

Introduction

- Wernicke's encephalopathy is a neurological emergency and thiamine supplementation can prevent permanent neurological damage and death.
- Classical Wernicke's encephalopathy symptoms include global confusion, ataxia, and ophthalmoplegia.
- Alcoholism, gastrointestinal bypass surgery, chronic malnutrition, and systemic illness are risk factors for Wernicke's encephalopathy.
- 25% of hospitalized cancer patients would have altered mental status due to infection and metabolic disturbance, organ failure, medication, or metastatic disease. Wernicke's encephalopathy should be considered as the differential diagnosis.
- Cancer patients are especially at risk for Wernicke's encephalopathy because of poor nutritional status, chronic nausea, and consumption of thiamine by rapid growing cancer.

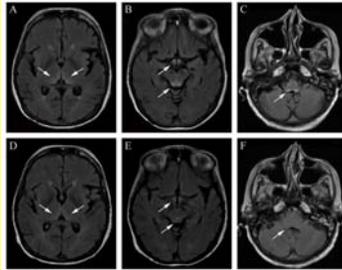
Case 1

- A 65 year-old woman with uterine leiomyosarcoma status post total abdominal hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection with anastomosis, lysis of adhesion, and transverse colectomy.
- She was treated with the first course of ifosfamide and doxorubicin with transient confusion and lethargy which resolved spontaneously
- After the second course of ifosfamide and doxorubicin, she developed disorientation, inattention, and tremor. She then became comatose.
- Brainstem reflexes were intact except for the absence of vestibulo-ocular reflex.
- MRI of the brain showed FLAIR hyperintensity in the dorsomedial nuclei of the thalamus, mamillary bodies, inferior colliculi, periaqueductal gray, and pontine tegmentum (Figure 1A-C).
- EEG showed diffuse slow waves without epileptiform discharges.
- She was treated with IV thiamine and her mental status improved as well as MRI findings (Figure 1D-F).

Case 2

- A 26 year-old man with acute myelogenous leukemia with complete remission.
- He had one relapse and was treated with clofarabine and cytarabine.

Figure 1



- The patient developed recurrent fungal pneumonia, chronic nausea and vomiting, neutropenic fever, sepsis, peritonsillar abscess, and dysphagia
- He subsequently developed seizure. On neurological exam, the patient had disorientation and confusion without diplopic or ataxia.
- MRI revealed bilateral FLAIR hyperintensity in the frontal cortex, subcortical area, mesial aspect of the thalami, and superior cerebellar vermis (Figures 2A-C). A focal epidural hematoma was noted in the posterior fossa (Figure 2D). DWI sequence revealed restricted diffusion in the areas mentioned above.(Figure 2E-F).
- EEG showed no posterior dominant rhythm and generalized 2-3 Hz delta activity.
- The patient then went into coma. CT of the brain demonstrated hemorrhage in the fourth ventricle with obstructive hydrocephalus (Figure 2G-H).
- Autopsy showed cerebellar hematomas obstructing the fourth ventricle (Figure 3A), microhemorrhages of thalamus and mamillary bodies (Figure 3B). Extravasations of red blood cells, hemosiderin deposition, and gliosis were noted under microscopy (Figure 3C).

Case 3

- A 48-year-old woman with stage IIIb inflammatory breast cancer received neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide followed by lymph node dissection and treatment with cyclophosphamide, etoposide, and cisplatin.
- Additional high-dose chemotherapy with cyclophosphamide, carmustine, and thiopeta was given prior to autologous bone marrow transplant (BMT).

Figure 2

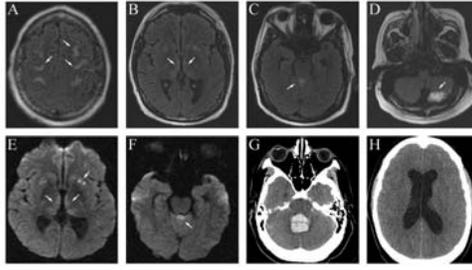
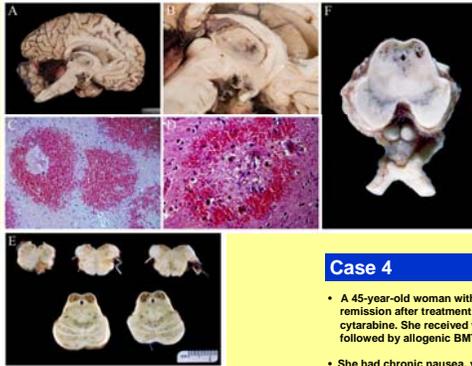


Figure 3



Case 4

- A 45-year-old woman with AML achieved complete remission after treatment with idarubicin and cytarabine. She received whole body irradiation, followed by allogeneic BMT.
- She had chronic nausea, vomiting, diarrhea, and stomatitis, which aggravated her preexisting poor nutritional status. Her hospital course was complicated by neutropenic fever and pneumonia.
- She had increasing confusion and disorientation without diplopia or ataxia.
- MRI of the brain revealed T2 hyperintensity in the inferior brain stem tectum and in the pulvinar bilaterally.
- The patient died and autopsy findings showed microhemorrhages in the thalami and also in midbrain tectum (Figure 3E).

- She developed chronic nausea, vomiting, and diarrhea, and, one month later, she was admitted for confusion and bilateral pneumonia. She was adequately treated for pneumonia but her mental status remained poor and she developed generalized tonic clonic seizures.
- MRI of the brain showed T2 hyperintensity in the dorsal mid brain and in the periaqueductal gray.
- She died several days later and autopsy findings showed extravasations of blood consistent with microhemorrhages in the thalamus and mamillary bodies (Figure 3D) inferior colliculi and medullary tegmentum were also involved (Figure 3E).

Table 1: Clinical presentations and risk factors for Wernicke's encephalopathy

Case	Sex	Age	Cancer type	BMT*	Predisposing factors	Chemotherapy regimen	Concomitant conditions	Symptoms
1	F	65	Pelvic sarcoma	No	Nausea, Vomiting, Poor intake	Ifosfamide and doxorubicin	Hypernatremia	Coma, absence of VOR
2	M	26	Acute myelogenous leukemia	Yes	Nausea, Vomiting, Poor intake	5-fluorouracil, doxorubicin, and cyclophosphamide	Sepsis	Confusion
3	F	48	Inflammatory breast carcinoma	Yes	Nausea, Poor intake, Diarrhea	Cyclophosphamide, carmustine, thiopeta	Pneumonia, Sepsis, Seizure	Confusion
4	F	45	Acute myelogenous leukemia	Yes	Nausea, Vomiting	Idarubicin and cytarabine	Renal failure, Pneumonia, Sepsis, GI bleeding	Confusion

Table 2: Diagnostic workup and clinical outcome for Wernicke's encephalopathy

Case	MRI findings	Albumin	Diagnosis timing	Pathology findings	Thiamine given	Outcome
1	T2 hyperintensity in medial thalamus, inferior colliculi, and periaqueductal gray	2.0	Ante-mortem	N/A	Yes	Improved mental status
2	T2 hyperintensity in medial thalamus, left caudate head, lentiform nucleus, superior vermis	3.6	Post-mortem	Cerebellar hematoma obstructing the fourth ventricle, microhemorrhages of thalamus and mamillary bodies.	No	Death
3	T2 hyperintensity in dorsal mid brain and periaqueductal gray	N/A	Post-mortem	Petechial hemorrhages in the thalamus and mamillary bodies. Inferior colliculi and medullary tegmentum were also involved.	No	Death
4	T2 hyperintensity in midbrain tectum, pulvinar,	N/A	Post-mortem	Petechial hemorrhages in the thalami and also in midbrain tectum	No	Death

Discussion

- Wernicke's encephalopathy is a neurological emergency associated with a high mortality rate. The classical symptoms comprising confusion, ataxia, and ophthalmoplegia rarely occur concurrently, making an accurate diagnosis a challenge.
- Confusion occurs in 92% of cases. Abnormal extra-ocular movement was observed in only half of the cases. Only 18% had ataxia. Other symptoms include pupillary abnormalities, tremor, hypo- or hyper-reflexia, and seizures. Bilateral vision loss can also occur.
- Due to thiamine depletion, blood brain barrier breakdown occurs followed by neuronal necrosis and irreversible brain damage in susceptible areas, including medial thalamus, mamillary bodies, periaqueductal gray, and brainstem tectum.
- Head CT had 13% sensitivity in detecting Wernicke's encephalopathy. The typical finding on CT is hypodensities in paraventricular regions of the thalamus.
- MRI of the brain has a sensitivity of only 53%, but a high specificity of 93%. MRI of the brain may show T2 hyperintensity in paraventricular regions of the thalamus, hypothalamus, mamillary bodies, periaqueductal gray of the midbrain, floor of the fourth ventricle, and midline cerebellum.
- Atypical findings of MRI include T2 hyperintensity in the caudate nucleus, splenium of the corpus callosum, and cerebral cortex.
- The radiological differential diagnosis of WE includes viral encephalopathy, bi-thalamic infarction (top-of-the-basilar syndrome), non-specific inflammatory processes, paraneoplastic encephalitis, demyelinating disease and primary CNS lymphoma.

- Although the major risk factor for WE is alcoholism, which can account for as many as 90% of cases, poor nutritional status, gastric bypass surgery, chronic nausea and vomiting, systemic illness, and magnesium depletion are also important.
- Patients with cancer actively undergoing treatment with chemotherapy may be particularly vulnerable. Hematological malignancies and sarcoma are rapidly growing tumors that may deplete thiamine stores. Chronic nausea and vomiting further exacerbates underlying poor nutritional status. Inadvertent use of intravenous fluids containing glucose may precipitate Wernicke's encephalopathy in patients with chronic nausea who are unable to maintain adequate oral intake.
- We found previous 24 reported cases of Wernicke's encephalopathy associated with cancer in the literature. 13 patients had a primary hematological malignancy, 5 had gastrointestinal cancers, and 2 had nasopharyngeal carcinoma. Other cancers that have been reported are osteosarcoma, lung cancer, and breast cancer. Confusion, stupor, and coma occurred in 75% patients. Ophthalmological symptoms including sixth nerve palsy, nystagmus, and diplopia were also present in 75% patients. Ataxia was less commonly seen (29%). Imaging studies showing characteristic findings only in 31% patients. Only 14 patients (58%) were treated with thiamine and among those, 13 patients showed clinical improvement (92%). The remaining 10 patients did not receive thiamine and died. (100% mortality)
- We propose that all cancer patients with confusion be treated empirically with thiamine while undergoing evaluation for other potential causes of altered mental status.