however, does not in itself allow a differentiation between Korsakoff syndrome and alcoholic dementia. Electroencephalogram is not useful in the diagnosis because it is normal in approximately half the cases.

Prognosis and complications

Some degree of recovery may occur within 1 to 3 months and may continue for up to 1 year or more. Nevertheless, the prognosis is generally bleak. Successful treatment generally is limited and may depend on a diversity of inter-related variables (Thomson and Marshall 2006). Only about 20% of patients make a substantial recovery (Victor et al 1989). A majority of patients are left with a devastating memory disorder that requires close supervision. Patients' lack of insight further complicates their behavioral management. Patients may survive for many years and their death is typically unrelated to the original neurologic disease. Some follow-up studies have shown that cognitive test performance of detoxified alcoholic Korsakoff patients remains stable over at least 2 years; conversely, no indication of either accelerated cognitive decline or onset of dementia-like symptoms is observed (Fujiwara et al 2008).

Fellgiebel and colleagues reported an alcoholic patient with acute ataxia, nystagmus, and a global confusional state (Fellgiebel et al 2003). An amnestic syndrome with confabulation was also observed. Under treatment with intravenous thiamine, the patient recovered completely from nystagmus and ataxia, whereas a severe amnestic syndrome persisted. Fluorodeoxyglucose positron emission tomography showed bilateral thalamic and severe bilateral temporal-parietal hypometabolism. Longitudinal assessment revealed improvements of clinical state and neuropsychological performance that were paralleled by recovered cerebral glucose metabolism. In contrast to metabolic rates that increased between 7.1% (anterior cingulate, left) and 23.5% (parietal, left) in cortical areas during a 9-month remission period, thalamic glucose metabolism remained severely disturbed over time (change: left +0.2%, right +0.3%).

Alcohol-induced damage to the liver is a common complication of Korsakoff syndrome. Chronic liver dysfunction in itself contributes to impaired cognitive performance in alcoholics (Butterworth 1995), but to what extent it further exacerbates the deficits seen in Korsakoff syndrome is unclear. In approximately 15% of patients, decompensated liver disease is the primary cause of death. Other complicating factors derive from the alcoholic's hazardous lifestyle and include trauma, anoxia, and the effects of polydrug abuse or drug overdose.

Management

Memory rehabilitation efforts have generally met with limited success. Although notebooks and other memory aids have been found to be useful in some amnesic patients, their utility in Korsakoff syndrome is limited because of patients' poor motivation and lack of insight into their problems.

A number of pharmacological treatments have been attempted. Modest success has been obtained with the serotonin uptake inhibitor fluvoxamine (Martin et al
Cholinergic treatment with the cholinesterase inhibitor donepezil has been also attempted but does not always provide marked beneficial effects in patients with Wernicke-Korsakoff disease (Casadevall-Codina et al 2002; Cochrane et al 2005). Treatment with rivastigmine, an acetylcholinesterase inhibitor, has not shown to be effective in restoring memory in these patients (Luykx et al 2008). This may be because pathways mediating channel and state-dependent functions are impaired in this disease, and enhancement of state-dependent cholinergic transmission may not be sufficient (Sahin et al 2002).

At present, pharmacological approaches remain unable to overcome the severe memory deficits seen in these patients.

**Pregnancy**
Not applicable

**Anesthesia**
Not applicable

**ICD codes**

ICD-9:
- Korsakoff disease, psychosis or syndrome (alcoholic): 291.1
- Korsakoff disease, psychosis or syndrome (nonalcoholic): 294.0

ICD-10:
- Korsakoff syndrome, alcohol-induced or unspecified: F10.6

**OMIM**
Wernicke-Korsakoff syndrome: %277730

**Associated disorders**
Alcoholic peripheral neuropathy
Cirrhosis of the liver

**Related summaries**
Alcohol abuse: acute and chronic neurologic illness
Donepezil
Drug-induced memory disturbance
Memory loss
Mental status examination
Nutrition and the brain
Nutrition-related neuropathies
Thiamine deficiency

**Differential diagnosis**
cerebrovascular accidents
rupture and surgical repair of anterior communicating artery aneurysms
encephalitis
anoxia
traumatic brain injury
head injury from falls and other accidents
Alzheimer disease
other severe memory disorders
alcoholic dementia

**Demographics**
For more specific demographic information, see the Epidemiology, Etiology, and Pathogenesis and pathophysiology sections of this clinical summary.

**Age**
- 19-44 years
- 45-64 years
- 65+ years

**Population**
None selectively affected.

**Occupation**
None selectively affected.

**Sex**
male>female, >1:1

**Family history**
family history may be obtained

**Heredity**
heredity may be a factor

**References cited**


Harper C. Thiamine (vitamin B1) deficiency and associated brain damage is still common throughout the world and prevention is simple and safe! Eur J Neurol 2006;13(10):1078-82.


**References especially recommended by the author or editor for general reading.**