RESEARCH PAPER

Wernicke-Korsakoff syndrome not related to alcohol use: a systematic review

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ABSTRACT

Objective Although Wernicke-Korsakoff syndrome (WKS) is a common condition, diagnosis remains difficult. WKS not associated with alcohol is rare and thought to present differently to alcohol-related WKS. We conducted a systematic review of WKS not related to alcohol to enhance understanding of WKS not related to alcohol and WKS in general.

Methods A systematic review was conducted of case reports, published in English, of Wernicke's encephalopathy and WKS in patients without a history of alcohol-use disorder. Main data sources: MEDLINE, Index Medicus. Eligible cases totaled 623. Publication dates ranged from 1867-2014. Comparisons of clinical presentation were made with published data on samples comprising, almost exclusively, alcohol-related WKS.

Results A wide array of illnesses precipitated WKS. When diagnosis of WKS was made postmortem, nonalcohol-related cases presented a similar number of signs of the classic triad as alcohol-related cases (p=.662, Cohen's w=.12) but more signs when diagnosed antemortem (p<.001, Cohen's w=.46). The most common sign was altered mental state. Korsakoff syndrome or ongoing memory impairment was reported in 25% of nonalcohol-related WKS, although cognitive status was not explicitly reported in many cases. When duration of memory impairment was reported, 56% had clinically obvious memory impairment lasting beyond the period of acute presentation. Nonalcohol-related WKS was more often associated with female gender, younger age, shorter duration of precipitating illness, and better survival rate compared to alcohol-related WKS.

Conclusions Thiamine deficiency in the absence of an alcohol-use disorder can cause the full clinical spectrum of WKS, including chronic cognitive impairment and Korsakoff syndrome.

INTRODUCTION

Wernicke-Korsakoff syndrome (WKS) occurs with a postmortem incidence of approximately 1-2%[1-4] and is most commonly associated with alcohol use disorder.[5-8] However the etiology of WKS and the links between the acute Wernicke's encephalopathy (WE) phase and the chronic Korsakoff syndrome (KS) phase remain a source of considerable controversy. Some authors have suggested that WKS is a heterogeneous disorder with highly variable course and severity irrespective of association with alcohol use.[9-11] In contrast, because much of our knowledge of WKS has been derived from alcohol-related WKS (alcWKS), speculation has arisen regarding the possible interaction between ethanol neurotoxicity and thiamine deficiency. For example, it has been argued that WE rarely if ever evolves into chronic KS in the absence of alcohol use disorder so KS cannot be caused by thiamine deficiency alone.[3, 12-15] The recently published DSM-5[5] classifies KS as 'alcohol-induced amnestic confabulatory neurocognitive disorder' distinct from WE, reinforcing the assumption that alcohol is necessary for the genesis of KS.

Because of its rarity, most of the literature on nonalcohol-related WKS (nonalcWKS) comprises individual case reports, clinical studies with limited sample size, or reviews that have restricted their focus to a single etiology.[16-19] Several excellent reviews of WE have appeared recently, but none have sought to make detailed comparisons of WKS with and without a history of alcohol use disorder.[3, 6, 15] Such comparisons may clarify the nature of WKS and the possible role of alcohol in the development of KS.

The aim of the present study was to conduct a systematic review of all accessible cases of nonalcWKS so as to enhance understanding of WKS in general. A subsequent aim was to compare clinical presentation and course in nonalcWKS with published data on alcWKS.[20, 21] Comparing

clinical presentation of nonalcWKS and alcWKS permits the separate examination of cases that only received a diagnosis of WKS at postmortem versus cases that received a diagnosis of WKS antemortem. Comparison of clinical presentation also includes details of memory impairment suggestive of KS, and patient outcomes.

Throughout this review, the term WKS will be used to describe the acute WE and chronic KS phases of the condition.[9, 21] Apart from severity of clinical presentation and acuteness of onset, there is no non-arbitrary clinical or pathological distinction between WE and KS phases.[9, 10, 22-24]

METHODS

Index Medicus, the MEDLINE online database, and the references section of all eligible articles were searched for all case reports of nonalcWKS published in English with data reported at the individual level. Articles published between 1889-2014 were systematically searched. In total, 435 articles reporting 623 individual case descriptions of nonalcWKS were included in the systematic review.

The online supplement includes full details of search strategy, data extraction, rater reliability, statistical analyses, and included cases with references.

RESULTS

Gender and age

Table 1 shows gender distribution according to age. The nonalcWKS sample included nearly twice as many female cases compared to male; a male to female ratio of 1:1.84 (*n*=614). There remained a significantly higher number of females than males after removal of the 115 cases precipitated by

hyperemesis gravidarum (adjusted ratio: 1:1.31, *n*=499), but the effect of gender was now small (*p*=.003, Cohen's *g*=.07).[25] In contrast, a significantly greater proportion of mostly alcWKS cases, as reported by Victor and colleagues[21] were male (*p*<.001, Cohen's *g*=.13).

Mean age of the nonalcWKS sample was 38.1 years (*SD*=19.7, *n*=604, range=1-89 years). Fifty-eight percent (*n*=350) of the nonalcWKS sample was under 40 years of age, compared to only 20% of the alcWKS sample.[21]

Table 1 Gender distribution by age (in decades) in nonalcohol-related WKS retrieved from the systematic review compared to alcohol-related cases[21]

Age (years)	nonalcWKS			alcWKS[21]		
	Male	**Female**	**M : F Ratio**	**Male**	**Female**	**M : F Ratio**
0-9	22	18	1.22 : 1	-	-	-
10-19	17	28	1 : 1.65	-	-	-
20-29	32	113	1 : 3.53	3	11	1 : 3.67
30-39	37	82	1 : 2.22	12	22	1 : 1.83
40-49	28	45	1 : 1.61	44	25	1.76 : 1
50-59	31	34	1 : 1.10	43	18	2.39 : 1
60-69	27	47	1 : 1.74	38	14	2.71 : 1
70-79	19	16	1.19 : 1	10	0	-
80-89	1	6	1 : 6.00	-	-	-
Not reported	2	9		4	1	
Total	**216**	**398**	**1 : 1.84**	**154**	**91**	**1.69 : 1**

Precipitating illness

A diverse range of conditions precipitated nonalcWKS and are summarized in Table 2. As shown in Figure 1, the length of time between the onset of precipitating illness and first presentation to case

author (duration of precipitating illness) was significantly shorter, representing a large effect, in nonalcWKS compared to alcWKS described by Victor and colleagues ($p<.001$, Cohen's $w=9.67$).[21, 25] Unlike the nonalcWKS sample, 99% of alcWKS cases had a precipitating illness (alcohol use disorder) of one year's duration or more.[21]

Table 2 Precipitating illness in cases of Wernicke-Korsakoff syndrome not related to alcohol

Precipitating illness	***n* (%)**	***Male***	***Female***	***Gender not reported***
Gastrointestinal tract disease or surgery	213 (34%)	78	135	0
(Bariatric surgery)	69 (11%)	11	58	0
(Cancer)	54 (9%)	29	25	0
(Obstruction)	25 (4%)	12	13	0
(Pancreatitis)	11 (2%)	6	5	0
(Crohn's disease)	6 (1%)	0	6	0
(Other)	48 (8%)	20	28	0
Hyperemesis gravidarum	115 (18%)	0	115	0
Dietary insufficiency, starvation or vomiting	106 (17%)	59	47	0
Leukaemia or cancer of lymphoid system	36 (6%)	17	19	0
Intravenous feeding or hyperalimentation	29 (5%)	10	11	8
Psychiatric Disorders	13 (2%)	4	9	0
(Schizophrenia spectrum)	7 (1%)	4	3	0
(Anorexia Nervosa)	6 (1%)	0	6	0
Dialysis	11 (2%)	7	4	0
HIV/AIDS	10 (2%)	7	3	0
Other or unspecified	90 (14%)	34	55	1

Clinical presentation in cases diagnosed at postmortem

Of the nonalcWKS cases retrieved, 116 were only diagnosed at postmortem. Comparing the nonalcWKS sample to the mostly alcWKS cases of Harper et al.[20] that were also only diagnosed postmortem, Figure 2A shows similar proportions of cases had recorded history of none, one, two, or all three signs of the classic clinical triad, with no statistical difference between proportions (p=.662, Cohen's w=.12). The classic clinical triad of signs of WKS includes altered mental state, oculomotor abnormalities, and ataxia.[6, 21, 26]

For cases only diagnosed at postmortem, altered mental state was the most common sign of the classic clinical triad for both nonalcWKS and Harper and colleagues' almost exclusively alcWKS sample.[20] Next most common were oculomotor abnormalities and then ataxia for nonalcWKS, but ataxia then oculomotor abnormality for alcWKS (Figure 2B).

Figure 2B also shows that the proportion of nonalcWKS cases presenting with altered mental state was not significantly different to the proportion of alcWKS (p=.111, Cohen's w=.15). A significantly greater proportion of nonalcWKS cases displayed oculomotor abnormality compared to alcWKS, a medium sized effect (p<.001, Cohen's w=.36).[25] A significantly smaller proportion of nonalcWKS than alcWKS presented ataxia or gait disturbance, also a medium sized effect (p=.001, Cohen's w=.30).[25]

Clinical presentation in cases diagnosed antemortem

Of the nonalcWKS cases retrieved, 507 were first diagnosed antemortem. As shown in Figure 2C, of cases diagnosed antemortem, the overall proportions of nonalcWKS cases presenting none, one, two, or all three signs of the classic clinical triad differed statistically, with medium effect size, to the

mostly alcWKS cases of Harper et al. that also received a diagnosis antemortem ($p<.001$, Cohen's $w=.46$).[20, 25] The largest discrepancies between nonalcWKS and alcWKS occurred for proportions with one and two clinical signs, with fewer nonalcWKS cases showing only one sign, and a greater proportion showing two signs.

For cases first diagnosed antemortem, altered mental state was the most common sign of the classic clinical triad in both nonalcWKS and alcWKS,[20] followed by oculomotor abnormality and then ataxia for nonalcWKS, but ataxia then oculomotor abnormality for alcWKS (Figure 2D). Figure 2D also shows that significantly more nonalcWKS cases compared to alcWKS presented with altered mental state, although the effect was small ($p<.001$, Cohen's $w=.18$).[25] A significantly greater proportion of nonalcWKS cases presented oculomotor abnormality compared to alcWKS, with large effect ($p<.001$, Cohen's $w=.60$).[25] Once Bonferroni adjustment was applied (critical p-value=.017), there was no significant difference between nonalcWKS and alcWKS for proportion of cases presenting with ataxia or gait disturbance ($p=.018$, Cohen's $w=.10$).

Memory and Korsakoff syndrome (KS)

Duration of memory impairment was reported in 166 nonalcWKS cases (Figure 3). Of these patients, 29% ($n=48$) had memory impairment for one month or less, 7% ($n=11$) between one and two months, 8% ($n=14$) between two and three months, and 56% ($n=93$) had memory impairment of three months duration or more, or ongoing memory impairment. Ongoing memory impairment was coded when memory impairment was noted to be present at, or persisted beyond the last presentation to case author, or there was no indication that reported memory impairment had improved, irrespective of time. Alternatively, 17% (107 of 623) of the total nonalcWKS sample had KS (or

synonyms) explicitly indicated in their case descriptions. A further 8% (*n*=50) of cases were not explicitly described as having KS, but were reported to have ongoing memory impairment.

In summary, in the nonalcWKS cases with duration of memory impairment reported, 71% (118 of 166) of cases had memory impairment for longer than one month, and 56% (93 of 166) had memory impairment of three months duration or longer or ongoing memory impairment. Alternatively, 25% (157 of 623) of the total nonalcWKS sample had KS explicitly reported or ongoing memory impairment. Both of the latter percentage figures were significantly less than the proportion of alcWKS cases with KS (84%), as reported by Victor et al.,[21] with large effect ($p<.001$, Cohen's $w=.78$, and $p<.001$, Cohen's $w=1.63$, respectively).[25]

Post hoc analysis was conducted to investigate the relationship between duration of precipitating illness and report of KS in nonalcWKS. Of the 390 cases with duration of precipitating illness reported, KS was explicitly reported in 16% (*n*=61). Duration of precipitating illness was coded using the same time intervals as in Figure 1. Analysis revealed no significant relationship between duration of precipitating illness and report of KS in nonalcWKS ($p=.162$, $\Phi=.11$).[25]

Patient outcome

Of 611 nonalcWKS cases with reported patient outcome, 29% died (*n*=179), 21% (*n*=129) made a complete recovery, 11% (*n*=66) were left with moderate to severe cognitive impairment, and 39% (*n*=237) were reported to have shown some improvement but were left with residual symptoms or full recovery was not explicitly specified. The survival rate of reported nonalcWKS cases (71%, *n*=611) was significantly better with small effect,[25] compared to the survival rate of the alcWKS sample reported by Victor et al.[21] (57%, *n*=216), $p<.001$, Cohen's $w=.28$. If nonalcWKS cases

diagnosed only at postmortem are excluded, that is, cases that did not receive a diagnosis of WKS during life, as was done by Victor and colleagues, the difference in survival rate is even greater, and effect size now large (nonalcWKS:87%, alcWKS:57%), $p<.001$, Cohen's $w=.61$.[25]

DISCUSSION

The present study systematically reviews over 125 years of case reports of WKS not related to alcohol. The review shows that despite significant differences in demographic profile and clinical settings of patients with WKS not related to alcohol, when compared to cases associated with alcohol, the similarities in clinical manifestations of both acute and chronic WKS are striking. In particular, chronic cognitive impairment is common in nonalcWKS. In contrast, other recent reviewers based on small samples or clinical opinion, have suggested that chronic cognitive impairment in WKS not associated with alcohol is rare or nonexistent.[3, 13, 15]

Gender and age

More females than males were reported with nonalcWKS, contrasting with the higher proportion of males than females reported by Victor et al.[21] for alcWKS. While the preponderance of males in alcWKS samples may be attributed to easier access by males to treatment services, the female preponderance of nonalcWKS remains after accounting for the prevalence of hyperemesis gravidarum. None of the other precipitating illnesses are known to be associated with a strong gender bias. Alternatively, there may be an identification bias, females being more readily detected or reported.

The nonalcWKS sample was younger than the alcWKS sample of Victor et al.[21] The fact that some nonalcWKS cases were infants and children, as opposed to the exclusively adult alcWKS

sample, did not entirely explain the discrepancy. The younger age of onset for nonalcWKS than alcWKS may be due to the shorter duration in the variety of acute illnesses predisposing to thiamine deficiency compared to the relatively long duration in patients with alcohol use disorder. In the sample of Victor et al., more females than males developed WKS before the age of 40, despite their total alcWKS sample containing more males.

Precipitating illness

A wide variety of precipitating illnesses led to nonalcWKS. Multiple risk factors for thiamine deficiency were also evident within individual cases. Typical combinations of multiple risk factors included, for example, gastrointestinal tract disease or surgery complicated by persistent vomiting and subsequent prolonged parenteral feeding with or without vitamin supplementation.[27-30] Other medical conditions not directly related to the onset of WKS were not reviewed.

Time between onset of precipitating illness and first presentation to case author was much shorter for nonalcWKS than alcWKS. Non-alcohol related aetiologies typically involve more acute illness, and may deplete thiamine stores more quickly than is the case with chronic alcohol use disorder, although exceptions to this interpretation were evident, for example, onset of WKS many years after bariatric surgery.[31, 32] It was also possible that difference in duration of precipitating illness may have been magnified by reporting bias, with published cases of nonalcWKS reflecting an overrepresentation of the most severe or more rapidly developing cases.

Clinical presentation

Contrary to the conclusion of previous reviewers, it is evident in the cases of nonalcWKS reviewed that thiamine deficiency alone, in the absence of alcohol use disorder, can cause the full spectrum of

clinical signs of acute or chronic WKS.[3, 13] Acutely, each one of the signs of the classic clinical triad was reported in at least half of all nonalcWKS cases. Although there were differences between nonalcWKS and alcWKS in the proportions showing oculomotor abnormalities and ataxia, the differences varied slightly depending on whether comparisons were made between cases diagnosed antemortem or postmortem. More importantly, all elements of the classic triad were evident in cases of nonalcWKS in proportions not dramatically different to the proportions reported in alcWKS. Like alcWKS, the most common sign in nonalcWKS was altered mental state.

Of the cases who received a diagnosis of WKS only at postmortem, approximately equal proportions of nonalcWKS and alcWKS[20] presented with zero, one, two, and three signs of the classic clinical triad. In cases diagnosed antemortem, nonalcWKS cases presented a higher number of elements of the classic triad more often than alcWKS cases. The higher number of signs in nonalcWKS diagnosed antemortem, but not when diagnosed postmortem, may reflect the tendency for clinicians who work with patients with alcohol use disorder to have a lower threshold of detection of WKS, whereas clinicians working with patients without alcohol use disorder, in general, may require the patient to present with more clinical signs before considering WKS as a diagnosis.

The present findings contrast with the recent guidelines paper that reported eye signs and the full clinical triad to occur more frequently in alcohol-related than nonalcohol-related cases.[6] Those guidelines also recommend awareness of the differences in clinical presentation between the two patient groups. The review on which such conclusions were made was not intended to be comprehensive, and analyzed a smaller sample of nonalcohol-related cases than was utilized in the present systematic review (116 versus 623). So, whilst different reviews report some differences between presenting signs in nonalcWKS and alcWKS, it is more important to emphasize the

similarities in clinical presentation to counter the recent trend to suggest fundamental aetiological differences between nonalcWKS and alcWKS.[6, 33] Emphasizing the differences between nonalcWKS and alcWKS may inflate the role alcohol is thought to have in WKS relative to thiamine deficiency, as well as create a misleading perception that nonalcWKS is comparatively mild in severity and relatively short in duration, when the present review clearly shows the potential for severe and chronic symptoms without any known history of alcohol use disorder.

Memory and Korsakoff syndrome (KS)

Thiamine deficiency alone, without alcohol use disorder, was sufficient to cause KS in many patients. Twenty-five percent (157 of 623) of all nonalcWKS cases reviewed were described as having KS or chronic memory impairment. However, chronic cognitive status, impaired or otherwise, was not explicitly described in a large proportion of patients. In cases in whom duration of memory impairment (*n*=166) was reported, 56% were described as suffering lasting memory impairment of three months duration or longer, or memory impairment was described as ongoing.

The view that without combined alcohol use disorder, thiamine deficiency does not lead to a lasting KS,[3, 12, 13, 34] is incompatible with the large number of nonalcWKS cases with KS or ongoing memory impairment. Several possible factors may explain the discrepant views, as well as the finding that a smaller proportion of nonalcWKS than alcWKS cases were reported to have KS.[21]

First, KS may be under-reported in patients without alcohol use disorder because of lack of clinical vigilance, vigilance reduced because of the views cited above.[12, 13] Second, although there was no statistically significant association between reported occurrence of KS and duration of precipitating illness, the duration of precipitating illness reported for alcWKS is vastly different to

that reported for nonalcWKS. If more detailed comparison were possible, it would be surprising if severity of cognitive complications was not related to duration of precipitating illness and associated thiamine deficiency, as experimental evidence suggests.[35] In addition, milder variants of the disease may enjoy more rapid or more complete recovery. Milder disease in the nonalcWKS cases may have been evident in the shorter duration of precipitating illness and better survival rates than was reported for alcWKS.[21] Finally, the nonalcWKS sample was compared to a sample of alcWKS patients many of whom may have experienced multiple episodes of thiamine deficiency over the course of many years of alcohol abuse.[3, 36] In contrast, most of the cases of nonalcWKS had experienced a single, acute episode of thiamine deficiency.

Patient outcome and treatment

Survival rate of nonalcWKS patients was significantly higher than for alcWKS, but this may be due to more severe precipitating illness in the latter group, longer observation of alcWKS patients, or multiple illnesses and multiple organ damage in alcWKS.[21] It should also be noted that the cause of death in cases of nonalcWKS was not always due to WKS, as precipitating illnesses included other potentially fatal diseases.

In many of the cases reviewed, information regarding thiamine treatment was not sufficient to allow for accurate and reliable analysis, therefore treatment details were not included in the review. Nevertheless, it was noted that treatment regimens varied across nonalcWKS cases. Variation in treatment is not surprising given the lack of research underlying current guidelines for the treatment of WKS.[6, 37] Timing of thiamine treatment, as well as route, duration, and dosage may have effected reported patient outcomes. Delayed or inadequate treatment of WKS has long been associated with poorer outcome.[3, 34] It has previously been suggested that treatment of alcWKS

may require larger doses of parenteral thiamine than that required for nonalcWKS and this question merits further investigation, although current guidelines recommend high doses of parenteral thiamine for all patients with known or suspected WKS.[3, 6, 34]

Also, given that nonalcWKS patients had medical conditions that compromised nutritional health, it is likely that some patients took oral vitamins. Information regarding such treatments was lacking and not included in the review. Differences in administration of vitamins other than thiamine may also have impacted on patient outcome.

Conclusions

Despite the systematic review spanning over 125 years of nonalcWKS case reports, much of the case material was relatively recent. Of the 623 cases, 388 (62%) were reported after 1990, during a period of greater awareness and understanding of WKS and after the publication of the two studies of alcWKS which were used for comparison.[20, 21]

Case reports may have been subject to detection, reporting, or publication bias, particularly an overrepresentation of atypical or more severe cases. However, many case reports identified through the literature retrieval were, aside from having no history of alcohol use disorder, described as 'typical' WKS or WE patients, reported because study author(s) thought WKS or WE rare in their respective patient populations. Additional limitations of this systematic review included restricting the review to cases published in English, and exclusion of cases lacking sufficient clinical detail or other study variables.

The results of the current systematic review clearly indicate that the full spectrum of clinical signs of WKS may be seen in patients without any known history of alcohol use disorder. Contrary to a

common view, the cases reviewed above show that alcohol use disorder is not a necessary precursor for any element of WKS, including chronic cognitive impairment or Korsakoff syndrome. The pattern of findings reinforces the inference that the similarities between nonalcWKS and alcWKS may be more important than the differences in clinical presentation.

Victor and colleagues argued for a unified conception of the acute and chronic effects of thiamine deficiency under the general term of WKS, primarily because of the similarities in the neuropathology in patients dying in any stage of the disease.[21] Nothing has changed in our understanding of the neuropathology to alter that view.[10, 24, 38] In this context, we would argue that the continued use of the term WE to describe acute presentations or the spectrum of the disease attributable to thiamine deficiency, as though clinically and etiologically distinct from chronic KS, is not justified. As noted, this separate usage of WE and KS appears to be based on the inference that KS not associated with alcohol is rare or nonexistent. Historically, this inference is understandable in view of the rarity of WKS in patients without alcohol use disorders. In light of the findings of this systematic review, the separation of WE from KS is no longer justifiable.

The greatest danger in separating WE from KS when attributable to known or suspected thiamine deficiency is the potential to underestimate the frequency of insidious development of WKS where cognitive impairment is the only prominent sign.[9, 10, 20, 21] A failure to recognize the frequency of insidious WKS may result in withholding of treatment to patients with KS because of confusion regarding the possible contribution of an alcohol-related dementia.[10, 11] Of note, a distinct neuropathological entity and accompanying clinical syndrome specifically attributable to ethanol neurotoxicity has always been controversial.[2, 9, 11, 38] Instead, in the absence of evidence-based

guidelines[37] more vigorous attention should be directed to establishing effective treatment of WKS in all its variants.

While we argue against the separate use of the terms WE and KS, it is important to keep in mind that early detection and prompt treatment of thiamine deficiency may prevent acute neuronal death and may prevent the disease from progressing to chronic disability.[3, 14, 26] However, the window for timely clinical intervention is narrow and is often not recognized until after long-term damage is done.[34, 39] Therefore, while the current review emphasizes the importance of detecting chronic disability, this in no way detracts from the critical importance of early diagnosis and treatment of acute thiamine deficiency.

Finally, although the current systematic review primarily demonstrates the similarities in clinical presentation between variants of WKS whether or not related to alcohol use disorder, it is possible that these variants share other similarities. For example, given that thiamine deficiency does not always lead to WKS, it is possible that patients with alcWKS and nonalcWKS share a similar genetic predisposition, such as vulnerable thiamine transporters.[3, 7, 34, 40]

WKS is a treatable and highly preventable disease.[3, 6, 14, 26] Clinicians need to be vigilant for WKS in any patient at risk of nutritional deficiency, irrespective of alcohol use history. Many aspects of WKS remain to be understood including the relationship between duration of illness, severity of acute episodes, severity of cognitive and neurological sequelae, and potential for treatment and recovery.[9, 21] Future research should focus on improving antemortem diagnosis including more sensitive neuroimaging techniques to identify early markers of thiamine deficiency.

CONTRIBUTORS

SJS contributed to study design, the literature search, data collection, analysis and interpretation of the data, and drafted the manuscript. SCB obtained research funding, contributed to design and conceptualization of the study, and analysis and interpretation of the data. MLA contributed to design and conceptualization of the study, the literature search, data collection, and analysis of the data. GW and MJC obtained research funding and contributed to design and conceptualization of the study. All authors revised the manuscript critically for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SJS and SCB are the guarantors of the study and accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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ETHICAL APPROVAL

Not required.

DATA SHARING

No additional data available.

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FIGURES

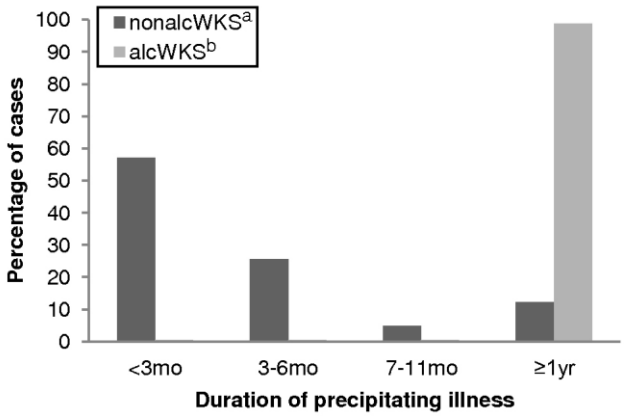

Figure 1 Duration of the Precipitating Illness Prior to Presentation to the Author(s) of Each Case.

[a]nonalcWKS – Present study (*n*=390), <3 months (*n*=223, 57%), 3-6 months (*n*=100, 26%), 7-11 months (*n*=19, 5%), ≥1 year (*n*=48, 12%);

[b]alcWKS – Victor et al., 1989 (*n*=239).

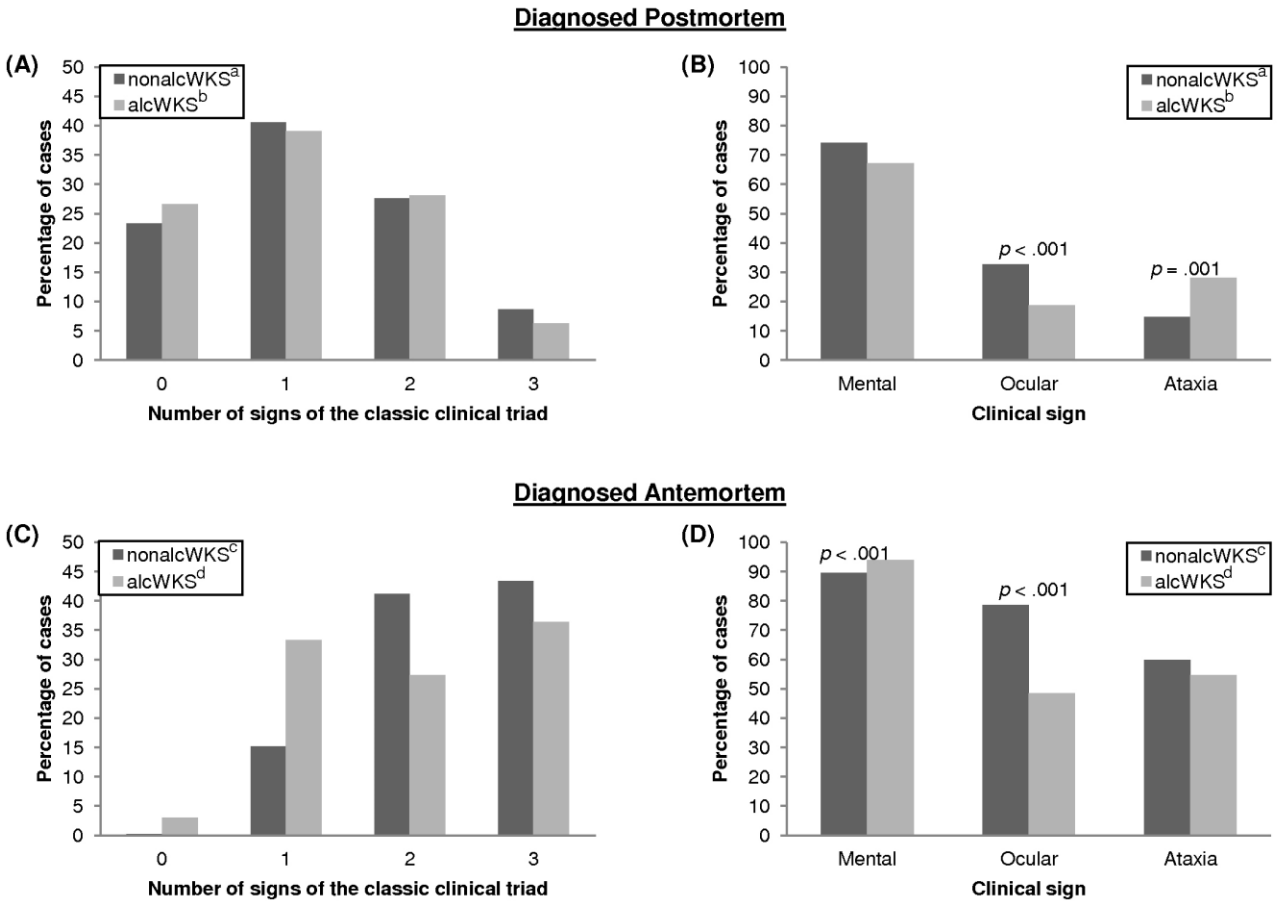

Figure 2 The Classic Clinical Triad in WKS Related (alcWKS) Versus Not Related (nonalcWKS) to Alcohol.

(A) Number of signs of the classic clinical triad detected in cases who did not receive a diagnosis of WKS until postmortem. nonalcWKS: no signs (*n*=27, 23%), one sign (*n*=47, 41%), two signs (*n*=32, 28%), all three signs (*n*=10, 9%).

(B) Percentage of cases reported to show signs of the classic clinical triad in cases diagnosed with WKS at postmortem. nonalcWKS: altered mental state (*n*=86, 74%), oculomotor abnormality (*n*=38, 33%), ataxia or gait disturbance (*n*=17, 15%).

(C) Number of signs of the classic clinical triad detected in cases who received a diagnosis of WKS antemortem. nonalcWKS: no signs (*n*=1, 0.2%), one sign (*n*=77, 15%), two signs (*n*=209, 41%), all three signs (*n*=220, 43%).

(D) Percentage of cases reported to show signs of the classic clinical triad in cases diagnosed with WKS antemortem. nonalcWKS: altered mental state (*n*=454, 90%), oculomotor abnormality (*n*=398, 79%), ataxia or gait disturbance (*n*=303, 60%).

[a]nonalcWKS cases not diagnosed until postmortem – Present study (*n*=116);

[b]alcWKS cases not diagnosed until postmortem – Harper et al., 1986 (*n*=64);

[c]nonalcWKS cases diagnosed antemortem – Present study (*n*=507);

[d]alcWKS cases diagnosed antemortem – Harper et al., 1986 (*n*=33).

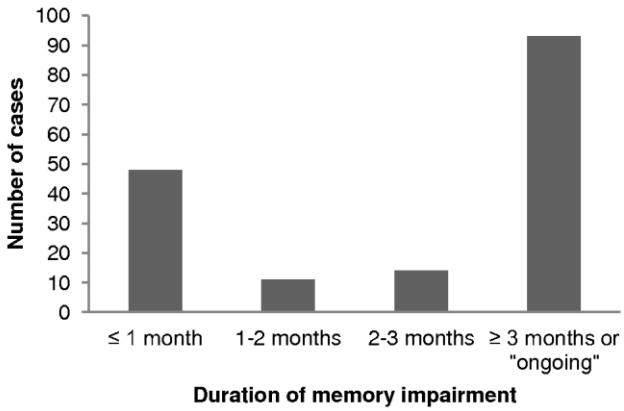

Figure 3 Duration of Memory Impairment Reported in Cases of nonalcWKS (*n*=166).