Teaching Course 17

Neurological presentations of systemic disorders - Level 1

Encephalopathies in metabolic disorders

Karin Weissenborn
Hannover, Germany

Email: Weissenborn.Karin@mh-hannover.de
Metabolic encephalopathies frequently cause the consultation of a neurologist, both in the emergency room as well as for in-patients of the departments of internal medicine or surgery. More than 2/3 of the patients who are referred to an emergency unit with altered consciousness show electrolyte disturbances, endocrinologic disorders, metabolic encephalopathies or intoxications (Plum & Posner 1982). The symptomatology of metabolic encephalopathies is manifold – including slight cognitive deficits and personality changes, sleep and mood alterations as possible first symptoms of the disorder as well as increasing alteration of consciousness from somnolence to coma, disorientation, confusion, hallucinations, and seizures. Motor symptoms include dysarthria, ataxia, tremor, asterixis, myocloni, choreoathetosis, dystonia, and Parkinsonism. Of interest, even focal neurological symptoms may be observed such as dysphasia, hemiparesis or hemichorea. Obviously the symptoms are unspecific. However, there are some characteristic findings indicating for example hepatic or uremic encephalopathy. Multifocal myoclonus is characteristic for uremic encephalopathy, while extrapyramidal or cerebellar symptoms are frequently seen in patients with liver cirrhosis and hepatic encephalopathy (Brouns & De Deyn 2004; Seifter & Samuels
2011, Jones & Weissenborn 1997). The diagnosis “metabolic encephalopathy” can be made only after exclusion of other possible causes of brain dysfunction. Thus, every patient with suspected metabolic encephalopathy needs a thorough diagnostic work up including of course a detailed clinical examination, consideration of the patients history and current medication, biochemical analysis of the blood (sometimes also of the urine or cerebrospinal fluid), brain imaging and electroencephalography (EEG). Again, there are no specific findings for one or the other type of metabolic encephalopathy, except of the indications of metabolic alterations such as increased serum urea and creatinine levels suggesting uremic encephalopathy or increased serum ammonia levels suggesting hepatic encephalopathy. However, these findings just indicate impairment of kidney or liver function, respectively, but do not prove uremic or hepatic encephalopathy. Considering laboratory findings only significant hypo- or hyperglycemia may be considered diagnostic in an individual case. But even in patients with severe alterations of blood glucose levels these can be taken as evidence for a metabolic alteration of brain function only, if the patient improves within a short period after normalization of the blood glucose levels.

Brain imaging using either cranial computer tomography (CCT) or magnetic resonance imaging (MRI) is done for the exclusion of other than metabolic causes of brain dysfunction, exclusively. None of the metabolic encephalopathies presents with specific CCT or MRI alterations. But, again there are some findings that hint at a metabolic cause of a patient’s neurological symptoms. About 90 % of the patients with liver cirrhosis, for example, show characteristic bilateral symmetric pallidal hyperintensities on T1-weighted MR images due to manganese deposition in the brain, with predominance in the basal ganglia (Morgan 1998; Rose et al. 1999). If a
patient presents with psychomotor slowing and Parkinsonism this MRI finding suggests liver cirrhosis as cause of the symptoms and gives reason to initiate a medical diagnostic work up of the patient. Recently the so called lentiform fork sign - a symmetric hyperintensity involving the caudate, putamen and thalamus girdled by a bright fork-like hyperintense rim in fluid-attenuated inversion-recovery (FLAIR) images has been repeatedly described as a characteristic MRI finding in patients with uremic encephalopathy (Fabiani et al. 2013; Kim et al. 2016). However, this MRI finding does not prove uremic encephalopathy but has been described also in patients with methanol intoxication, for example, as well as in other conditions with metabolic acidosis (Kumar & Goyal 2010). If a patient’s MRI shows hyperintensities in diffusion weighted images in a region that does not correspond to the patients’ clinical symptoms hypoglycemia should be considered and blood glucose levels checked, immediately (Katoh et al. 2016).

The EEG shows a generalized slowing in patients with metabolic encephalopathy with excess theta and delta activity. In uremic patients also bilateral spike wave complexes may occur (Brouns & De Deyn 2004). The extent of EEG alterations correlates with the extent of clinical symptoms. However, it has been shown in patients with chronic hepatic encephalopathy that the EEG may normalize in case of stable clinical symptoms (Penin 1967). In general, however, the EEG alterations precede changes in the clinical status, and thus may announce a bout of hepatic encephalopathy in patients with liver cirrhosis or uremic encephalopathy in patients with renal dysfunction. With successful treatment the EEG normalizes. The improvement, however, may be delayed in uremic patients with initiation of hemodialysis.
Hepatic encephalopathy (HE)

Hepatic encephalopathy is a frequent complication of liver cirrhosis and an inherent attribute of acute liver failure. Three types of HE are differentiated: Type A in patients with acute liver failure, type B in patients with porto-systemic shunts in the absence of liver dysfunction, and type C in patients with liver cirrhosis. Hepatic encephalopathy is characterized by alterations of cognition, motor function and consciousness. With regard to the alteration of consciousness patients are classified into 4 grades: HE I in case of attention deficits and psychomotor slowing, HE II in case of lethargy and disorientation, HE III in the presence of somnolence or semi-stupor and HE grade IV in case of coma (so called West Haven criteria). Alterations of cognition and consciousness can be accompanied with extrapyramidal, cerebellar and pyramidal signs in all grades of HE. Most characteristic are hypomimia, hypokinesia, rigor, tremor, dysarthria, dysdiadochokinesia and ataxia. Hyperreflexia and positive pyramidal signs can be observed predominantly in patients with grade III and IV HE, but can be present also in the other stages, on principle. Asterixis may be present in the absence of any other alteration, but is most frequently observed in patients with grade II or III HE. Considering the time course of symptom development episodic, recurrent and chronic progressive/persistent forms are distinguished. An excellent and extensive description of the clinical presentation of HE is given by Sherlock et al. (1954) and Summerskill et al. (1956).

The chronic progressive or persistent form of hepatic encephalopathy has predominantly been observed in patients with extensive porto-systemic shunts. The prevalence is unclear. We detected chronic progressive cirrhosis-related Parkinsonism - one of the clinical features of chronic
progressive HE – in a prospective study of 214 patients with liver cirrhosis on the waiting list for transplantation in about 4%. Two percent of the patients presented with hepatic myelopathy – another rare complication of extensive porto-systemic shunts that develops predominantly in men with liver cirrhosis and leads to severe spastic paraparesis without any sensory deficits or bladder or bowel disturbance within months.

Up to 60% of the patients with liver cirrhosis but no clinical symptoms of HE show significant alterations of brain function in psychometric testing or neurophysiological examinations such as electroencephalography (EEG). These patients are considered to suffer from the so called minimal hepatic encephalopathy (mHE). They show deficits in attention, visual perception, visuo-constructive abilities, and motor speed and accuracy. Since the patients’ language is preserved mHE remains undetected in the standard medical examination. The characteristic pattern of cognitive deficits, however, explains why mHE affects the working ability of blue collar workers, predominantly, while white collar workers appear unaffected for a long time (Schomerus & Hamster 2001). Although mHE appears to be only of minor significance on the first view diagnosis and treatment of mHE is recommended by experts in the field. MHE impairs health related quality of life and working ability and it interferes with the patients driving ability. In addition it indicates an increased risk for the development of clinically overt HE. (Weissenborn 2015)

A diagnosis of HE can be made only after exclusion of other possible causes of brain dysfunction. The diagnosis can be considered proven only if the symptoms resolve with HE therapy. One of the main differential diagnoses of HE is Wernicke’s encephalopathy. Since the rapid substitution of thiamine is crucial in Wernicke’s encephalopathy, patients should
be treated with 100 mg thiamine i.v. in every suspected case, before a diagnosis can be made based on thiamine serum levels or the characteristic MRI findings.

Several tools have been used for the diagnosis of minimal HE. Currently the most frequently used and recommended tools are the PSE-Syndrom-Test (available at Hannover Medical School), the assessment of the critical flicker frequency (CFF) and EEG (Vilstrup et al. 2014).

Therapy of HE aims at the reduction of gut ammonia production and absorption. Hyperammonemia and increased levels of inflammatory cytokines are considered the main causes of HE. In case of increased plasma ammonia levels increased amounts of ammonia reach the brain, where ammonia is detoxified via glutamine production within astrocytes. At first astrocytic osmolytes - such as myoinositol - leave the cells to counterbalance the increasing intracellular amount of glutamine. If this resort is spent astrocytic swelling is inevitable leading to astrocytic dysfunction, disturbances of neuron astrocyte interaction and brain dysfunction. Astrocyte swelling can be induced not only by increased ammonia and inflammatory cytokine levels, but also by hyponatremia and benzodiazepines. This observation explains why HE episodes are often precipitated by electrolyte dysbalance, use of benzodiazepines or infection. In these cases correction of the precipitating factor is the first line therapy. In addition plasma ammonia level lowering drugs can be applied. The most frequently used drug is lactulose in a daily dose of 30 - 60 mg (45-90 ml). In more severe cases lactulose may be combined with antibiotics, such as rifaximin or metronidazole. A combination therapy using lactulose and rifaximin for six months after a HE episode has been shown to reduce the risk for recurrent HE and re-hospitalisation (Vilstrup
et al. 2014; Bass et al. 2010). A further drug that can be used for the treatment of HE is L-ornithine-L-aspartate (LOLA). So far, positive data in regard to LOLA therapy relate to intravenous application in patients with grades II-IV HE, predominantly (Kircheis et al. 1997).

Of note plasma ammonia level lowering therapy is of no use in patients with cirrhosis-related Parkinsonism or hepatic myelopathy (chronic progressive HE or acquired hepatolenticular degeneration). These patients, however, might benefit from liver transplantation early in the development of their neurological symptoms.

In contrast to liver cirrhosis pronounced HE in acute liver failure is frequently accompanied by significant brain edema (25 - 35 % in grade III HE; 65 - 75 % in grade IV HE). Since intubation and mechanical ventilation has to be performed in these patients brain edema cannot be detected by clinical examination. Assessment of intracranial pressure by intracranial bolds is used by some centers, but is difficult since the coagulopathy in acute liver failure holds a significant risk of intracranial bleeding (Karvellas et al. 2014). Cardoso and colleagues (2017) recently recommended the following approach to intracranial hypertension and brain edema in patients with ALF: 1) head of the bed greater than 30°; (2) minimize patient stimulation; (3) sedation and invasive mechanical ventilation; (4) treat fever ; (5) treat seizures (prophylaxis has unclear value); (6) aim for a mean arterial pressure of at least 75 mm Hg with fluids and/or vasopressors, with the goal being to maintain an intracranial pressure less than 25 mm Hg and a cerebral perfusion pressure greater than 50 mm Hg; (7) consider using renal replacement therapy to promote more effective ammonia clearance; (8) aim for a serum sodium of 145 to 155 mmol/L with hypertonic saline (3%-30% infusion) for prophylaxis in
patients with grade III-IV HE; (9) consider using mannitol (0.5-1 g/kg bolus) to transiently reduce intracranial pressure when there is established intracranial hypertension (repeat if serum osmolality < 320 mOsm/L); and (10) consider using hyperventilation (aiming for a PCO₂ 25-30 mm Hg) in cases of established intracranial hypertension despite optimized treatment to try to delay the progression to tonsillar herniation.

Drugs which are used for the reduction of plasma ammonia levels in patients with cirrhosis such as lactulose or LOLA have not shown a significant effect in ALF; neither with regard to plasma ammonia levels, nor with regard to survival (Lee et al. 2011, Acharya et al. 2009)

Liver transplantation is the only definitive treatment in patients with acute liver failure. Since part of the patients has a good prognosis even without transplantation one of the most difficult tasks in the care of ALF patients is the risk stratification in regard to death without transplantation. Several criteria have been elaborated worldwide. Currently the most often used are the King's College criteria (O'Grady et al. 1989).

**Uremic encephalopathy**

Uremic encephalopathy is considered to be caused in particular by guanidino compounds that accumulate due to renal dysfunction. These compounds are supposed to interfere with glutamatergic as well as GABA-ergic neurotransmission, finally leading to an enhanced excitability. In addition secondary hyperpara-thyroidism is suggested as leading to increased neuronal calcium levels and neuroexcitation, as well (Weissenborn & Lockwood 2015; Seifter & Samuels 2011).
Knowledge about the pathophysiology of uremic encephalopathy, however, is sparse compared to hepatic encephalopathy, for example, probably due to the fact that it is to be observed today only in patients in whom a decision has been made not to start dialysis.

Clinical symptoms range from emotional alterations, especially depression, and slight attention and memory deficits to severe alterations of consciousness and cognition including (mostly agitated) confusion, psychosis, seizures and coma. Action tremor, asterixis and myoclonus, as well as hyperreflexia are characteristic features of uremic encephalopathy. Occasionally, choreatic movements have been described. Both asterixis and myoclonus may be provoked by several drugs such as opioids, antiepileptic drugs, phenothiazines or metoclopramide in patients with impaired renal function due to increased plasma levels. This is important in clinical practice since very often older people are referred to the emergency unit due to an impairment of consciousness who present the combination of diabetic renal dysfunction, pregabalin prescription for neuropathic pain, opioid treatment for lumbar pain and chronic metoclopramide treatment due to chronic nausea. Of note, a metabolic-toxic encephalopathy can be suspected in these patients even in the presence of only moderately increased creatinine and urea levels. The diagnosis is proven if the symptoms recede after withdrawal of the drugs. Moreover, uremic encephalopathy is proven if symptoms disappear with successful renal replacement therapy. Usually the improvement takes days or even weeks, and slight cognitive dysfunction may persist.

Cognitive dysfunction in patients with end-stage renal disease has other causes in addition to the accumulation of uremic toxins, such as renal anemia, hyperparathyreoидism and chronic obstructive sleep disorder.
Addressing these accompanying disorders is mandatory to improve the patients’ brain function and quality of life. Of note, hemodialysis patients may develop thiamine deficiency. Thiamine is a water soluble vitamin, and thus may be lost in the dialysis procedure. If this is accompanied by a decreased ingestion of thiamine due to whatever cause the patients may develop Wernicke’s encephalopathy (Hung et al. 2001; Ihara et al. 1999).

**Hypoglycemia**

Hypoglycemia is one of the main differential diagnoses in patients with focal neurological symptoms of acute or sub-acute onset. Amazingly severe hypoglycemia may result in speech arrest, hemiparesis, or hemichorea, for example, but of course focal and generalized seizures and severe disturbance of consciousness including coma may be expected as well. Most often hypoglycemia occurs as an unintended adverse effect of antidiabetic therapy with insulin or sulfonylureas. In treating patients with sulfonylurea induced hypoglycemia the very long half-life of these substances must be considered as patients may show relapsing hypoglycemia for more than 24 h even after glucose substitution. Considering the risk of hypoglycemia, on principle, and the increased risk of hypoglycemia with sulfonylurea therapy in case of renal dysfunction, the use of sulfonylureas in the treatment of type II diabetes is currently under discussion (Inzucchi et al. 2015).

Hypoglycemia is a medical emergency and should be treated in case of severe neurological symptoms with parenteral application of glucose (20-50 ml of 40% glucose) - if needed repeatedly.
Hyperglycemia

Hyperglycemic emergencies - diabetic ketoacidosis (DKA) and nonketotic hyperosmolar coma (also called hyperosmolar hyperglycemic state (HHS)) - are rare in a neurological emergency unit. Diabetic ketoacidosis predominantly affects patients with type I diabetes, and may even be the first manifestation of the disease. DKA is an insulin-deficient state, thus insulin application is the cornerstone of therapy. Replacing fluid and electrolytes is also required since with increased blood glucose levels finally glucosuria and a forced osmotic diuresis ensue. Patients usually need 7-10 l fluid replacement over the first 24 h of therapy, starting with about 1 l/h over the first 3 hours. Insulin substitution includes a bolus of 10-20 International Units (IU) of regular insulin followed by continuous intravenous application of 5-10 IU/h. Blood glucose levels need to be monitored during the therapy and should not decrease more than 50 mg/dl/h, otherwise the patients are at risk to develop brain edema. In addition to blood glucose levels also electrolyte levels must be closely monitored, as potassium levels may substantially decrease with ongoing insulin and fluid therapy. The treatment goal is to maintain serum potassium levels within the normal range of 4-5 mEq/l.

Involvement of a neurologist in the treatment of a patient with severe hyperglycemia is more likely in HHS than in DKA. Alterations of consciousness, seizures and focal neurological deficits are more frequent in patients with HHS than in DKA. Of note, stroke might accompany HHS, either as a complication due to the procoagulant status or as precipitant. Available evidence suggests that hyperglycemic emergencies are associated with an inflammatory and procoagulant state, which both contribute to an increased risk of thrombotic complications. Thus, heparin should be...
administered subcutaneously for prophylaxis of thrombosis. A protocol for the treatment of adult patients with DKA or hyperosmolar hyperglycemic state is given for example in Katabchi et al. (2009).

Two characteristic, though rare, complications of HHS are epilepsy partialis continua (Kojewnikow) and hemichorea. The latter is accompanied with characteristic CCT and MRI signal alterations in the contralateral striatum, and may persist for several days after the normalization of blood glucose levels (Kandiah et al. 2009).
References


18. Morgan MY (1998); Cerebral magnetic resonance imaging in patients with chronic liver disease. Met Brain Dis 13(4): 273-290
22. Rose C, Butterworth RF, Zayed J et al. (1999) Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology 117(3): 640-644

