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Pontine and extrapontine myelinolysis associated with rapid correction of hyponatremia - a review

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Abstract

Introduction

Pontine myelinolysis was first described in 1959 by Adams, Victor and Mancall and reported in alcoholic patients.[1] It is characterized, above all, by acute non-inflammatory symmetrical lesion of myelin sheath and apoptosis of oligodendrocytes affecting the central part of the *basis pontis*.[5]

Demyelination may also appear in other parts of central nervous system such as thalamus, basal nuclei and cerebellum. Involvement of the regions beyond pons is called extrapontine myelinolysis. These two manifestations- pontine and extrapontine myelinolysis are combined in one neurological entity- osmotic demyelination syndrome.
Pontine and extrapontine myelinolysis are mainly caused by rapid increase in extracellular fluid osmolarity; usually in situation of iatrogenic correction of chronic hyponatremia.[7] The other causes include severe electrolyte disturbances other than hyponatremia (hypokalemia, hypophosphatemia, hypernatremia), anorexia nervosa, AIDS, acute alcoholic hepatitis, liver transplantation, Vernickes syndrome, chemotherapy, chronic renal failure.[11,12] Osmotic demyelination syndrome vary in clinical manifestations. The most common presentations include encephalopathies, pareses, dystonias. The method of choice in diagnostic process is MRI imaging. Treatment of osmotic demyelination syndrome is still in an experimental phase.

Aim: The aim of the study was to revise the current knowledge about ODS including pontine and extrapontine myelinolysis- rare although severe units that might have a fatal outcome.

Keywords: osmotic demyelination syndrome; pontine myelinolysis; extrapontine myelinolysis; hyponatremia; rapid serum electrolyte correction; CNS lesions

Review

Pathophysiology of chronic hyponatremia

Plasma sodium level is a relatively constant value ranging from 135 to 145 mEq/l. If the sodium level decreases below the normal extent the condition is called hyponatremia. There are three types of severity in hyponatremic patients:
-Mild – 130- 134 mEq/l

-Moderate – 125- 129 mEq/l

-Severe – below 125 mEq/l.

In response to hyponatremia, extracellular water is shifted into the cells by osmosis in order to normalize the gradient between two compartments. As a result, the brain oedema appears. Chronic hyponatremia (defined as lasting more than 48 hours or of unknown duration), caused by excessive sodium loss or water retention, causes changes in distribution of osmotically active substances, brain water and electrolytes. [10]
The CNS tissue responds and adapts to hyponatremia by transporting the organic osmolytes such as glutamate, creatine, phosphocreatine, inositol, betaine and electrolytes into the extracellular space. [10] This attenuates intracellular water flow and the cell volume normalizes.
When hyponatremia is corrected rapidly, the intervention can outweigh the capability of the system to recapture osmolytes from extracellular compartment into the cells. The osmotic stress causes cell contraction, apoptosis and demyelination.[2,5]

Course and symptoms

Symptoms in osmotic demyelination syndrome depend on regions affected by the ongoing process. First signs of demyelination tend to appear from 1 to 14 days after the occurrence of triggering factor. Initially, an improvement in clinical state can be observed, due to the applied treatment of hyponatremia. It is followed by deterioration of patient's state with onset of neurological symptoms in the next days. [5] Central pontine myelinolysis may affect corticospinal tract which leads to spastic tetraparesis, corticobulbar tract with pseudobulbar palsy and presence of dysphagia, dysartria. Engagement of tegmentum causes coma or delirium. In extreme cases, locked-in syndrome, also known as pseudocoma, may develop.[5] The patient in this condition is unable to move or speak, having near all 'voluntary' muscles paralyzed. The vertical eye movement, blinking and consciousness are preserved.

Extrapontine myelinolysis has multiple clinical manifestations, starting with extrapyramidal motor symptoms (tremor, dystonia, myoclonus, akinesia) through ataxia up to epileptic seizures. Some case reports point out loss of cognitive functions, behavioral disorders and deterioration of ability to concentrate in patients with ODS.[5] There are also mild presentations of ODS. The lesions are revealed in MR imaging but the clinical symptoms remain discreet or the patient is symptom-free.

Diagnosis

Diagnosis is based on clinical picture and presence of the risk factors. Prior severe hyponatremia and its rapid equalization are the most common triggering factors. It is vital to examine laboratory markers such as serum sodium, potassium, phosphate and liver enzymes. Nutritional evaluation is also advisable.[5] MRI remains radiological method of choice in suspected ODS as it is more sensitive than CT. The abnormalities are starting to be visible from the onset of neurological symptoms up to few days after and they change in time. Characteristic image is seen on DWI and include diffusion restriction of central pons with sparing of its periphery. This is the initial change that becomes visible in imaging.[2] Typical MR lesions, usually visible later, are high-signal areas in the central part of the pons (or in extrapontine structures) in T2-weighted images and FLAIR sequences and accordingly, hypointense signals in T1-weighted images in the same regions. [2,6,12] The autopsy studies of CPM patients revealed altered protein to lipid ratio in the brain,

preserved axons and tissue oedema. The last element is responsible for abnormalities visible in MRI, in early stages of syndrome. Chronic lesion is characterized by fibrillary gliosis and astrocyte proliferation. Those are responsible for hypointense signals in T1 and hyperintense in T2.[6]

MR images change in time, they follow the clinical picture with a delay and can be a confirmatory data for prognosis. However, MR is insufficient by itself in predicting the clinical course as the changes, especially the size of lesions, do not correlate reliably with the presentation.[6]

CT is significantly less sensitive than MR, although it may also be used to detect and confirm ODS when the second method is not available. [5,6]

Treatment

There is no specific or evidenced treatment in case if ODS occurs. Management is only supportive and focused on avoiding secondary complications. The treatment, in general, is aimed at prevention. Appropriate proceeding in equalizing chronic hyponatremia can significantly reduce the risk of pontine and extrapontine damage. Improving future outcome is based on early recognition of patients at risk, avoiding overcorrection of hyponatremia and early diagnosis of ODS.[2]

In some of the described cases use of glucocorticosteroids, reintroduction of hyponatremia (by using 5% dextrose in water and desmopressin), application of organic osmolytes (e.g. myoinositol) and intravenous immunoglobulin have been tried and shown favorable results.[2,5,12] However, no clinical trial on humans has been performed and the experimental methods mentioned above are not yet recommended in case of ODS. Plasmapheresis was also applied as a method of treatment in a small number of case studies. The results were favorable as the neurological state of the patients improved. Plasmapheresis is thought to extract high-molecular myelinotoxic substances released during osmotic stress.[2]

Correction of chronic hyponatremia

Patients with documented chronic hyponatremia, especially when the Na^+ level is below 120 mEq/l, are at risk of developing osmotic demyelination syndrome. There are different guidelines concerning velocity for equalization of natremia. According to European Guidelines- the speed of correction cannot exceed 10 mmol/L during first 24 hours

and 8mmol/L thereafter. The US Guidelines indicate that the velocity should not be greater than:

- 4-8 mmol/L/d if low risk for demyelination syndrome,
- 4-6 mmol/L/d if high risk of demyelination syndrome, e.g. hyponatremia ≤105 mmol/L, concurrent hypokalemia, alcoholism, malnutrition, female gender, advanced liver disease. For patients with severe symptoms of hyponatremia, the first day's increase can be accomplished during first 6 h.[8,9]

Avoiding harm in asymptomatic patients can be achieved by correction 10-12 mmol/L/d, but maximally 18 mmol in 48 h if at low risk for ODS and 8 mmol/L/d if at high risk of ODS. The treatment of chronic hyponatremia is based on fluid restriction and infusion of fluids containing sodium - normal saline. Hypertonic 3% saline should be considered when severe neurological symptoms due to hyponatremia are present or in case of inadequate response. [8,9] Use of vasopressin antagonists (vaptans) is another possible management in chronic hyponatremia. Tolvaptan is a selective competitive vasopressin receptor (V2) antagonist, it enhances the elimination of free water with electrolyte retention. The drug has been approved in treatment yet it is reserved for severe cases as it is at high risk of overcorrection.[5]

Prognosis

Osmotic demyelination syndrome can be fatal or entailed with major disability. The condition of a patient is correlated with location and extent of CNS damage, previous diseases and underlying primary cause.

According to data, 33-55% of the patients are claimed to depend on nursing care or die. The prognosis for patients with ODS has improved in reference to reports from 1980, when the mortality rate reached up to 90-100%. [5]

Nowadays, a good outcome can be expected in 30-50% of the cases [5,12], mainly as a result of progress and approach in modern medicine. A greater emphasis is put on early rehabilitation. The system of electrolyte measurement is more precise. The data base and guidelines are widely available and reliable.

Patients with risk factors for poor prognosis include those with severe hyponatremia, hypokalemia and low GCS during hospitalization. Patients with favorable outcome are those

with prompt diagnosis and without secondary complications, such as deep venous thrombosis or aspiration pneumonia.[2]

MR images can be a confirmatory data for prognosis and have diagnostic value, nevertheless the clinical picture remains the most important element for predicting the course of the disease. [6]

Summary

The first description of pontine myelinolysis dates back to 1959 and was described in four alcoholic patients with concomitant malnutrition.[1] Around 1970, case studies and researches have shown its connection with rapid equalization of sodium levels. [1,2] The pathophysiology of osmotic demyelination syndrome is complex. The cells in chronic hyponatremia remain in hypertonic extracellular compartment. Osmotic stress, linked with iatrogenic intervention, causes demyelination, shrinkage of the cells and apoptosis. Retrieving osmolytes from extracellular space in patients with chronic hyponatremia takes too long to prevent the damage. [2]

Other than hyponatremia electrolyte imbalances might also be the reason for ODS, usually the abnormalities co-exist with other underlying diseases. Increased incidence of central pontine and extrapontine myelinolysis was reported in patients who have undergone liver transplantation, with most cases during first 10 days after surgery.[2,3] Clinical suspicion of ODS should also rise in patients with prior malnutrition, anorexia and alcohol abuse. The course of the ODS, associated with rapid hyponatremia correction, has two phases- initially, improvement after serum sodium level correction, followed by variously manifesting neurological damage. The most common are encephalopathies, spastic paresis, dystonias, consciousness disturbances, seizures.

MRI remains the gold standard in imaging. Diffusion weighted imaging is positive within the first few hours after the onset of symptoms. [4] Treatment is, for the time being, preventive and, in case of onset of the symptoms, supportive, aimed at avoiding complications. [2]

Conclusion

Managing of central pontine and extrapontine myelinolysis is challenging as it requires experience, cooperation between health professionals and close patient surveillance to achieve positive outcome. Favorable results may be achieved by work of interprofessional team that include physicians, nurses, rehabilitation professionals and psychologists.[2]

Pontine and extrapontine myelinolysis are relatively rare units, nevertheless they might occur in patients at any hospital department. Although osmotic demyelination syndrome involving pontine and extrapontine myelinolysis is an entity notably caused by rapid correction of chronic hyponatremia [7], there are many comorbidities and concomitant abnormalities that may trigger it. Common to all is an occurrence of prior severe disease, with co-existing electrolyte disturbances. Patients who rank into the group of risk are: chronic alcohol abusers, individuals after liver transplantation, patients with malnutrition, anorexia nervosa, patients admitted to intensive care units, etc. [11]

The ability to correctly equalize serum electrolyte values appears to be fundamental. Chronic hyponatremia is a common disorder, often seen in elderly, alcohol abusers and residents of nursing homes. Even though hyponatremia appears as a condition to be easily dealt with, it is important to remember that its inadequate correction might be fatal in outcome. The supportive care and treatment ought to be started immediately after diagnosis. Despite persistently significant number of patients with a poor outcome, the prognosis of ODS has become more favorable throughout the years and the clinical improvement can be expected in a long term follow-up.[5]

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