Carcinomatous meningitis

A delusive, but lethal enemy

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Summary

A 58-year old woman with a long-standing history of chronic recurrent headache, depression and anxiety presented with new onset occipital headaches, tinnitus, gait instability and worsening of mood disorder. A first extensive work-up failed to objectify a somatic disorder and a psychiatric origin was suspected. However, 6 weeks later focal neurological deficits including complex visual disturbances, seizures and cognitive decline appeared, initially parallelled by fever. Cerebrospinal fluid (CSF) analysis showed increased opening pressure and mild pleocytosis. After exclusion of infectious and auto-immune meningoencephalitis, carcinomatous meningitis was diagnosed on repeated CSF analysis. Due to a signet ring cell morphology of the malignant cells in the CSF, a gastric origin was suspected despite absence of any primary tumour after another extensive diagnostic work-up. Detection of serum anti-Ma2 auto-antibodies is in line with the hypothesis of an underlying intestinal neuroendocrine tumour, albeit there was no evidence of a paraneoplastic syndrome in this patient. The patient died within 2 months of new onset headaches. Carcinomatous meningitis is a rare condition which can manifest itself by multifocal neurological signs including neuropsychiatric symptoms and complex visual disturbances long before tumour diagnosis. A high index of suspicion with consequent and if necessary repeated CSF cytological analysis is crucial for correct and rapid diagnosis of this potentially fatal condition.

Key words: occult gastrointestinal cancer; visual disturbance; intracranial hypertension; CSF cytology; paraneoplastic syndrome

Abbreviations

CM = Carcinomatous meningitis
CNS = Central nervous system
CSF = Cerebrospinal fluid
PNS = Paraneoplastic syndrome

History

In January 2012, a 58-year old patient with multiple cardiovascular risk factors was admitted because of new onset occipital headaches and gait instability with recurrent falls. She also complained of a pulsatile low frequency tinnitus, provoked by head flexion and regressive in the seated position. She had suffered from ischaemic stroke in the left basal ganglia at the age of 42 years with residual slight right-sided hemiparesis. In 2001, 7 years later, she was investigated for tension type headaches and dizziness, which were spontaneously regressive, but fluctuating thereafter. The patient was known for chronic anxiety and depression. She was euthyroid under a treatment of carbimazole for toxic multinodular goitre. In November 2011, gastric ulcers were diagnosed with eradication of *Helicobacter pylori*, biopsies being notably negative for malignancy.

A clinical exam in January 2012 was normal except for residual, mild, right-sided hemiparesis and significant anxiety. Cerebral angio-MRI confirmed sequels of the former ischaemic stroke and Doppler of pre-cerebral vessels was normal. Routine blood tests were unremarkable. Glucose in the cerebrospinal fluid (CSF) was at the lowest normal limit (2.7 mmol/l), but CSF analysis was otherwise normal. In particular, opening pressure was normal at 22 cm H_2O and cytology for malignant cells was negative, as was the search for oligoclonal bands (table 1). Headaches and falls were progressive over the following 2–3 weeks, and the patient also reported poorly characterised visual problems and episodic nausea in association with hypertensive peaks. The clinical exam was still non-contributive. EEG was normal. 24–h blood pressure monitoring confirmed first degree arterial hypertension without any suspect peaks or orthostatic falls. Abdominal CT revealed non-specific mesenteric lymphadenopathy. Given the lack of a somatic explanation for the patient's complaints and a long-standing psychiatric history, a psychiatric assessment was undertaken. A diagnosis of probable atypical depression with somatoform pain syndrome and dissociative motor dysfunction was made. The patient agreed to treatment in a psychiatric hospital.

During psychiatric hospitalisation two episodes of altered consciousness occurred. The patient became suddenly unresponsive (formally GCS 3) on one occasion and less responsive (formally GCS 12) on a second occasion. There were neither abnormal movements nor urinary or faecal incontinence. Vital signs and blood glucose were normal, however,

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Table 1
Overview of results of lumbar puncture.

Date	27.1.2012	24.2.2012	27.2.2012	13.3.2012	14.3.2012
Opening pressure (cm H_2O)	22	50	40	52	30
Cell count/µl and morphology	4 Mononuclear	8 Mononuclear	5 Mononuclear	5 Suspect for malignancy	1 Malignant of signet cell type
Protein (g/l)	0.25	0.29	0.25	0.30	0.26
Glucose (mmol/l)	2.7	4.3	2.4	4.3	3.8
Lactate (mmol/l)	2.3	5.6	4.7	4.3	4.2
Cytology	Negative	N.d.	N.d.	Positive?	Positive
Oligoclonal bands	Negative	N.d.	Positive	N.d.	N.d.

Normal values: Opening pressure = 8–25 cm H_2O; cell count/µl ≤4; Protein = 0.15–0.45 g/l; Glucose = 2.8–5.0 mmol/l (normoglycaemic patients); Lactate = 1.1–2.5 mmol/l; N.d. = not done.

diaphoresis and poorly reactive, bilateral mydriasis were noted. Both episodes resolved spontaneously in less than one hour. By the end of February 2012, the patient developed acute right facial palsy, parallelled by fever, and then she was finally re-admitted to the somatic county hospital after initiation of empirical ceftriaxone treatment.

Clinical findings, evolution and final diagnosis

On admission, the patient was febrile with moderate psychomotor slowing, but orientated. In addition to the symptoms detailed above, she complained of diplopia. Clinical exam confirmed the appearance of moderate to severe right facial palsy of the peripheral type, combined with complete right-sided abducens palsy and anisocoria with a smaller, but still reactive pupil on the right side. There was moderate neck stiffness. Blood tests revealed leukocytosis of 30.4 G/l without left deviation and elevated CRP at 179 mg/l. Infectious meningoencephalitis was suspected and a lumbar puncture was repeated. Opening pressure was raised to 50 cm H_2O. CSF analysis revealed 8 mononuclear cells/µl (reference value ≤4/ µl), elevated lactate (5.6 mmol/l, reference value 1.1–2.5 mmol/l), but normal levels of protein and glucose (table 1). There was absence of bacteria on Gram staining, but cytological analysis was not available during the weekend. Ongoing antibiotic therapy was switched to meropenem to cover *Listeria monocytogenes*. Intravenous acyclovir was initiated although *Herpes simplex virus* infection seemed unlikely on clinical and radiological grounds (cerebral MRI unchanged from January 2012).

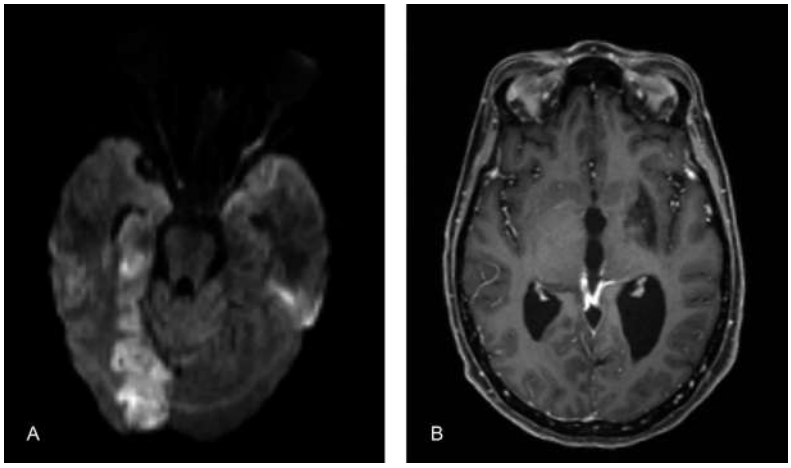
Fever resolved under antibiotic treatment, but the patient deteriorated further despite repetitive lumbar puncture to lower intracranial hypertension. She became confused, and appearance of visual hallucinations and complex visual disturbances combined with decreased visual acuity, apperceptive agnosia and optic ataxia were noted. There was bilateral papilloedema, accompanied by fluctuating consciousness, excessive vomiting and an inability to stand. A few days later, the patient suffered from right focal and secondary generalised epileptic seizures, controlled by levetiracetam. A brain CT scan excluded hydrocephalus, haemorrhage or mass effect. Lumbar puncture still showed 5 mononuclear cells/µl with persistently elevated lactate, slightly diminished glucose and normal protein level. Oligoclonal bands were now positive (table 1).

An extensive microbiological work-up including blood and CSF culture, screening for HIV (blood serology), syphilis (RPR, TPHA), *Borrelia species* (blood serology), *Cryptococcus neoformans* (serum Ag), *Listeria monocytogenes* (CSF PCR, culture), *Mycobacterium tuberculosis* (CSF PCR, culture), *Tropheryma whipplei* (CSF PCR), *Herpes simplex virus* (CSF PCR) reasonably excluded CNS infection and antibiotic treatment was interrupted. Systemic inflammatory signs were retrospectively attributable to Escherichia coli urinary tract infection.

Meningoencephalitis of autoimmune origin was considered in the differential diagnosis. Vasculitis screening blood tests and thyroid auto-antibodies were negative. Low levels of angiotensin converting enzyme, normal thoracic CT and absence of uveitis made systemic sarcoidosis highly unlikely, but were not excluding CNS-limited sarcoidosis. A diagnosis of autoimmune paraneoplastic encephalitis was also considered despite the fact that increased intracranial pressure is unusual in this entity. Anti-Ma2 auto-antibodies were indeed positive in serum (non-quantitative assessment), but negative in CSF. Anti-Ma1, anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CRMP-5 and anti-Recoverin were negative in serum. Thoraco-abdominal CT scan, mammography, a gynaecological exam and finally 18F-FDG PET failed to reveal any primary tumour. Repeated CSF analysis including cytological examination raised the suspicion of carcinomatous meningitis. Total cell count in CSF remained low at 5 cells/µl, but 72% of these were of carcinomatous aspect. Protein and glucose levels remained normal with lactate still elevated (table 1). In the meantime, empirical high dose corticoid treatment (methylprednisolone IV 500 mg/d for 5 days, followed by prednisone in slowly tapering dose) did not lead to any improvement.

In view of progressive clinical deterioration including appearance of a major left-sided hemiparesis associated with hemianopia and hemineglect, the patient was transferred to the university hospital for further diagnostic and therapeutic evaluation. Cerebral MRI confirmed a new acute ischaemic lesion in the territory of the right posterior cerebral artery (fig. 1), probably favoured by paraneoplastic hypercoagulability and increased intracranial pressure. MRI of the spinal axis showed marked contrast enhancement of the meninges

Figure 1 Cerebral MRI (14.3.2012). Acute posterior infarction on the right side (A) and chronic infarction in the basal ganglia on the left side (B). However, note absence of meningeal enhancement suspicious of carcinomatous meningitis (B).



without intramedullary lesions (fig. 2), highly suspicious of carcinomatous meningitis. Repeated CSF analysis confirmed malignant cells by the fact of positive staining for the epithelial marker Ber-EP4 (fig. 3). Due to the signet ring cell morphology, an occult gastric/gastrointestinal primary tumour was favoured in the differential diagnosis. Gastric biopsies with the diagnosis of ulcerative gastritis due to *Helicobacter pylori*, an important risk factor for development of gastric malignancy, had been obtained in November 2011.

Faced with a very poor prognosis with a median survival of only a few weeks despite eventual radio- and chemotherapy as well as the patient's advance directives, palliative care was introduced. The patient died 10 days after definite diagnosis of carcinomatous meningitis and 1 month after appearance of nuclear facial palsy respectively. An autopsy was denied by her family.

Figure 3 CSF cytology (14.3.2012). Presence of malignant signet ring cells, staining positively for the epithelial marker Ber-EP4 (original magnification 400×).

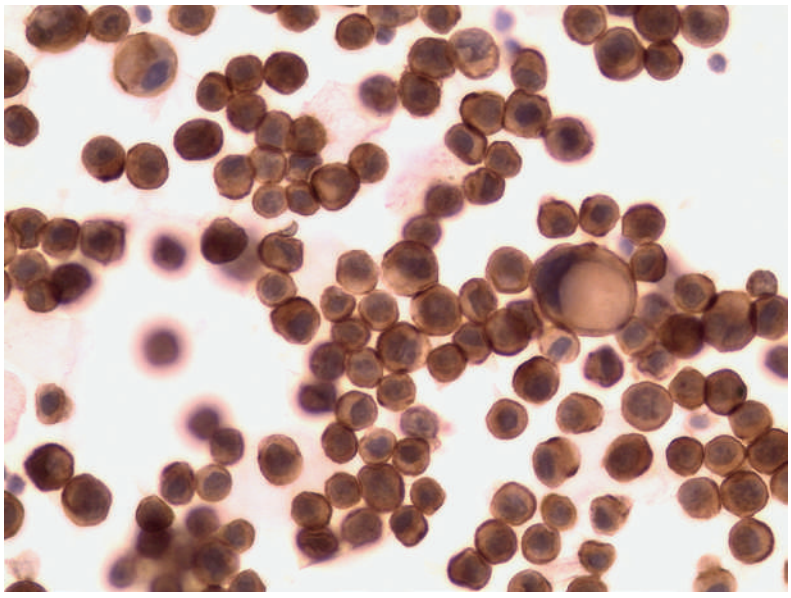
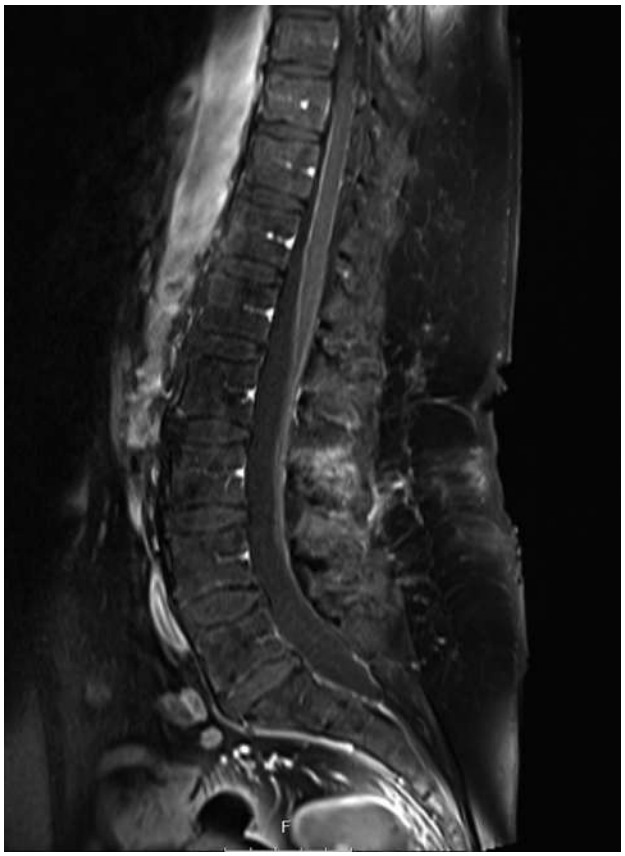


Figure 2
MRI spinal axis (14.3.2012). Meningeal enhancement along the spinal cord without intramedullary lesions. A pure post lumbar puncture effect seems unlikely in view of the importance of enhancement.



Discussion

We report a patient with a long-standing history of chronic recurrent headaches, anxiety and depression who presented with unspecific symptoms for which initially no somatic cause could be identified despite extensive diagnostic work-up. A few weeks later, multifocal neurological signs appeared, parallelled by increased CSF opening pressure and slight CSF pleocytosis in a febrile patient. Whereas infectious and autoimmune meningoencephalitis were considered early in the differential diagnosis, carcinomatous meningitis (CM) was not consequently taken into account in this patient without any evidence of a primary tumour and a normal cytological CSF analysis at an earlier occasion. The low index of suspicion of CM with omission of repeated cytological CSF analysis led to substantial delay in the final diagnosis, further complicated by an acute stroke. Although the prognosis of patients suffering from CM due to gastric cancer is poor with a median overall survival of only 6.7 weeks even in case of chemo- and/or radiotherapy [1], the diagnostic delay in our patient may have further limited the therapeutic options, resulting in a rapidly fatal outcome within 1 month after appearance of unequivocal multifocal neurological signs.

CM is the result of invasion of malignant cells to the CSF and the leptomeninges (arachnoid and pia mater). Tumour

cells may gain access to the CNS by haematogenous spread (through venous plexus of Batson or arterial dissemination), by migration along perineural and perivascular spaces or by direct extension from contiguous tumour deposits [2, 3]. CM affects 1–5% of patients suffering from solid tumours and 5–15% of those diagnosed with haematological cancers [2, 4–6], a number probably underestimated as it can be increased up to 19% in some autopsy series [7]. Prevalence is increasing given the population's ageing, the prolonged survival of tumour patients and improvement in diagnostic accuracy. In only about 5 to 10% of cases, CM is the first manifestation of cancer, but CM in the absence of primary tumour is exceptional [8]. CM is characterised by pleomorphic and multifocal symptoms and signs, according to the importance of accompanying intracranial hypertension and the different areas potentially involved, making diagnosis difficult especially if the disorder is not systematically included in the differential diagnosis [2].

Prevalence of gastric cancer is especially high in Japan and Korea (20.8% of all cancer diagnosed in Korea in 2000), but CM consecutive to gastric cancer remains rare, affecting 0.16% to 0.69% of the patients [9]. However, for the reasons mentioned above, the prevalence overall is rising. Lysenko et al. reported 8 patients with CM due to gastric cancer, with the majority suffering from poorly differentiated adenocarcinomas with signet ring features [10]. These authors also noted a clinical propensity for diffuse involvement of epithelial surfaces (CM, peritoneal carcinomatosis, linitis plastica and dermal metastases) instead of intraparenchymal involvement of visceral organs, in line with the notion of a preponderance of cancers Bormann type IV (infiltrative, predominantly intramural lesion, poorly demarcated). Such primary tumour lesions might obviously be more difficult to diagnose by biopsy or imaging (including PET scan).

CSF examination remains the gold standard for diagnosing CM, with a sensitivity of cytological analysis of 50–70% at first puncture, reaching 80 to 95% if the test is repeated twice or three times [2, 11]. Increasing the volume of CSF to >10 ml and immediate processing of the specimen enhances the sensitivity of the procedure even more [11]. Besides positive cytology, CSF opening pressure is frequently raised in CM, abnormalities of CSF cell count, glucose and protein levels as oligoclonal bands might be present. In a clinical study on 19 patients suffering from CM in gastric cancer, high opening pressure was found in 83.3%, decreased glucose in 41.2%, elevated protein in 64.7% and pleocytosis in 88.2% [9]. It is noteworthy that the protein level was

normal in all 5 lumbar punctures performed in our patient (table 1). Contrast enhanced MRI is far superior to cranial CT scan for detection of CM (sensitivity 70% vs 30%) [12]. However, even the combination of CSF cytology and MRI does not reach a sensitivity of 100% if performed only once.

Paraneoplastic neurological syndrome (PNS) is a rare, probably autoimmune mediated disorder not associated to metastatic presence of neoplastic cells and affecting less than 1/10 000 patients with cancer [13]. Paraneoplastic auto-antibodies reliably predict the presence of an underlying tumour (positive predictive value >70%) [14], but are not necessarily associated with PNS, especially if present in low concentration (<1:1000) [15, 16]. Interestingly, anti-Ma2 auto-antibodies are detected in almost 50% of patients with intestinal neuroendocrine tumours without evidence of PNS, but anti-Ma2 positive patients seem to be at risk for early tumour relapse [17]. This might explain the finding of anti-Ma2 auto-antibodies in the serum, but not in the CSF of our patient.

In conclusion, CM is a rare condition characterised by pleomorphic symptoms and signs including headache, behavioural changes, poorly characterised gait instability and complex visual disturbances. Diagnostic procedures including CSF analysis and MRI have limited sensitivity, and repeated CSF analysis including measuring of opening pressure and cytological analysis may be needed to prevent diagnostic delay. CM may rarely be diagnosed in the absence of a primary tumour despite extensive laboratory work-up and can be associated with low titres of paraneoplastic auto-antibodies without clinical PNS.

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Preisausschreibung

Ausschreibung Hermann-Emminghaus-Preis 2015

Gesucht: Exzellente Arbeiten im Fach «Kinder- und Jugendpsychiatrie und -psychotherapie»

Bereits zum fünfzehnten Mal wird zum Gedenken an Hermann Emminghaus, den Pionier der kinder- und jugendpsychiatrischen Forschung, der Hermann-Emminghaus-Preis verliehen. Wissenschaftler können sich mit ihren Arbeiten in der Kinder- und Jugendpsychiatrie und -psychotherapie ab sofort unter www.emminghaus-preis.de für die durch die Lilly Deutschland GmbH (Bad Homburg) geförderte Auszeichnung 2015 bewerben. Der Preisträger wird mit der Hermann-Emminghaus-Medaille und einem Preisgeld in Höhe von 5500 Euro gewürdigt. Bewerbungsschluss ist der 5. November 2014.

Der Hermann-Emminghaus-Preis ist der älteste kinder- und jugendpsychiatrische Forschungspreis im deutschsprachigen Raum. Er richtet sich an Wissenschaftler, die empirische Forschung auf dem Gebiet der Kinder- und Jugendpsychiatrie und -psychotherapie, insbesondere der biologischen Kinder- und Jugendpsychiatrie, betreiben und in der Regel nicht länger als zehn Jahre im Fach wissenschaftlich tätig sind. Es können ausschliesslich Arbeiten eingereicht werden, die noch nicht anderweitig ausgezeichnet worden sind.

Psychodynamisch, genetisch oder zerebralorganisch orientierte Forschung kommt ebenso für eine Bewerbung in Betracht wie epidemiologische, katamnestische oder therapeutische Studien. Die Arbeit ist in deutscher oder englischer Sprache einzureichen.

Die Verleihung des Hermann-Emminghaus-Preises 2015 wird Anfang März 2015 im Rahmen des XXXIV. Kongresses der Deutschen Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie e. V. (DGKJP) in München stattfinden.

Mit der letzten Auszeichnung im Jahr 2013 wurde der Kinder- und Jugendpsychiater PD Dr. med. Timo Vloet vom Universitätsklinikum Aachen in Anerkennung seiner wissenschaftlichen Arbeiten zum Thema «Neurobiologische Aspekte dissozialer Störungen» geehrt.

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Über Hermann Emminghaus

Hermann Emminghaus wurde am 20. Mai 1845 in Weimar geboren. Er studierte Medizin in Göttingen und anschliessend in Jena. An der Grossweimarer Landesirren-, Heil- und Pflegeanstalt promovierte Emminghaus 1869 mit der Arbeit «Ueber hysterisches Irresein». Von 1880 bis 1886 hatte Emminghaus den ersten Lehrstuhl für Psychiatrie in Dorpat, heute Tartu/Estland, inne. Emminghaus verfasste die erste deutschsprachige Abhandlung zu «Psychischen Störungen des Kindesalters», welche 1887 im «Handbuch für Kinderkrankheiten» veröffentlicht wurde. 1886 erhielt Emminghaus den Ruf an die Freiburger Universität für den neu eingerichteten Lehrstuhl für Psychiatrie. Hermann Emminghaus starb am 17. Februar 1904 in Freiburg.

Das Kuratorium: Prof. Dr. Dr. M.H. Schmidt, Mannheim (Vorsitzender), Prof. Dr. F. Häßler, Rostock, Prof. Dr. K. Becker, Marburg, Prof. Dr. J.M. Fegert (amtierender Präsident der DGKJP), Prof. Dr. G.E. Trott, Würzburg, Prof. Dr. Dr. R.W. Dittmann, Mannheim, Dr. S. Kraemer, Bad Homburg.