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Nephrotic Syndrome and Posterior Reversible Encephalopathy Syndrome

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Abstract

Introduction: The nephrotic syndrome presents with a mixture of proteinuria, hypoalbuminemia, hyperlipidemia, hypertension and edema. Posterior reversible encephalopathy syndrome (PRES) is a combination of symptoms affecting the central nervous system characterized by headache, nausea, vomiting, visual disturbances, altered mental status, decreased alertness and seizures. CT and MRI show areas of vasogenic edema, especially in the parieto-occipital regions. Several case reports and studies have shown nephrotic syndrome as a possible risk factor for the development of PRES, and this review will discuss them.

Aim of Work: The aim of this study is to discuss nephrotic syndrome as a possible risk factor for PRES.

Materials and Methods: This review is a comprehensive search of PUBMED from the year 1995 to 2018.

Conclusion: This review discusses nephrotic syndrome and its possible connection with posterior reversible encephalopathy syndrome. Several studies and case reports have described a series of nephrotic syndrome patients who developed PRES. Hypertension, together with the use of calcineurin inhibitors in nephrotic syndrome, seems to be the main culprit for the development of PRES. More research needs to be done to clearly define the risk factors for PRES and draw precautionary outlines for nephrotic syndrome patients to avoid PRES.

Keywords: *Nephrotic Syndrome; Posterior Reversible Encephalopathy Syndrome; Hypertension Cyclosporine*

Introduction

The nephrotic syndrome presents with a mixture of proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Proteinuria can be massive (greater than 40 mg/m^2 per hour), which leads to hypoalbuminemia (less than 30 g/L) and in turn, causes hyperlipidemia, edema and various complications, one of which is Posterior reversible encephalopathy syndrome [1]. Posterior reversible encephalopathy syndrome is a combination of symptoms affecting the central nervous system. It is characterized by headache, nausea, vomiting, visual disturbances, altered mental status, decreased alertness, seizures, and, infrequently, focal neurological signs. Neuroimaging such as CT and MRI shows edema in the white matter of the parieto-occipital regions. A greater prevalence is seen in patients with kidney disease, of which nephrotic syndrome is of focus in this review [2].

Nephrotic syndrome

Primary causes: Minimal-change nephropathy, focal glomerulosclerosis and membranous nephropathy [3].

Secondary causes: Diabetes mellitus, lupus erythematosus, antibody vasculitis, HIV, hepatitis B virus and other infections [3].

Clinically nephrotic syndrome can be classified as steroid-resistant, steroid-sensitive, steroid-dependent, or frequently relapsing. It can manifest as having:

- Frothy urine (protein makes urine frothy)
- Swelling in legs, abdomen and face (loss of protein changes oncotic pressure)
- Loss of appetite, fatigue, muscle cramps [3].

The pathogenesis of nephrotic syndrome involves various etiologies disrupting the glomerular epithelium or podocytes which causes leakage of proteins from glomerular capillaries into bowman's capsule and finally urine. This clinically shows proteinuria and hypoalbuminemia because protein, i.e. albumin, is lost from blood into the urine. The reduced oncotic pressure of blood cause extravasation of fluid, leading to generalized edema and reactive lipoprotein synthesis from the liver, causing hyperlipidemia [4]. With the progression of kidney disease and loss of GFR, hypertension may also set in some cases and others might also be affected by increased blood pressure due to side effects of drugs [5].

Generally, management is with steroid therapy, i.e. prednisolone administration over several weeks with tapering doses. If serious side effects of steroids are observed, cases may be administered cyclosporine, a calcineurin inhibitor. Monitoring of blood pressure and renal function should be done as it could predispose to Posterior reversible encephalopathy syndrome [6].

Posterior reversible encephalopathy syndrome (PRES)

PRES was first reported in 1996 by Hinchey., *et al*. where they described 15 patients with characteristic neurological signs and symptoms. Due to its unclear clinical and radiological descriptions, the probability of undiagnosed cases could be very high. Since 1996, many people have retrospectively tried to study this syndrome as well [7].

PRES presents itself with signs of encephalopathy, such as disordered consciousness and epileptic seizures. Due to the involvement of occipital lobes, visual disturbances and hallucinations are common. Other neurological symptoms include headache, nausea, and vomiting [7].

Diagnosis is based on clinical findings, laboratory work, and neuroimaging. Electroencephalography (EEG) can be used for the detection of non-convulsant seizures. Increased albumin levels in CSF have been observed and raised CSF/serum albumin quotient, which may signify disruption of the blood-brain barrier. CT scans display vasogenic edema distributed over both hemispheres. Hyperintense lesions are seen on T2 weighted MRIs. Edema distribution is predominantly subcortical, bihemispheric and in the parieto-occipital regions [8].

Since there is no specific therapy for the management of PRES, treatment is usually symptomatic, and management is focused on the underlying disease-causing PRES. Hypertensive cases in PRES are usually recommended 25% reduction in blood pressure from baseline. In the case of seizures, no specific antiepileptic drug or duration of treatment is defined. Anti-epileptics should be tapered off once their symptoms have faded and lesions on neuroimaging have reversed. Although immunosuppressive drugs such as Tacrolimus and cyclosporine are known as triggering factors for PRES, their sudden discontinuation or tapering is controversial [8].

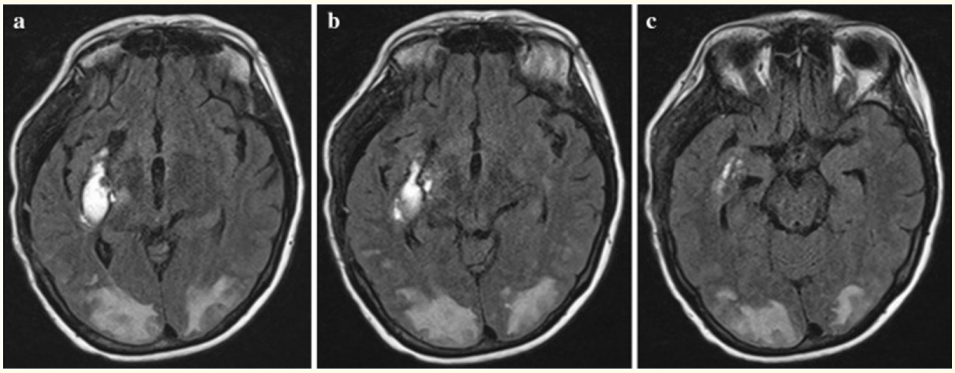

Figure: *a-c Axial MR image (fluid-attenuated inversion recovery sequence) demonstrates extensive vasogenic edema in the occipital region bilaterally and right insular hemorrhage [9].*

Relationship of nephrotic syndrome with PRES

Several case series and individual reports have been published describing the relationship between nephrotic syndrome and PRES. Richard B Schwartz, 1995 studied the relationship between hypertensive encephalopathy with the use of cyclosporine in various organ transplant patients. Sixteen such patients who were on cyclosporine therapy developed symptoms like headache, seizures, visual abnormalities, hypertension and CT/MR imaging showed edema in the brain. Patients were generally managed with antihypertensives and antiepileptics and most (14) of them recovered from their neurological abnormalities, while two succumbed to the disease. This study depicts both cyclosporine and hypertension that comes with it as possible culprits of encephalopathy [10].

Another case report by Ewan R in 1999 reported a 55-year-old woman with episodes of seizures, headache, and vomiting. She was hypertensive on examination and was initially diagnosed as a case of meningitis and later as viral encephalitis. She deteriorated later with visual disturbances, which led to further examinations. She was found with proteinuria on urine analysis and also showed vasogenic edema on neuroimaging. On administration of antihypertensives, the encephalopathy reversed and so did proteinuria on taking immunosuppressives [11].

M Ikeda., *et al*. in 2001 reported a 9-year-old nephrotic syndrome boy who was admitted to hospital with acute renal failure and altered consciousness. He developed clinical symptoms of PRES and an MRI showed brain edema. The patient was hypertensive with hypoalbuminemia, proteinuria and hypercholesterolemia. He was taking high doses of methylprednisolone but was not taking cyclosporine and it was one of the cases where a nephrotic patient developed PRES without cyclosporine use [12].

Duygu Yazgan., *et al*. (2004) reported two middle-aged female patients with hypertension, hypoalbuminemia, and proteinuria who developed encephalopathy-like symptoms and were admitted to the hospital. Neuroimaging showed signs of edema that were reversed once symptoms of PRES subsided. Both patients recovered with antihypertensives, antiepileptics, and fluid management [13].

Ishikura., *et al*. (2008) researched minor patients with the idiopathic syndrome who developed PRES from 1999 to 2005. They studied seven such patients, out of which six of them were in a nephrotic state (average serum albumin was 1.88 g/dl and average total cholesterol was 614.8 mg/dl). Most patients had moderate to mild hypertension and were taking cyclosporine. Six of them also developed altered consciousness, visual disturbances and seizures in five, headache in four, and vomiting in three. Neuroimaging showed areas of the lesion

in the brain, especially in the occipital region. All patients in the study recovered both clinically and radiologically from PRES, as the name of the syndrome suggests [14].

The primary risk factors associated with nephrotic syndrome patients that lead to the development of PRES are hypertension and the use of calcineurin inhibitors, i.e. Cyclosporine. Most case reports describe both hypertension and cyclosporine as possible causes for PRES, but M Ikeda., *et al*. in 2001 described a patient with PRES who was hypertensive, taking steroids but not calcineurin inhibitors. Possible pathophysiology is the vasogenic brain edema caused due extravasation of fluid from intracerebral arteries. A number of factors may influence fluid extravasation, such as hypertension which causes autoregulation failure of cerebral blood flow. The use of calcineurin inhibitors causes endothelial dysfunction, and with high blood pressure, the process of fluid extravasation probably augments. Decreased oncotic pressure and fluid overload from the nephrotic syndrome are also possible influences in the pathophysiology of PRES [14].

Conclusion

This review discusses nephrotic syndrome and its possible connection with posterior reversible encephalopathy syndrome. Several studies and case reports have described a series of nephrotic syndrome patients who developed PRES. Hypertension, together with the use of calcineurin inhibitors in nephrotic syndrome, seems to be the main culprit for the development of PRES. More research needs to be done to clearly define the risk factors for PRES and draw precautionary outlines for nephrotic syndrome patients to avoid PRES.

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