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CASE REPORT

MULTIPLE CEREBRAL METASTASES MIMICKING WERNICKE'S ENCEPHALOPATHY IN A CHRONIC ALCOHOLIC

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Abstract — Aims: Alcohol dependent patients in withdrawal display a wide spectrum of neurological and neuropsychological symptoms that complicate diagnosis. We report the case of a 53-year-old male alcoholic with disorientation, ataxia and nystagmus in alcohol withdrawal probably due not to initial supposed Wernicke's encephalopathy (WE) but rather due to multiple cerebral metastases of a non-small cell cancer of the lung. **Results:** The findings illustrate the importance of initially maintaining a tentative attitude toward causation of symptoms and the role of brain imaging in formulating an accurate diagnosis.

Alcohol dependent patients in withdrawal can demonstrate a wide spectrum of neurological and neuropsychological symptoms and sometimes pose great challenge to physicians.

Mr A was a 53-year-old undernourished, unemployed, cook who had been transferred to our clinic by a general practitioner due to confusion and disorientation with the onset of acute symptoms a few days before admission. A diagnosis of intoxication due to inadvertent high intake of prescribed medication (ranitidine, lansoprazole, propyphenazone and drofenin) and ethanol had been made.

Mr A had a history of alcohol dependence of 30 years duration with three previous treatments for alcohol withdrawal. He had been admitted to our clinic 3 years before, when oxazepam was prescribed for alcohol withdrawal symptoms. Due to poor compliance, he only stayed 3 days. He did not agree with a rehabilitation program for maintenance of abstinence. After discharge he recommenced consuming alcohol in large quantity.

The first time Mr A was admitted to our clinic, by his general practitioner because of uncontrolled alcohol consumption, in the same year the detoxification treatment with a rehabilitation program (55 days) was complicated due to a general tonic–clonic epileptic seizure. Along with oxazepam, he received antiepileptic therapy with carbamazepine. The third hospitalization was one year before the present admission and lasted for 56 days followed by four months of intensive rehabilitation program in a clinic outside.

Mr A had also been dependent on benzodiazepines (75 mg oxazepam/day and an unknown dose of bromazepam) for the past 3 years and nicotine for 35 years at a level of 70–100 pack years (Fagerstrom score: 9). Six years prior to the final admission he had undergone excision of pancreatic pseudo cysts as complication of a chronic pancreatitis.

We usually recommend all alcohol-dependent patients 600 mg thiamine, 30 mg riboflavin, 20 mg pyridoxine, 20 μg cobalamine, 0.3 mg biotine, 50 mg panthotenacid, and 100 mg nicotinamid orally per day for vitamin supplementation, but Mr A did not agree to vitamin therapy.

During the three past hospitalization periods of overall 114 days Mr A received orally only on 19 days, 600 mg thiamine/day for vitamin supplementation. The patient had also not taken vitamin supplements outside of our clinic.

At admission, his height was 173 cm and his weight 52 kg, corresponding with a body mass index of 17 kg/m^2 (age-adjusted reference of the body mass index 22–27). Clinical signs of vitamin deficiency such as disturbance of nails or hair growth were not detectable. His wife reported that he had consumed alcohol daily during the four months before admission.

Mr A was awake but disorientated to person, location, situation, and time. Reduced attention and short memory deficit were readily observable. Thought disturbance, phobia, compulsion, delusions, hallucinations, and depersonalisation were not detectable. His affect was slightly dysphoric and he was restless as well as impulsive. He denied suicidal ideation. In the Mini-Mental-State test (MMS) (Folstein *et al*., 1975) he achieved a score of 15 out of 30 points.

Neurological examination revealed gaze-evoked nystagmus in all directions. Meningism was not found. No abnormal functioning of the other cranial nerves, paralysis or sense disturbances were detected. All deep tendon reflexes were symmetrically elevated. Pathological reflexes were not detectable. The finger–nose test was atactic. Standing and gait with open eyes evidenced a distinct non-directional ataxia with tremors of the upper extremity. The Romberg sign was positive.

Apart from a slightly elevated gammaglutamyl transferase (GGT) (94 U/l; reference 11–66 U/l) and mean corpuscular hemoglobin (MCH) (32 pg; reference 27–31 pg), routine blood parameters including hemogram, chemogram, coagulation, C-reactive protein, and ammoniac were normal.

Confusion, ataxia, and nystagmus suggested acute Wernicke's encephalopathy (WE). He received 100 mg thiamine intramuscular directly after neurological examination (Day 0). Simultanously, we applied for neuro-imaging for exclusion of other possible causes of the very distinctive disorientation and ataxia. On the next day his status had not improved. Cranial computed tomography revealed multiple

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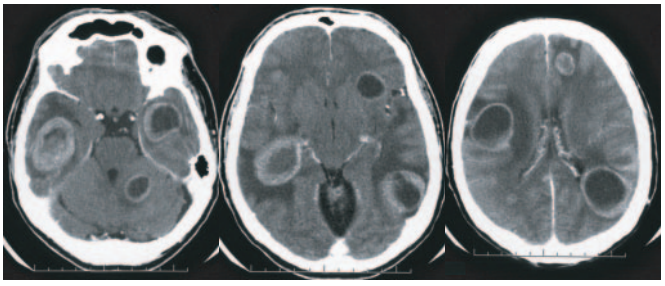

Fig. 1. Axial cranial computed tomography with contrast injection (slide thickness 3 mm): multiple round, cystic space occupying lesions with central hypodensity, perifocal edema, mass effect and marginal contrast enhancement frontal, fronto-temporal and parietal. Maximal size: 4.5 cm.

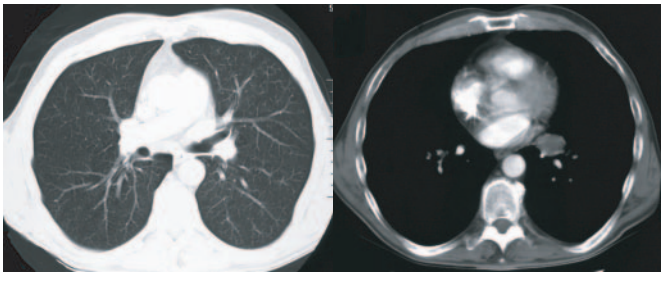

Fig. 2. Thoracal computed tomography with contrast injection (slide thickness 7 mm): space occupying lesion in the left hilus, central discrete dorsal replacement of the vessels.

infra- and supra-tentorial, hyperdense, space-occupying, maximally sized 4.5 cm lesions with distinctive perifocal oedema, central hypodensity, and compression of the side ventricle due to elevated intracerebral pressure (Fig. 1), indicating possible metastases. The corpora mamillaria were not hypotrophic. Magnetic resonance tomography imaging was not possible due to the patient's poor compliance.

To locate the primary tumor, computed tomography of thorax was performed and revealed a space occupying lesion in the left pulmonal hilus between the bronchus of the lingula and lower lobe with mass effect and dorsal replacement of the vessels without hints of angio-invasion (Fig. 2).

Skeletal scintigraphy showed multiple diffused elevated enhancements particularly in the ribs suggesting multiple bone metastases. The diagnosis of a less differentiated malignant non-small cell bronchial carcinoma was corroborated by bronchoscopy and transbronchial biopsy.

Multidisciplinary therapy was planned with radiotherapy, oncology, neurology, and psychiatry. After beginning palliative radiation treatment on Day 15, disorientation and gait disturbances initially became much worse. We used repeated doses of 10–20 mg haloperidol as reserve medication for agitation and 175 mg fentanyl for skeletal pain. The patient declined further vitamin supplementation. From Day 46, Mr A received prednisone 100 mg/day to reduce brain edema. In the following days, the neurological and neuropsychological symptoms improved markedly. On Day 61, the patient was discharged with significantly improved disorientation, pain, and gait ataxia, receiving palliative medication, prednisone 100 mg/day and fentanyl 175 mg/day. He was orientated to person, location, and situation, but not to time. He was able to stand alone and walk with help. He died about 2 months after his discharge in the circle of his family.

DISCUSSION

To the best of our knowledge, this is the first case reporting multiple intracerebral metastases in a chronic alcoholic with observable signs of WE.

WE is an acute, preventable, life-threatening metabolic disease of the central nervous system caused by thiamine deficiency. Thiamine dependent enzymes such as transketolase and pyruvate dehydrogenase are essential for cerebral myelinization. WE is probably caused by decreased energy metabolism caused by citric acid cycle disturbance, and decreased synthesis of neurotransmitter such as acetylcholine (McCandless *et al*., 1969). Thiamine deficiency and WE may occur in anorexia nervosa, hyperemesis gravidarum, small-bowel obstruction, AIDS, dialysis, prolonged intravenous feeding, or other conditions associated with prolonged poor intake (Reuler *et al*., 1985; Homewood *et al*., 1999; Togay-Isikay *et al*., 2001; Ogershok *et al*., 2002). However, malnourishment is the most common basis for WE in alcoholics. The daily thiamine requirement for healthy individuals is between 1 and 2 mg/day but both alcohol and malnutrition may interfere with the absorption of thiamine (Thomson *et al*., 2006a). Already 17 years ago, Gastaldi *et al*. (1989) found that ethanol can damage the intestinal mucosa of rats with consecutive thiamine malabsorption. Low plasma levels of thiamine have been reported in up to 80% of alcoholic patients (Cook *et al*., 1998).

Autopsy studies reveal that WE is often under-diagnosed: Naidoo *et al*. (1991) found histological changes of WE in 17 out of 29 consecutive alcohol-related deaths. The classical clinical triad of WE are oculomotor findings, ataxia, and mental confusion (Reuler *et al*., 1985). Typically, oculomotor deficits include weakness of abduction, gaze-evoked nystagmus, internuclear ophthalmoplegia, vertical nystagmus in primary position, and decreased vestibule-ocular-reflex. The oculomotor finding in Mr A was an omni-directional gaze-evoked nystagmus.

It is difficult to diagnose WE clinically since only a third of the cases display the classical triad symptoms. Clinical signs can be masked by level of consciousness or other neurological symptoms (Harper, 1983; Reuler *et al*., 1985). Due to the variable symptom-pattern of WE, the possibility of thiamine deficiency should be considered in any patient with documented or suspicious history of alcoholism showing any neurological features including even coma (Wallis *et al*., 1978). Thiamine should also be supplemented fully in malnourished alcoholics. The administration of intravenous fluids containing glucose without adequate thiamine supplementation in alcoholics could aggravate the thiamine deficiency leading to irreversible cerebral lesions and death (Yokote *et al*., 1992; Koguchi *et al*., 2004).

In 1997 Caine *et al*. (1997) developed improved operational criteria for the diagnosis of WE in alcoholics: WE can be identified by the presence of malnourishment, oculomotor abnormalities, cerebellar dysfunction, memory impairment, or altered mentation. Mr A demonstrated all of these criteria.

During recent years, brain imaging has proved useful in confirming the diagnosis of WE and in contributing to earlier detection (Antunez *et al*., 1998). The usual findings at MR imaging in patients with WE include high signal intensities in the mamillary bodies, medial thalami, tectum of the midbrain, and the periaqueductal region. The chronic stage may show atrophy of of the mamillary bodies and midbrain tegmentum, as well as dilatation of the third ventricle (Yokote *et al*., 1991; Doraiswamy *et al*., 1994). Unfortunately, we could not perform MRI in our patient due to poor compliance.

Although we have not determined plasma thiamine level as it is not a routine parameter on admission we believed that Mr A's initial symptoms were not due to WE but due to the multiple brain metastases. There are some hints that support this hypothesis. First, due to poor compliance Mr A got only one administration of 100 mg thiamine intramuscular. Intramuscular doses of >200 mg daily are believed to be required to show improvement in disorientated WE-patients (Ambrose *et al*., 2001; Thomson *et al*., 2002). Second, the neuropsychological improvement of Mr A occurred too late to attribute it to the administration of thiamine: Mr A received a singular dose of 100 mg thiamine on admission day and improved after the Day 46. We attributed his eventual neurological and neuropsychological improvement to the palliative whole brain radiation therapy (WBRT) and prednisone treatment. The initial worsening of neurological symptoms is typical for WBRT. WBRT is the treatment of choice for brain metastases because it prolongs the mean survival rate from 1 to 6 months (Zabel *et al*., 2004), affords a good local control, eliminates any micrometastases, reduces the risk of recurrent brain metastases, improves overall survival and quality of life as in our case, and can prevent death due to brain compression syndrome (Ellis *et al*., 1998).

Mr A's case demonstrates that the clinical criteria for WE are not pathognomic. The spectrum of differential diagnoses is quite broad and includes intracranial haemorrhage, stroke, brain tumor, intracerebral metastases, hepatic failure, central pontine myelinolysis, as well as, cerebral infections such as meningitis. According to recent published recommendations it is good clinical practice that patients at risk of WE receive 250 mg thiamine intramuscular for 3–5 days (Thomson *et al*., 2006b) but if there is no rapid response, further neurological examination are required in order to establish the correct diagnosis and serve optimal medical treatment.

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