WERNICKE'S ENCEPHALOPATHY: LOST AND FOUND

"PLUS CA CHANGE, PLUS C'EST LA MEME CHOSE"

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Abstract-Aim: To develop clinical guidelines to identify individuals who misuse alcohol and are at risk of developing Wernicke's encephalopathy (WE). **Method:** Non-systematic literature review of studies which include a careful clinical record of the development of signs and symptoms of thiamine deficiency and in which the diagnosis of WE has been confirmed at autopsy. The review includes a translation into English of the original paper by Carl Wernicke in 1881. **Conclusions:** The assessment of the degree of thiamine deficiency and the diagnosis of WE remain a clinical evaluation and guidelines are suggested to help the clinician. Since neurotoxicity due to the metabolism of excessive alcohol in patients with chronic and severe alcohol dependence may be an important factor in determining long-term outcome of treatment, this must form part of the evaluation.

It is 125 years since Carl Wernicke published his *Lehrbuch der Gehirnkrankheiten fur Aerte and Studirende* in 1881 (Figure 1) in which he described a new disease, based on clinical and pathological observations in three patients. (Wernicke, C 1881). It is also 100 years since the first description of Alzheimer's disease (Alzheimer, 1904). Both of these diseases cause devastating neurological sequelae and neither have specific antemortem diagnostic tests. Recent publications estimate that approximately 24.3 million people in the world have some form of dementia. (Ferri et al, 2005) indicating an urgent need, where possible, to identify the cause of the dementia and to institute preventative or early and effective treatment before irreversible damage occurs.

FIGURE 1. Wernicke, C. (1881). Lehrbuch der Gehirnkrankheiten fur Aerzte und Studirende. Vol 2 Kassel Theodor Fischer 229-242
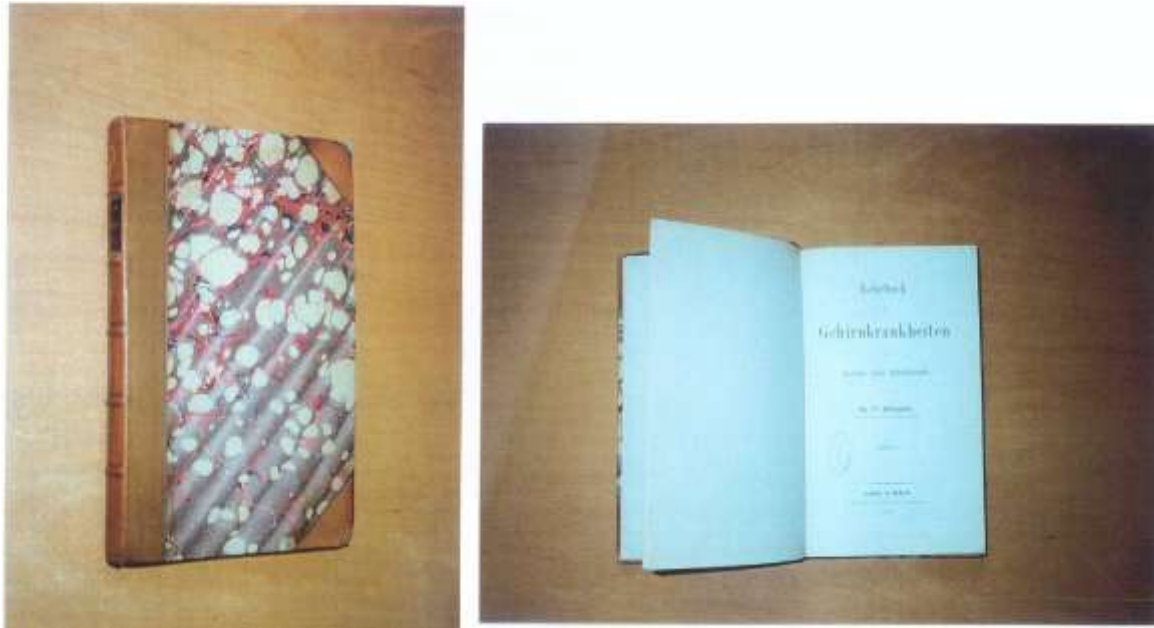
WE, is a neuropsychiatric condition that can lead to dementia and occurs as a result of thiamine (vitamin B1) deficiency. It has classically been described as presenting with an acute onset, characterised by nystagmus, ophthalmoplegia, ataxia and global confusion, occurring together or in various combinations. (Lishman, xxxx). WE can be prevented and treated successfully before the onset of irreversible brain damage. It is thought that patients can suffer recurrent episodes of WE, some of which might be subclinical, leading to a more chronic form of the disease (Lishman, 1998). Many of these patients develop a severe amnesic syndrome that is known as Korsakoff's psychosis (Lishman, 1998). Autopsy studies have shown that the diagnosis of WE and KP is not made during life in 80% of cases (Harper et al, 1986). Although a great deal has been learnt about the natural history and pathophysiology of WE (Thomson and Marshall, 2006a), early diagnosis still depends upon clinical judgement and experience.

While only approximately 16% of patients with WE have the classic triad of signs described above (Harper et al 1986: Naido et al, 1991), there are often early clinical indicators that the patient is thiamine deficient and at risk of developing WE. Unfortunately, these indicators are not widely known and are often attributed to the effects of excessive alcohol intake (Thomson and Marshall, 2006). In reviewing the literature, we have been struck by the consistency of the reported signs and symptoms attributed to WE. Despite this, clinicians continue to focus on the triad, almost in a perseverative manner! In exploring why this is, we have taken an historical/investigative perspective on the situation and returned to the primary literature sources. The original detailed descriptions of Wernicke's patients would seem a good place to begin. In 1989 Victor and his colleagues reviewed the three cases described by Wernicke, together with many published case reports from the early 20th century (Victor et al, 1989). We are not aware of any English translation of Wernicke's original German paper so this was organised (CCHC) and is incorporated below. Wernicke described the early signs and symptoms of his eponymous encephalopathy in three untreated patients. We have compared these findings with those in a number of subsequent studies of patients with WE, either due to malnutrition alone or in association with alcohol misuse.

The combination of thiamine deficiency and alcohol misuse is a common scenario – in some studies almost 90% of cases of WE have a history of alcohol misuse (Harper et al, 1995). It is important to identify this association with alcohol because it appears to increase significantly the amount of thiamine required to treat the patient successfully, compared to individuals with a predominantly nutritional thiamine deficiency. It is also necessary when alcohol misuse is involved, to give the thiamine parenterally, because of alcohol-related malabsorption of

thiamine across the intestinal mucosa (Thomson et al, 1970: Thomson, 2000). It is possible that the other thiamine transport systems, particularly those present in the brain, may be similarly affected (Thomson and Marshall, 2006a).   Since alcohol neurotoxicity can also interfere with the effective utilisation of thiamine, it may be critical to intervene early in thiamine deficient individuals with alcohol misuse. In other words, **success in preventing the amnesic aspects of WKS** requires prophylactic thiamine replacement and reduction/cessation of alcohol intake to occur at the earliest possible time.   With this in mind, we will suggest guidelines for early intervention.

WERNICKE'S CLINICAL DESCRIPTIONS

The clinical findings from Wernicke's original descriptions of patients are summarised in Table 1.

A 20-year old seamstress, was admitted to the Charité on *5 December 1876* with sulphuric acid poisoning, and was discharged, cured, on *6 January 1877*. She said that she had vomited very soon after leaving the institution but had otherwise been well until *3 February 1877*, after which she was confined to her bed and was noticeably sleepy, yawned a good deal and staggered as she walked whenever she attempted to leave her bed. The patient also noticed a deterioration in her eyesight, and later also a constant, very irritating flickering and a strong dislike of light, as well as giddiness and heavy-headedness. Since all these complaints increased and the vomiting persisted, she had herself admitted to the Charité on *11 February 1877*. There had never been a specific infection. On *12 February* her condition was as follows: The patient, very pale, and showing some loss of weight, is lying with her eyes half closed. She opens the lids [/ palpebral fissures] only about 1 cm and cannot open them further even if her eyes are shaded. When looking upwards she opens the eyes a little wider. The opening of the right eye [/ palpebral fissure] **[234]** is normally, and also when looking upwards, somewhat narrower than that of the left. The eyes close completely but with little energy, without the formation of a fold, nor can the eye be induced to close more firmly as a reflex response to being touched. When looking fixedly straight ahead the two eyeballs are stationary and slightly convergent.

When looking upwards, spasmodic movements occur in large excursions, but in the end the movement succeeds to a great extent. The same is observable when the patient looks downwards. The movement of both eyes to the left is significantly impaired. When doing this the left eye will not, despite visible effort and spasmodic movements, go beyond the mid-line, while the right eye can move further inwards, but the inner edge of the cornea can be brought close to the caruncle only for a few moments; generally the inner edge of the cornea only reaches the line of the lower lacrimal point. Movements to the right are similarly impaired: the right eye can also only be brought to the mid-line, while the left can move better than the right to the inner corner, but is still noticeably restricted. When the visual axes are made to converge (by fixing on the point of the nose), the same behaviour is apparent; the left eye is better at turning inwards than the right. When at rest, the aberration of the ocular axes is not very noticeable, although there is clear convergence. The pupils, which are equal and at medium dilation, react sluggishly to light. When the face is at rest the right-hand corner of the mouth is lower and the right cheek is somewhat affected [abnormally smooth?], while on the left side the nasolabial fold and also the fold marking the edge of the lower eyelid are strongly visible. The right corner of the mouth is less open than the left. The expression is as though on the verge of tears, stubborn, and at the same time apathetic. When the patient laughs or opens her mouth wide the same difference remains, whereas when other voluntary movements are made no difference is perceptible between the two halves of the face. There is no other evidence of paralysis, but there is a great feeling of weakness. Patient can walk with support. No loss of sensation; the extremities are cold. Patient complains of extreme tiredness, and her speech is also tired and as though she had just woken from sleep. Repeated vomiting in the course of the day. T. 37.0 -- 37.4. *13 February*. Somnolence persists, patient merely emits a groan from time to time or calls out the name of her fiancé, she is altogether disorientated and seems not to know where she is; when she is wide awake, e.g. at meals, she talks rationally with the staff but suddenly interrupts the conversation, complaining of pain in the small of her back and heavy-headedness. Urine passed sparingly, of a peculiarly oily consistency, contains peptone, no protein, no sugar. Cool extremities. T. 36.4 -- 37.2. *14 February.* Patient has to be woken up, answers but remains disorientated. Complains of headache and stiff neck. Shows extreme anxiety [235] and fear of falling when she is about to be carried. Frequent yawning and groaning. She answers only when questioned repeatedly. Pupils dilated by atropine. Ophthalmoscopically, neuritis optici in both eyes, with only moderate swelling and many streaks of blood. Abdomen bloated, very tight and painful. T. 37.3--37.5. P. 120, barely perceptible. Very restless during the night, often crying out. *15 February*. Soporous state, whimpering with pain, does not answer when spoken to. Death during the afternoon.

Autopsy. There is no flattening of the gyri, the cerebral ventricles contain only a few drops of fluid, tela and plexus are bright red. On section of the central ganglia one sees, along the full length of the third ventricle, in its walls, for a distance of about 3--5 mm, an overall pink coloration of the adjacent cerebral mass, in which numerous small, punctate haemorrhages are present. The lesions are, with almost mathematical precision, equal on both sides. The section shows them very clearly in the area of the middle commissure, which is well developed and is also permeated with haemorrhages; no similar lesions can be observed any longer in the quadrigeminal bodies, nor is there anything in the cerebellum. The pia on the medulla oblongata has a smoke-grey colouring; in the pons and med. oblongata there are no lesions of any size. In the spinal cord no macroscopically visible lesion is present. Numerous haemorrhages in both retinae. Apart from that, traces of the sulphuric acid poisoning. Anatomical diagnosis: encephalitis haemorrhagica substantiae griseae ventricul. III. Haemorrhagiae retinae utriusque. Stenosis pylorica ventriculi; Gastrectasia intorixatione sulfurica, chronica, ulcerosa. The examination made after hardening revealed that the haemorrhages mostly enclosed [/ invaginated?] the vessels, the punctate ones varied in size and in isolated cases attained the size of a pinhead. The small vessels and capillaries much distended and very full, the vessel wall showing no noticeable lesions, only here and there there appeared to be swelling of the capillaries and endothelial cells of unusual size. Close to the haemorrhages there were always granular cells. As for the distribution of these lesions, they never reached the formations and fibre masses adjacent to the grey

floor. Only in the posterior quadrigeminal ganglion on the left-hand side was there, right at the centre, an isolated, pinhead-sized haemorrhage. Going downwards this same lesion in the grey floor reached, with gradually decreasing intensity, to the area of the striae acusticae. The basal arteries appear normal.

A 36-year-old Scot, a piano teacher and allegedly a professor, is a heavy drinker and has drunk cognac, in particular, in large quantities. **[236]** He is admitted to the Charité in a delirious state on *18 June 1877*, has a sleepless night, continuously delirious but not noisy. Condition on *19 June* as follows: a well-nourished, somewhat corpulent man with no disease of the inner organs, talking in delirium in a low voice, shows great motor restlessness [/ superactivity] and very strong tremor, is utterly drenched in sweat. Taken from his bed, patient can walk only very unsteadily and with support, his gait is atactic, interrupted by jerky, purposeless movements, with legs wide apart and trunk held rigid. The patient's restlessness precludes further examination of him lying on the bed, except that it is noted that he responds to pin-pricks to the sole of his foot. His hands move freely, their movement impaired only by the tremor. His speech also extremely tremulous; difficult to assess it, as patient speaks Scottish and only mutters disjointed sounds to himself, and it is impossible to capture and hold his attention. Both pupils very much contracted, almost to the size of pinheads; both the same. The mobility of the eyes seems to be impaired, but it is impossible to assess this more precisely as patient does not focus. Skin temperature not raised. Respiration accelerated, pulse also accelerated, fairly weak, regular. In the following days the delirium continued unchanged, the patient's general condition showed no cause for anxiety. It was seen in the course of repeated observation that the patient barely moved his eyes at all, and was able to focus on objects only by moving his head. With the decline in restlessness there began a somnolent state combined with extreme weakness; patient was unable to maintain a standing position. The pulse, always very soft, became ever weaker, faster and also irregular, the respiration too became irregular and patient died after a fairly long sopor on *26 June*. In his calm period it was possible to test more effectively the mobility of his eyes, and it could be seen that the eyes were almost wholly fixed in the middle position, but there was no ptosis. The pupils, which were otherwise narrowed, dilated with the use of atropine. Ophthalmoscopically the papilla of each eye appeared noticeably reddened, but without any swelling, and in the right eye there was a linear haemorrhage along one vessel.

Autopsy. In the brain the same findings as in the previous case. The haemorrhages are nowhere more than punctate and are confined to the central cavity grey [matter] of the third and fourth ventricle and the aqueduct. The area of the ganglion hanenulae is also affected on both sides. Microscopically the lesions are exactly like those in the previous case. Basal arteries normal.

33-year-old man is admitted to the Charité on *10 March 1878* after the onset of delirium tremens in the morning. A heavy schnapps drinker, especially in the previous few months. Since the last campaign **[237]** frequent complaints of aches in his legs, on an earlier campaign had typhus, once infected as a young man. In the last 4 weeks his walking had been poor at times. 3 weeks ago he had difficulty in passing water, lasting for a week. 8 weeks ago patient is said to have once fallen from a wagon, perhaps on to his head, but without any resultant symptoms. In the last 4 weeks giddiness and headaches at times, and also vomiting in the mornings, especially after heavy drinking. In the past 2 days patient has complained of double vision, and has had jaundice for about the same length of time. Has never had a stroke or attacks of cramp. On *11 March* condition as follows: A very strong, well-nourished individual with slightly icteric colouring, an old scar from a bubo in the right inguinal area. On the transitional fold of the penis a stringy, shiny, scar-like cord; on the lower legs several circular, clearly-outlined patches lacking pigmentation. Since his admission patient has behaved wholly like a man in delirium, is disorientated as to place and surroundings. Now very considerable motor restlessness [/ superactivity], his hands constantly pluck at the blanket, patient throws his body about and turns his head to focus on people who are not there, he calls out the names of acquaintances and also imagines frightening things. As he gesticulates energetically, a strong tremor is present. Voice hoarse, speech hasty, words falling over each other, somewhat tremulous, not incoherent, and no

anarthria. Face covered with sweat, respiration much accelerated, apparently as a result of mental agitation, no cough. Complexion slightly cyanotic, bloated appearance. The lips and teeth have a crusted, bark-like coating. A staggering gait, also impaired by sudden atactical movements and tremors. Is able to stand for a short time on either leg. When asked, patient complains of weakness in his legs. Stretched posture of trunk and head. Tongue somewhat dry, without traces of biting, is stretched out straight but with a strong tremor. In the face, very slight facial paresis on right-hand side. Patient is not confused, his attention can be held for some moments by questioning. P. 110--120, even, fairly full, very soft, T. 39.3. Urine free of protein and sugar. Organs of the chest normal, hepatic dullness extends beyond the costal arch by the width of two fingers. There is total paralysis of the abducens on both sides. Neither eye can be moved outwards beyond the mid-line. The other eye movements seem intact. Pupils of both eyes react to light and convergence of the axes of vision, are half-dilated and show no inequality. There is a prompt reaction to being pricked with a needle in the face and on the hands, but only slight reaction when pricked on the feet. Patient feels a deep prick with a needle in his right big toe only after some time, and then complains of a very strong burning sensation; in the left [toe / foot] most pricks produce no reaction. Tapping on the head not painful, nor is pressure on the spine and the neck muscles. In the evening **[238]** intense reddening of the papillae, but no swelling, was observed ophthalmoscopically; the edges of the papillae not quite sharp. No haemorrhages. Further increase in motor restlessness [/ superactivity] and sweating. P. 120, T. 39, resp. 28--30. *12 March*. In the night the patient was delirious, [muttering] quietly to himself, somewhat calmer towards the morning. Patient is now lying peacefully with eyes closed, but when examined immediately wakes up and is delirious, [muttering] quietly to himself. No jactitation any more. Resp. 24--30, P. 100, regular, still very soft, T. 38,9. Sometimes bursts of coughing with catarrhal sputum. Yesterday an enema with vinegar added produced a copious, mushy stool. Neck is still held rather stretched, especially when the patient is raising himself into a sitting position. Pressure on the processus spinosi of the upper dorsal vertebrae and on the neck muscles produces a strong facial grimace, but stroking the skin of the back does not have this effect. The reduced sensitivity of the lower extremities has given way to hyperaesthesia, which is especially notable in relation to the patient's confusion and shows itself particularly in response to pressure on the calf muscles on either leg. Paralysis of the eyes unchanged, tongue trembles more when stretched out, facialis as yesterday. Pupils dilated with atropine. Evening T. 38.7, P. 90. *13 March*. P. 114. Resp. 26. T. 37.9. Patient is coughing less, still talking to himself, is delirious and disorientated. Gives a start when touched. Hyperaesthesia of the muscles no longer present. With support, patient can walk a few steps, though unsteadily, walks with legs wide apart and stiffly. Eyes and face unchanged. In the evening P. 100--110. T. 37.8. *14 March*. P. 98--100. T. 37.8. Pulse small and very soft, but regular. Patient was delirious for most of the night but this morning is less confused than yesterday and is beginning to orientate himself. As patient is focusing well, his eye movements are more closely examined. The outward mobility is as before, today inward mobility also seems to be impaired, upward and downward mobility intact. When sitting up, definite stiffness of the neck. In the evening P. 100, T. 38.0. Urine free of protein and sugar, strong colour. *15 March*. During the night the patient was delirious at times, mostly quiet. Now patient is in sopor, from time to time there are twitching movements, now of an arm or a leg, now of the whole body. Pulse very small, soft, regular, c. 96, about half an hour ago it was barely perceptible. Respiration is snoring, irregular, and there are quite long pauses, followed first by weak, then by increasingly deep inward breaths. This lacks the regularity of the sequence in [Cheyne-]Stokes respiration. Pressure on either big toe results in the leg being energetically drawn back, and in the case of the right one also facial grimace. Still starts when touched unexpectedly. **[239]** The patellar reflex can be investigated in the left [leg] and is not present. Patient can be awakened by calling to him, and he then says that he is fine. Strong thirst, dry lips, no great impairment of speech. When rising into a sitting position still has stiffness of the neck and facial grimace. *Evening*: P. 100, T. 38.2. *16 March*. P. 96, beginning to become somewhat irregular, T. 38.5. General state little changed, patient still delirious at times but is on the whole quieter, the weakness has increased, patient mostly lies with his eyes half closed, only the whites visible. Frequent

coughing, no expectoration. Taken from his bed the patient also shows greater weakness and his legs give way after a number of unsteady, stiff paces. When one calls to him the patient is fairly conscious for some moments, is orientated and makes an effort to focus on objects held in front of him. Complains of great weakness. The mobility of the eyes has declined further, in both eyes the inward movement is very limited and is accompanied by twitching movements, the movement downwards is also considerably reduced, upward movement is the best preserved but also appears somewhat limited. Ophthalmoscopic finding: the right eye clearly presents the signs of neuritis optici. P. intensely reddened, perhaps somewhat swollen, the edges unclear. The arteries not visible, the vein very blocked and all its branches filled. Close to the p. a small vessel pointing towards the macula is enclosed by a spindle-shaped haemorrhage. No other haemorrhages. In his left eye the patient is only hyperaemic, the edges somewhat unclear, arteries and vein very full, right to the very smallest branches. Towards midday death occurred.

    Autopsy. Pia equally transparent on the convexity and base, very slightly oedematous. Dura not stretched, no lesions, pia also shows no lesions. The hemispheres themselves show nothing significant, only a slight reddening at the cortex. No lesions on the base. Upon removal of the roof of the 3rd ventricle one can see that the substance of the middle commissure is permeated with small punctate haemorrhages. After removal of the cerebellum, the greyest parts of the grey floor are also sprinkled with tiny red dots; possibly also containing capillary haemorrhages. Otherwise nothing noteworthy. Bone marrow without abnormality. Heart somewhat enlarged, walls not hypertrophic. On the side of the mitral valve facing the atrium, several rather old, very coarse, knotted thickenings. Lungs both of considerable volume, oedematous, containing much blood. Organs of the neck very cyanotic, mucous membrane of the larynx thickened, superficial ulcerations on both vocal cords. Spleen broad, cake-shaped, also somewhat enlarged in thickness. Kidneys both very hyperaemic. Anatomical diagnosis: haemorrhagiae punctiformes multipl. commissurae mediae, **[240]** ventriculi tertii et substantiae griseae ventricul. quarti, Oedema et hyperaemia pulmonum. Endocarditis chronica mitralis. Hyperplasia lienis. Infiltratio adiposa hepatis, Ulcera ligg. vocal. The examination of the hardened preparation revealed exactly the same lesion as in the two cases already described, except that the haemorrhages nowhere reached the size of a pinhead. The lesion, which on the basis of the [autopsy] findings is to be interpreted as inflammatory, nowhere extended beyond the grey floor of the fourth ventricle, in the third ventricle it was not so pronounced as in the previous case, but it extended somewhat further downwards into the uppermost area of the calamus scriptorius.

What is present is an independent, inflammatory, acute nuclear disease in the area of the nerves of the eye muscles, leading to death in a period of 10--14 days. The focal symptoms consist of associated paralyses of the eye muscles, which rapidly arise, progress and finally lead to almost total paralysis of the eye muscles; but even then with the exception of certain muscles, such as the sphincter iridis or levator palpebrarum. The patient begins to stagger when walking and his gait shows a combination of stiffness and ataxia, which is most reminiscent of the ataxia of alcoholics. The general signs are very striking and consist of alterations of consciousness, either somnolence from the outset or a final phase of somnolence preceded by a longer phase of agitation. In addition, in all three cases the visual nerves were affected, with inflammatory lesions of the papillae. In every case the onset of the disease had been preceded by taking harmful substances, in the one case sulphuric acid poisoning, which had healed [leaving?] pyloric stenosis, in the other two cases an uncommonly high level of alcohol abuse. The question of whether in these latter cases the signs of delirium potatorum should be regarded as a complication or as a separate general manifestation pertaining to this disease may be posed but cannot be decided; at any rate what was present was not an instance of common delirium tremens but, at the least, delirium tremens complicated by the symptoms of poliencephalitis. However, it should be pointed out that the characteristic disorientation was also observed in the first case, the features of which were totally different from those of delirium [tremens]. Whereas the first observation **[241]** had not been at all understood while the patient was still alive, in the second and third cases I was able to make the

diagnosis despite the difference in the general signs. I think that this provides a justification for drawing attention to these cases as [representing] a particular syndrome.

Only one analogous case is to be found in the literature, and I only learned of it later. The similarity in the main symptoms and in the autopsy findings is unmistakable, even though it was not, as in our cases, only the nuclear region that was affected. The course [of the disease], lasting for five months, corresponds more to a sub-acute form of the disease.

Gayet. Affection encéphalique (encéphalite diffuse probable) localisée aux étages supérieurs des pédoncoules cérébraux et aux couches optiques, ainsi qu'au plancher du quatrième ventricule et aux parois latérales du troisième. Arch. de phys. 1875. 28-year-old man, is admitted on *23 November*. In the middle of September he had been working in an engine-room when suddenly a boiler exploded not far from him. Although this caused great damage, he sustained no injury at all, but he became quite beside himself, could not sleep and was extremely agitated. He was able to work for three more days, but then he discovered that he could no longer read and write properly. After that he remained in a state of general weakness, exhaustion and apathy, and in addition, after a time, constant sleepiness. On admission he is able to answer perfectly intelligently, but slowly, and has to be kept alert. His facial features are mask-like, the orbicularis oris and palpebrarum are pressed close to the bones beneath them, there is ptosis on both sides and the lids [/ palpebral fissures] are 3/4 closed. Despite the very noticeable atonia there is no actual facial paralysis, all movements can be performed, but speaking, for instance, takes place as it were in isolation, without participation by the rest of the physiognomy. There is general weakness, of equal degree, in the whole musculature, to the extent that the patient is incapable of keeping himself upright or pressing firmly with his hand. Both oculomotorii are almost wholly paralysed in all their branches, only the pupils and accommodation are normal. The vision is good. All the special senses and all qualities of sensitivity of the skin are normal. Patient is so sleepy that he falls asleep while being examined, while eating, etc., and can only be kept awake by vigorous shaking. Up to *18 December* the weakness increases further and becomes more pronounced on the right side. The sleepiness continues. *5 January*. Ophthalmoscopically no definite finding, p. perhaps somewhat reddened, more so in the left eye. *8 January*. Total **[242]** hemiplegia on the left side with somewhat reduced sensitivity, continues until *18 January*, on that day it seems to have disappeared; at the same time great agitation has taken the place of apathy, the patient complains of pain in his right leg, his facial expression is somewhat more lively. In the evening slightly raised temperature, for the first time some tracheal râle. The next day is very good, on *20 January* extreme sleepiness again. Varying behaviour until *7 February*, when it is noted that the sensitivity on the right side is somewhat less acute but otherwise normal, that the special senses are functioning and the intelligence is normal once the patient has been woken up. The left pupil is dilated. *8 February*. Ophthalmologically no change. *10 February*. Increasing weakness and weight loss, bladder incontinence begins. Incipient pressure sores are noted on *15 February*, on *17 February* death occurs. In the last month the temperature varied between 37.4 and 38.5, rising when the patient awoke. The urine taken from the bladder after death contained neither protein nor sugar, but upon addition of alkaline copper solution a black precipitation formed, the nature of which could not be determined.

Autopsy. The central cavity grey [matter] of the 3rd and 4th ventricles thickly permeated with capillary apoplexies. The lesion begins at the front, at the anterior commissure, coats the interior walls of both thalami, encompasses the taeniae of the thalamus, the pineal gland, infundibulum and tuber cinereum, as well as the enormously enlarged middle commissure, and also the area around the Sylvian aqueduct and the grey floor of the 4th ventricle as far as the tip of the calamus scriptorius. Apart from the punctate haemorrhages the illustration shows a general yellowish-grey discoloration and a very noticeable injection of the fine vessels. A frontal section of the area of the crus of the cerebrum, just in front of the pons, shows, according to the text, that the lower level -- that of the pes -- has remained healthy, while according to the illustration the left side is for the most part also affected; the lesion,

considered by the author to be inflammatory, encompasses the whole transverse section of the tegmentum including the left brachium conjunctivum. Both thalami are affected all over but in an irregular fashion, in such a way that there are parts that are normal in between the affected parts; on the left the lesion seems more significant and also extends to the wall of the lateral ventricle. Microscopic sections of the inner surface of the right thalamus, made using the fresh preparation, confirm the assumption of an inflammatory process. The vessels were carefully examined and showed no lesion.

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THE CORRELATION BETWEEN CLINICAL SIGNS/SYMPTOMS OF WE AND AUTOPSY FINDINGS

The concept of a "classic triad" of signs and symptoms in WE was based on the original description by Wernicke. The triad consists of an abrupt onset of a confusional state and impairment of consciousness, ataxia and eye signs (nystagmus and ophthalmoplegia). Similarly, Victor et al (1989) in their famous monograph concluded: "*The diagnosis of*

Wernicke's disease is made most readily on the basis of the acute appearance of ocular palsies, nystagmus, ataxia of gait, and disturbances of consciousness and mentation, which may present singly or in various combinations. More than 80% of patients show signs of polyneuropathy as well, and associated liver disease is found in two thirds of the patients" (Victor et al, 1989, page 195).

However, as Wernicke himself described, and in subsequent studies, other important clinical signs and symptoms are often present before the later "classical" signs appear.

In 1887, six years after the description by Wernicke, Korsakoff gave the first comprehensive description of the unique amnesic syndrome which is designated by his name – Korsakoff's psychosis (Korsakoff, 1887). The syndrome was elaborated in a series of articles between 1887 and 1891 [Korsakoff (1887); Korsakoff (1889a); Korsakoff (1889b); Korsakoff (1890a); Korsakoff (1890b); Korsakoff (1891)]. His third article, published in 1889, was translated into English by Victor and Yakovlev (1955). These authors felt that this was important because "many of his original observations and ideas have been misquoted, distorted or even completely lost in the secondhand treatment of the subject by subsequent writers" (Victor & Yakovlev, 1955).

"IN VIVO" CLINICAL FINDINGS IN PATIENTS WITH WE, LATER CONFIRMED BY POSTMORTEM DIAGNOSIS

Table 1 summarises the clinical findings in the patients reported by Wernicke and Korsakoff, together with those from other studies in which autopsy confirmation of the diagnosis of WE was made. We begin with the premise that: "The pathological features of WE are characteristic with little likelihood that the wrong diagnosis could be made" (Harper et al, 1995). The papers are presented below, in chronological order. In Table 1 symptoms and signs were recorded as being present if they were present in any of the patients. Unfortunately the information available did not allow us to express this as a frequency, except in the papers of Harper et al (l986) and De Warderner and Lennox (1947), where the percentages have been added to the table. The symptoms and signs selected for recording are, to some extent, arbitrary and dependent upon the knowledge and specialism of the clinicians and what they considered to be the diagnosis at the time. Despite this, there seems to be consistency in those signs and symptoms that were recorded.

Campbell and Biggat (1939) from Edinburgh described 12 cases of WE, aged between 3½ and 68 years; only one was alcoholic (3 male; 9 female). Riggs and Boles (1944) studied 42 cases from Philadelphia (13 men) between 1934 and 1943 - only 18 of the patients who "volunteered a history of heavy alcohol intake were judged to be alcoholic". In 1947, De Wardener and Lennox wrote a famous paper on their experience of 52 male soldiers, held as prisoners-of-war by the Japanese, who developed WE due to dietary thiamine deficiency. Barrie (1947) also described WE occurring in three patients in Sheffield. Cravioto et al (1961) described 28 cases of WE from Bellevue Hospital, New York. These authors provided detailed autopsy findings on the 18 men and 10 women aged between 32 and 82

years (mean 54 years). In 1969, Grunnet compared the earlier findings from Riggs and Boles' (1944) series with a later (1965-1968) series from the same hospital in Philadelphia.

Victor and colleagues collected a substantial series of patients with WE over several years in Boston. Preliminary findings were reported in 1971 (Victor et al, 1971). Of their final series of 245 patients with WE, 82 had a complete autopsy examination (Victor et al, 1989). The group comprised 154 men and 91 women, aged 30-70 years, predominantly in their 5-6th decade. Most of these patients were heavy drinkers and malnourished. This work was published as a monograph, sadly now out of print, containing the clinical and pathological findings of these patients. The unique value of their observations was that a substantial proportion of their patients survived the acute stage of WE and remained under observation for many months or years. Clive Harper, a neuropathologist, continued work on WE in Australia, publishing a series of very important, pioneering studies which have done much to establish the incidence of WE in alcoholics and the general population around the world. He also demonstrated, very clearly, that the diagnosis is only made clinically in about 20% of cases prior to autopsy. Harper, (1986) please add other references. Wallis et al (1978) described 4 alcoholic patients (2 male) who presented in a comatose state.

These retrospective studies have been based upon the clinical records of patients who often presented late in the course of their illness, and in whom the diagnosis was clinically uncertain. It should be emphasized that the clinical signs and symptoms in these patients were usually recorded before the definitive diagnosis was made. In other words, the doctors recorded what they observed and considered relevant often without making the correct diagnosis. Torvik et al (1982) described their findings from 8,735 autopsies performed over a

5-year period in Oslo. They documented 70 cases of WE (0.8%) and 152 cases of alcoholic cerebellar atrophy (1.7%). The latter was found to be present in 26.8% of all alcoholics examined.   Twenty two of their WE cases were active (acute or subacute) and 48 were chronic.   Clinically, stupor and coma were documented as the dominant symptoms.   This study was followed, in 1989, by a paper from Lindboe and Loberg who reported a 5-year study of 6,964 autopsies with 52 cases of WE, of which 12 (23%) had occurred in non-alcoholics.   There were 18 acute cases in their study and 7 of these (39%) were not alcoholics.   Only 4 of the active (acute) cases of WE had been diagnosed clinically and all of these were alcoholics. The predominant clinical symptoms in this series were disorientation and depressed levels of consciousness, with eye signs being recorded in only 3 cases. Thiamine was often given too late, prompting the authors to comment that even the slightest suspicion of WE should initiate the immediate parenteral administration of large doses of thiamine. In 2005, Fattal-Valevski et al reported findings on 9 infants (6 male; 3 female, aged 2 to 12 months) who had received a soy-based formula which was deficient in thiamine. The babies responded promptly to treatment with thiamine but unfortunately two deaths occurred (Vikhanski, 2004). We have also included previously unpublished data on 44 patients with the Wernicke-Korsakoff Syndrome (WKS) diagnosed on post-mortem which one of us (CH) has collected more recently.

WHAT THESE STUDIES TELL US ABOUT THE CLINICAL DIAGNOSIS OF WE

The reports from all these studies show a remarkable similarity in patterns of signs and symptoms, even though some patients were not exposed to alcohol. However, care must be

taken in the interpretation of these studies as the findings are dependent, in part, on how accurately and carefully the clinical findings were recorded, especially when the diagnosis was not made. Torvik et al, (1982) have emphasized that the classic symptoms of WE may not always be as prominent and striking as generally believed (Victor et al, 1971). Stupor and coma, which have been said to be rare in WE (Victor et al, 1971; Plum and Posner. 1980) develop rapidly and were the main findings in their case series. In their view, this did not imply that there were two different populations of WE.

In Figure 2 we have summarized the development of signs and symptoms of WE in the prisoners-of-war described by De Wardener and Lennox (1947). They also suggested a method for grading the severity of the clinical picture of WE which is highly relevant to the early diagnosis of WE. It is clear from the figure that the mild, moderate and severe/terminal phases of WE have distinctive signs and symptoms. Thus, mild WE was characterized by anorexia, nausea, vomiting and eye signs, the moderate phase by memory loss, and emotional changes and the severe phase by confusion, confabulation and coma. What is even more interesting is that de Warderner and Lennox observed that these symptoms were reversed in approximately the same chronological order following treatment. Unfortunately, we do not have such a carefully documented development of signs/symptoms for alcoholic patients who often present later in the illness and in whom the findings may be modified by alcohol withdrawal or by hepatic encephalopathy (Caine et al, 1997)

In Table 3 we summarise factors predictive of thiamine deficiency and related neurotoxicity (Thomson and Marshall, 2006a). It includes the early symptoms and signs

associated with early thiamine deficiency, evidence of malnutrition together with factors predisposing to neurotoxicity since thee is evidence that alcohol permanently damages the thiamine-depleted brain to a greater degree than thiamine depletion alone (Price et al, 1993, Ciccia and Langlais, 2000; Crowe and El-Hadj, 2002.). For further discussion the reader is referred to Thomson and Marshall, 2006.a **Need to summarise the most important outcomes from this summary here**

THE DIAGNOSIS OF PATIENTS AT RISK AND THOSE WHO HAVE DEVELOPED WE

Little has changed since Wernicke described his disease in 1881 and the diagnosis today is still based on careful clinical observation. An important advance in the diagnosis of WE was made by Caine et al, 1997 when they developed operational criteria to differentiate between Werncike's encephalopathy alone or in combination with Korsakoff's psychosis or hepatic encephalopathy. The criteria for WE require two of the following signs; (1) dietary deficiency (2) oculomotor abnormalities (3) cerebellar dysfunction and (4) either altered mental state or mild memory impairment. This retrospective study, in which the diagnoses were confirmed at autopsy, showed that using the operational criteria, antemortem identification of WE an be achieved with a high degree of specificy although the accuracy of diagnosis was reduced when hepatic encephalopathy was present. In our present paper, we are concerned with the early identification of patients at risk of developing WE and who have developed the prodromal

symptoms of thiamine deficiency. Approximately 10% of patients die in the acute phase of WE and between 56%-86% may develop KP when given inadequate parenteral thiamine. (Victor et al, 1989; Thomson and Marshall, 2006a). In Table 1, we have seen some of the early prodromal symptoms of thiamine deficiency their diagnosis having been confirmed at autopsy If these symptoms are taken in conjunction with other predisposing factors to WE, it may be possible to identify patients who need parenteral thiamine prophylaxis which will protect them from developing WE and from dying in the acute phase of the disease or being at risk of developing KP or some other less well defined degree of brain damage. Caine et al,(1997) carefully selected their subjects to include those drinking more than 80 g of ethanol per day for most of their adult life, with neurological and clinical assessments at more than one point, full necropsy, interview with general practitioner or relatives and systematic neuropathological examination to exclude conditions other than those directly attributable to chronic alcohol consumption. In Table 2, we compare the clinical findings from a number of other studies. There is a large variation in the number of cases studied in each group, the collection of clinical data was not always as meticulous and patients presented at different stages of their disease and some received thiamine therapy. However, there is general agreement about the importance of these signs.

As new techniques of neuro-imaging are developed and resolution increases, so anatomical structures like the mammillary bodies can now be visualized, thus aiding the clinical diagnosis of WE (White et al., 2005; Celik & Kaya, 2004; Aupe et al., 2001), However, these are unlikely to help us identify patients at risk.   Recent investigations have identified an abnormal gene present in some patients with WE which is involved in thiamine transport and may, if future work confirms these findings, be the basis of a diagnostic test (Guerrini et al, 2004).   It has become apparent that recovery following thiamine replacement may be limited by too small a dose of thiamine and/or by thiamine being given too late, or via the wrong route (Thomson et al, 2002**). However the neurotoxicity which occurs as a result of heavy alcohol use and possibly the syndrome of alcohol dependence itself, probably explain why patients misusing alcohol require much larger doses of thiamine than non-alcoholics and often do not recover completely** (Thomson and Marshall, 2006a). We have prepared some guidelines for identifying early thiamine deficiency and to aid the doctor in predicting whether the patient has WE (Table 3).

Although we have concentrated on thiamine replacement it must not be forgotten that many nutrients are required for normal brain function and that alcoholic patients may need a wide spectrum of nutritional therapy (Bonner et al, 2004).

DISCUSSION

Review of the clinical findings in cases of WE that have been diagnosed pathologically at autopsy show a consistent pattern of signs and symptoms. The patterns appear to be similar regardless of whether the thiamine deficiency is related to nutritional problems alone or associated with alcohol misuse. Ideally, studies would need to be set up both in alcoholic and non-alcoholic patients carefully to list the order in which symptoms appeared as well as an extremely detailed clinical (including neurological and psychiatric) ongoing assessments. The groups would need to be large enough to allow for the varying stages in the disease process at which the patients presents and a meticulous neuropatholoical examination will need to be carried out on all patients. Long- term follow up is required to evaluate the effectiveness of any therapy given to the patient. However, it is also evident that in approximately 80 % of cases the diagnosis of WE was not made prior to death. This means that it is virtually impossible to establish accurate prevalence rates of WE in various populations without significant numbers of autopsies. In recent years, there has been a marked decline in the numbers of hospital and Coroner's autopsies carried out (REF). Even in situations where autopsies are performed and the brain is examined, often no sections of the appropriate brain areas are taken. Many families object to an autopsy being carried out, cases are given death certificates which would have previously required an autopsy and there seems to be a general lack of interest by many clinicians for hospital autopsies to be performed. (The Royal College of Pathologists of Australasia Working Party, 2004) Indeed in the UK there is concern about the low numbers of consultant pathologists, and the crisis re: recruiting into the specialty (ref). It is therefore

clear that we will never be able to establish the true incidence of WE by this method, nor how many patients with WE have remained undiagnosed. However it is possible that future neuro-imaging techniques will be able to diagnose the lesions accurately, and thus facilitate treatment.

During the past 15 years attempts have been made to develop postmortem MRI imaging (Pfefferbaum et al 2004).

The responsibility of the clinician is to identify patients at risk of WE as early as possible, and to institute effective prophylactic therapy (Thomson and Marshall 2006b). The diagnostic criteria in Table 3 will aid in making this assessment. The extent to which the early signs of thiamine deficiency reflect biochemical changes in the body, and when they begin to affect the brain in man, remain speculative. Studies in rats, however, have demonstrated that a single episode of thiamine deficiency can selectively damage cortical white matter tracts, while at the same time sparing the thalamus or mammillary bodies, and may be responsible for the behavioural changes observed in alcoholic patients without WE (Langlais and Zhang 1997).

Doctors have come to rely too much on the "classic triad" of signs for diagnosing WE which only occurs in 10% of patients, although it has been known for many years that other indications suggest that the patient is at risk. It remains to be demonstrated that our early intervention will be effective in preventing permanent brain damage. We will no longer have the gold standard of autopsy changes to help us establish the optimum dose of thiamine

required to prevent or treat WE, the duration of treatment necessary, nor the route of administration required. Careful long term follow-up studies will be required to demonstrate that the patients are not left with KP or otherwise cognitively impaired. Wernicke could be forgiven for thinking that 120 years after he correctly diagnosed his patients, not a lot has changed!

Acknowledgements

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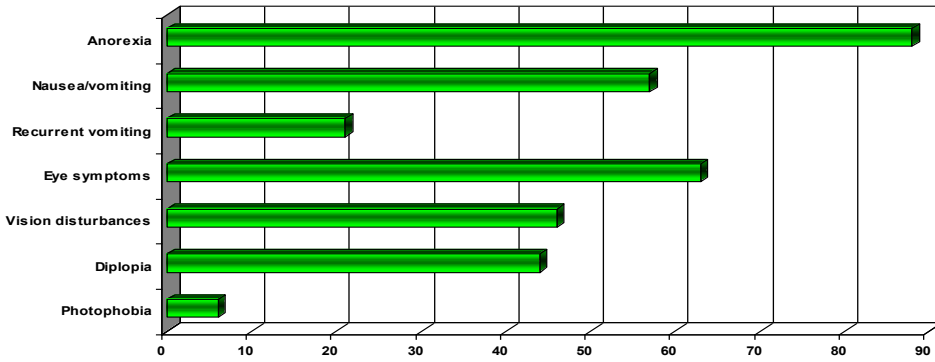
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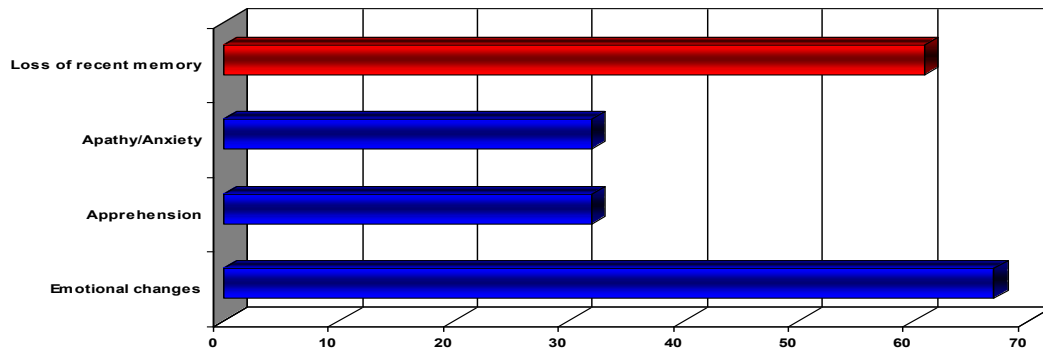
FIGURE 2:

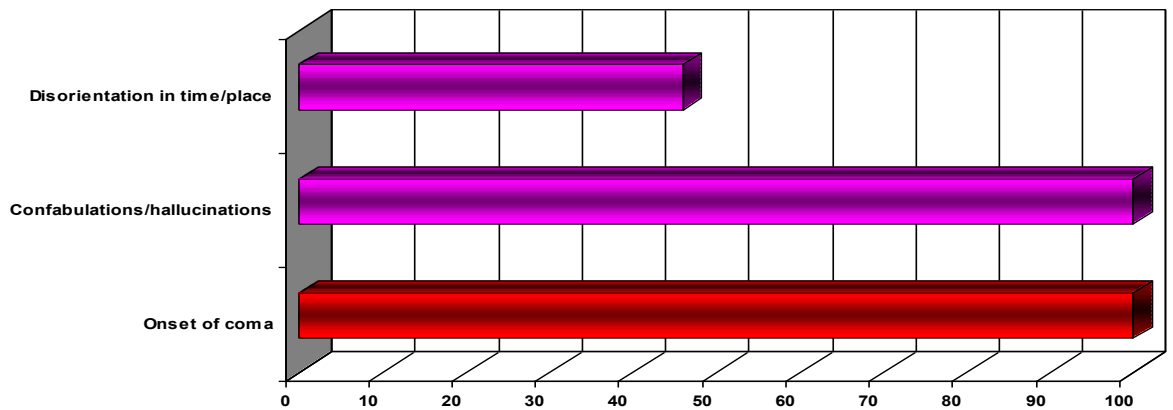## DEVELOPMENT OF SIGNS/SYMPTOMS IN NON-ALCOHOL RELATED WE

TABLE 1. Recorded clinical findings in patients whose diagnosis of Wernicke Korsakoff Syndrome (WKS) has been confirmed at post-mortem

	Wernicke			Korsa koff	Campbell et al.	Raggs et al.	De Wardener	Barrie	Craviato	Grunnet et al.	Victor	Wallace et al.	Torvik et al.	Harper	Lindbo &loberg	Fattal	Harper*
	1881			1889	1939	1944	1947	1947	1961	1969	1971-9	1978	1982	1986	1989	2005	2006
PTS. No.	F 20	M 36	M 33		12	42	52	3	28	24	245	4	70	97	52	9	44
Loss of appetite				Y			Y (88%)				Y						
Weight loss	Y						Y	Y			Y						Y (25%)
Nausea & Vomiting	Y		Y	Y			Y (78%)				Y					Y (89%)	Y (7%)
Fatigue & weakness		Y		Y							Y	Y					
Apathy & lethargy	Y		Y	Y	Y		Y (32%)		Y		Y		Y			Y (78%)	
Fear	Y	Y															
Apprehension					Y	Y	Y (32%)										
Emotional Instability						Y	Y (67%)										
Confusion	Y			Y	Y	Y	Y (100%)	Y	Y	Y (50%)		Y	Y				Y (34%)
Impaired memory				Y			Y (61%)	Y	Y		Y		Y	Y (30%)			Y (40%)
Giddiness	Y		Y				Y (21%)										
Insomnia		Y				Y	Y (38%)										
Anxiety/Depression	Y			Y			Y				Y						
Difficulty in concentration					Y		Y				Y						
Disorientation	Y		Y				Y (46%)		Y	Y (50%)	Y	Y		Y (42%)	Y		Y (5%)
Confabulation				Y	Y		Y (100%)		Y	Y (12.5%)	Y						
Hallucinations					Y		Y			Y (8%)	Y						
Stupor		Y		Y							Y		Y				
Staggering/Ataxia		Y		Y			Y			Y	Y (12.5%)	Y	Y		Y (37%)		Y (25%)
Ophtalmoplegia Diplopia/Ocular Abnormalities	Y	Y			Y	Y	Y (98%)	Y	Y	Y (16.7%)	Y	Y		Y (4%)*	Y		Y (3%)
Nystagmus					Y	Y	Y (100%)		Y	Y (8%)	Y	Y	Y	Y (10%)	Y	Y (22%)	
Delirious		Y	Y	Y	Y	Y	Y				Y						
Motor Restlessness		Y	Y	Y									Y				

Peripheral neuropathy			Y	Y			Y (52%)	Y	Y	Y (12.5%)	Y	Y					Y (25%)
Coma					Y		Y (100%)	Y			Y	Y	Y		Y		
Fits						Y	Y (2%)			Y (2%)	Y						Y (7%)

*combined nystagmus plus ophthalmoplegia in 15% of the sample

Table 2. Incidence of clinical signs in the Wernicke Korsakoff Syndrome: review of the literature

Author	Cases (no.)	Eye signs	Ataxia	Mental changes
Harper (unpublished data)	44	3%	25%	79%
Fattal-Valevski et al., 2005	9	33%	22%	56%
Lindboe & Loberg, 1989	52	21%	NA	6%
Harper et al., 1986	97	29%	37%	76%
Victor & Adams, 1983	163/232	100%	100-81	99%
Wallis et al., 1978	4	0%	NA	100%
Groen & Hoff, 1977	50	80%	46%	88%
Grunnett, 1969	24	25%	13%	75%
De Wardener & Lennox, 1947	52	100%	NA	100%
Cravioto et al., 1961	28	32%	18%	93%
Barrie, 1947	3	67%	0%	100%
Riggs & Boles, 1944	42	24%	10%	86%
Campbell & Biggart, 1930	12	42%	0%	92%

TABLE 3. Patients at risk of Thiamine Deficiency and/or Neurotoxicity

Factors predisposing to Thiamine Deficiency

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

Factors predisposing to Neurotoxicity

- **Genetic predisposition to alcohol dependence and neurotoxic effects of alcohol**
- **Quantity / frequency of alcohol use**
- **Severity of dependence**
- **Frequent episodes of acute intoxication**
- **Withdrawal syndromes**
- **Concurrent drug use, particularly cocaine**
- **Frequency of occurrence of "memory blackouts"**
- **Alcohol-related liver damage**

Early signs-symptoms of Thiamine Deficiency

- **Loss of appetite**
- **Nausea/vomiting**
- **Fatigue, weakness, apathy**
- **Giddiness, diplopia**
- **Insomnia, anxiety, difficulty in concentration**
- **Loss of memory**

Operational criteria for Wernicke Encephalopathy
Two of the following four signs according to Caine et al. (1997):

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

<div align="right">

DeWardener and Lennox, 1947
Caine et al., 1997
Thomson and Marshall, 2006a

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