Novel diagnostic procedure

Elevated cerebrospinal fluid tau in Wernicke encephalopathy

Daphne W Frijlink,¹ Joachim J Tilanus,² Gerwin Roks¹¹Department of Neurology, St Elisabeth Hospital, Tilburg, Netherlands²Department of Psychiatry, St Elisabeth Hospital, Tilburg, Netherlands

Correspondence to Dr Gerwin Roks, g.roks@elisabeth.nl

Summary

Wernicke encephalopathy (WE) commonly presents with oculomotor abnormalities, gait ataxia and confusion. WE can mimic rapidly progressive dementia syndromes, such as Creutzfeldt-Jakob disease (CJD). Cerebrospinal fluid (CSF) tau is frequently used for diagnosis of several dementia subtypes, predominantly CJD and Alzheimer's disease. The combination of very high CSF tau (tau) and normal phosphorylated tau (p-tau) levels is almost exclusively seen in aggressive diseases, such as CJD. The authors present a case of a woman with WE, caused by chronic insufficient dietary intake, with highly elevated CSF tau and normal p-tau. The clinical symptoms and CSF findings raised the suspicion of CJD. However, shortly after immediate treatment with thiamine the patient clinically improved. At follow-up, 2.5 months later, she had made a good recovery. This case of rapidly progressive dementia illustrates that, even in the case of a highly elevated CSF tau, clinicians should be alert for treatable causes such as WE.

BACKGROUND

Wernicke encephalopathy (WE) is a neurological disorder that results from thiamine deficiency.¹ Although the most common clinical setting for WE is chronic alcoholism, it also occurs in a number of other conditions.¹ Diagnosis of WE is not difficult when patients present with the classic clinical triad of gait ataxia, ophthalmoplegia and confusion. However, only one-third of the patients present with this triad,¹ and earlier case reports have shown an overlap between the clinical features of WE and other rapidly progressive dementia syndromes, such as Creutzfeldt-Jakob disease (CJD).²

Discriminating WE from other neurodegenerative disorders is extremely important, because WE is a treatable disorder with a possible good outcome, as long as thiamine is given without delay. CJD can be confirmed with cerebrospinal fluid (CSF) analysis, which shows very high levels of tau and a positive 14-3-3 protein.³ We present a case of a woman with WE, caused by chronic insufficient dietary intake, and highly elevated CSF tau which raised the suspicion of CJD.

CASE PRESENTATION

A 56-year-old woman with a 4-week history of confusion was admitted to the psychiatry department because of the clinical suspicion of a major depressive disorder with psychosis-like symptoms, complicated by malnutrition. She was hospitalised because of significant weight loss. She was unable to give a history, and background information was obtained from family members. They described a progressive confusion over the last 4 weeks. For about 6 months, she had had an insufficient oral intake followed by significant weight loss. She rapidly deteriorated during her stay at the hospital. She became apathic and had diminished spontaneous speech. The medical history included depression, non-insulin-dependent diabetes mellitus and a severe sensory diabetic polyneuropathy. There was no history of alcohol abuse.

Internal examination revealed no abnormalities. On neurological examination, she had spontaneous eye opening without verbal response and variable responses to one-step commands. She had an upbeat and horizontal jerk nystagmus with a full range of ocular movements. She moved all limbs spontaneously but movements were ataxic. She was able to stand assisted by two persons, but was unable to walk. No myoclonus was present. Deep tendon reflexes were normal. Plantar responses were flexor.

INVESTIGATIONS

Serum investigations, including thyroid functions, were unremarkable. Serology for *Borrelia burgdorferi* and lues were negative. Vitamin B₁₂ was normal at 304 pmol/l (normal >210 pmol/l). Serum thiamine was reduced at 27 nmol/l (100–170 nmol/l). CSF was acellular with a normal protein. Total tau protein was 2380 ng/l (<350 ng/l), p-tau-181 31 ng/l (<85 ng/l), amyloid β -42 protein 436 ng/l (>500 ng/l), 14-3-3 protein was negative. Electroencephalography showed generalised slowing consistent with an encephalopathy. MRI showed increased signal on T2 imaging in the periaqueductal area.

DIFFERENTIAL DIAGNOSIS

After neurological examination WE or a rapidly progressive neurodegenerative disorder were considered and further analysis was performed.

TREATMENT

Treatment included low-dose lorazepam, rehydration and dietary supplements, including thiamine 100 mg daily intramuscular.

OUTCOME AND FOLLOW-UP

Shortly after thiamine admission, the patient clinically improved confirming the diagnosis of WE. She became alert, her speech became more coherent and fluent. The

jerk nystagmus disappeared. She still had an ataxic gait, but now was able to stand and walk with the help of one person. Repeated EEG showed normalisation of the background pattern. Repeated MRI scan revealed normalisation of periaqueductal area. Repeated lumbar puncture, 1 month later, showed reduction of total tau protein to 1300 ng/l (<350 ng/l), and unchanged p-tau-181 protein at 37 ng/l (<85 ng/l) and amyloid β -42 protein at 457 ng/l (>500 ng/l).

The patient was discharged in a fairly good condition. No depressive symptoms were present anymore. At follow-up, 2.5 months later, only a subtle gait ataxia was present.

DISCUSSION

This case illustrates that very high CSF tau levels without increased p-tau can be present in patients with WE. It is the first case described with such high levels of tau and the first with malnutrition as the cause of thiamine deficiency.

In recent years, we have seen a rapid increase in the number of studies being published on CSF tau in Alzheimer's disease (AD)^{4 5} and other dementia syndromes.⁶ CSF tau has been proposed as a general marker for neuronal degeneration.⁷ The level of increase in CSF tau is highest in disorders with the most extensive neuronal degeneration, such as CJD.^{8 9} In a study of CSF analysis in CJD patients tau levels higher than 1260 ng/l had a positive predictive value of 90% for the diagnosis CJD.¹⁰ p-tau is thought to represent the phosphorylation state of tau and thus possibly the formation of neurofibrillary tangles as is seen in AD.¹¹ The combination of very high CSF tau levels and normal p-tau levels is almost exclusively seen in aggressive diseases such as CJD and stroke.^{8 10} In these disorders, there is a high rate of neuronal cell death without phosphorylation.

It has been postulated that especially the p-tau/tau ratio is a marker to discriminate sporadic CJD from other dementias, with CJD having a very low p-tau/tau ratio with no overlap between AD. No cases of WE were included in this study.¹⁰

At autopsy, Bertrand *et al*¹² found five cases of WE in 647 patients with a clinical suspicion of CJD. This stresses the necessity of remaining alert to the diagnosis of WE when CJD is suspected.

In this case, CJD was suspected given the CSF results. Fortunately, serum thiamine was also determined and turned out to be very low. This case illustrates that WE should be considered in patients with isolated increased CSF tau and thiamine should be determined in cases with rapidly progressive dementia even in the absence of alcohol abuses. Further research is needed on the prognostic value of CSF tau. Whether the CSF tau level in these

patients represents a prognostic factor as shown in AD⁴ is unclear.

Review of similar published cases/case series:

Matsushita *et al*⁶ describe a case series of acute WE in alcohol-dependent subjects and found elevated CSF tau level in all of them. The mean level of CSF tau was 1069 and the highest level found was 1995 ng/l.

Learning points

- ▶ Wernicke encephalopathy (WE) is a treatable disorder with possible good outcome, as long as thiamine is given without delay.
- ▶ WE can mimic Creutzfeldt-Jakob disease.
- ▶ Clinicians should consider WE in patients with isolated increased CSF tau.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Victor M**, Adams RA, Collins GH. *The Wernicke-Korsakoff syndrome and related disorders due to alcoholism and malnutrition*. Philadelphia: FA Davis, 1989.
2. **Stone R**, Archer JS, Kiernan M. Wernicke's encephalopathy mimicking variant Creutzfeldt-Jakob disease. *J Clin Neurosci* 2008;**15**:1308–10.
3. **Chohan G**, Pennington C, Mackenzie JM, *et al*. The role of cerebrospinal fluid 14-3-3 and other proteins in the diagnosis of sporadic Creutzfeldt-Jakob disease in the UK: a 10-year review. *J Neurol Neurosurg Psychiatry* 2010;**81**:1243–8.
4. **Kester MI**, van der Vlies AE, Blankenstein MA, *et al*. CSF biomarkers predict rate of cognitive decline in Alzheimer disease. *Neurology* 2009;**73**:1353–8.
5. **van Harten AC**, Kester MI, Visser PJ, *et al*. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. *Clin Chem. Lab Med* 2011;**49**:353–66.
6. **Matsushita S**, Miyakawa T, Maesato H, *et al*. Elevated cerebrospinal fluid tau protein levels in Wernicke's encephalopathy. *Alcohol Clin Exp Res* 2008;**32**:1091–5.
7. **Blennow K**, Wallin A, Agren H, *et al*. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Mol Chem Neuropathol* 1995;**26**:231–45.
8. **Riemenschneider M**, Wagenpfeil S, Vanderstichele H, *et al*. Phospho-tau/total tau ratio in cerebrospinal fluid discriminates Creutzfeldt-Jakob disease from other dementias. *Mol Psychiatry* 2003;**8**:343–7.
9. **Otto M**, Wiltfang J, Tumani H, *et al*. Elevated levels of tau-protein in cerebrospinal fluid of patients with CJD. *Neurosci. Lett* 1997;**225**:210–12.
10. **Chohan G**, Pennington C, Mackenzie JM, *et al*. The role of cerebrospinal fluid 14-3-3 and other proteins in the diagnosis of sporadic Creutzfeldt-Jakob disease in the UK: a 10 year review. *J Neurol Neurosurg Psychiatry* 2010;**81**:1243–8.
11. **Hesse C**, Rosengren L, Andreassen N, *et al*. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. *Neurosci Lett* 2001;**297**:187–90.
12. **Bertrand A**, Brandel JP, Grignon Y, *et al*. Wernicke encephalopathy and Creutzfeldt-Jakob disease. *J Neurol* 2009;**256**:904–9.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Frijlink DW, Tilanus JJ, Roks G. Elevated cerebrospinal fluid tau in Wernicke encephalopathy. *BMJ Case Reports* 2012;10.1136/bcr-2012-006661, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow