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Polyneuropathy, Myopathy and Hepatitis in a Child with Nephrotic Syndrome

Nefrotik Sendromlu Çocuk Hastada Polinöropati, Miyopati ve Hepatit Birlikteliği

ABSTRACT

Acute sensorimotor polyneuropathy that resembles Guillain-Barre syndrome (GBS) and hepatitis is rarely accompanied with nephrotic syndrome. Its underlying immunological mechanisms are unclear. Involvement of immunological processes against common antigens in the glomerulus, peripheral nervous system and liver has been suggested. We describe a 5-year-old boy patient with acute sensorimotor polyneuropathy, myopathy and hepatitis that was accompanied with nephrotic syndrome. Renal biopsy showed membranoproliferative glomerulonephritis (MPGN). He was in remission on nephrotic syndrome and polyneuropathy at his 6-month follow-up. Approximately 40 cases have been reported in the literature and to our knowledge he is the first patient with these four conditions. In conclusion, this case report suggests that the same underlying immunological mechanisms appear in relation with each other.

KEY WORDS: Child, Hepatitis, Nephrotic syndrome, Myopathy, Polyneuropathy

ÖZ

Nefrotik sendromda Gullian-Barre sendromuna benzeyen akut aksonal duysal-motor polinöropati, miyopati ve hepatit nadiren eşlik etmektedir. Altta yatan immünolojik mekanizmalar belli değildir. Glomerülleri tutan immünolojik mekanizmaların benzer şekilde periferal sinir sistemi, kas ve karaciğeri tuttuğu düşünülmektedir. Burada nefrotik sendromu nedeniyle takip edilen 5 yaşındaki erkek hastada akut duysal motor polinöropati, miyopati ve hepatit tablosu birlikteliği sunulmuştur. Böbrek histopatolojik incelemesinde membrano-proliferatif glomerülonefrit (MPGN) olarak raporlanmıştır. Tedavi sonrası altı aylık takibinde remisyon altında izlenmektedir. Literatürde buna benzer 40 olgu bildirilmesine rağmen bu dört tablonun birarada olduğu ilk olgu bizim olgumuzdur. Sonuç olarak bu olgu sunumunda altta yatan benzer immünolojik mekanizmalar sonucu bu klinik durumun oluştuğu düşünülmektedir.

ANAHTAR SÖZCÜKLER: Çocuk, Hepatit, Nefrotik sendrom, Miyopati, Polinöropati

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INTRODUCTION

Acute sensorimotor polyneuropathy, resembling Guillain-Barre Syndrome (GBS), myopathy and hepatitis, is rarely accompanied with nephrotic syndrome. Its underlying immunological mechanisms are unclear. Involvement of immunological processes against common antigens in the glomerulus, peripheral nervous system, muscle and liver has been suggested (1,2).

We report a 5-year-old male patient with acute sensorimotor polyneuropathy, myopathy and hepatitis with nephrotic syndrome. A literature review outlined approximately 40 similar cases, though to the best of our knowledge this is the first patient showing all four conditions.

CASE

A 5-year-old male patient was referred to our department with the complaints of periorbital oedema and weakness. He had suffered an upper respiratory track infection ten days ago. There was no past disease history, neither any recent immunisation.

He had no family history of kidney disease. His height was 117 cm (96p). The 90 p of blood pressure for his height was 112/70 mmHg. Physical examination demonstrated a normal blood pressure (BP: 110/70 mmHg), and (+2) oedema. He was afebrile and he did not show organomegaly. Neuromuscular examination showed symmetrical weakness (3/5) in his lower extremities with normal tone and deep tendon reflexes. Urine output was 2 ml/kg/h. Laboratory findings at admission were hemoglobin 11.8 g/dl, white blood cell count 26.200/mm^3, and platelet count 328.000/mm^3. There was no hemolysis and no atypical cells on peripheral blood smear. Blood serum urea nitrogen (BUN) 85 mg/dl), creatinine 1.15 mg/dl (creatinine clearance of 52 ml/min/1.73 m^2), uric acid 11 mg/dl, sodium 128 mmol/L, potassium 6.2 mmol/L, calcium 8.48 mg/dl, phosphorus 8.2 mg/dl, total protein 6.1 g/dl, albumin 2.4 g/dl, GGT 22 U/L(N 0-55), ALP 63 U/L (86-315), CK 29385 U/L (N 20-200), LDH 1285 U/L, erythrocyte sedimentation rate (ESR) 39 mm/h, C-reactive protein 0.3 mg/dl, serum complement C3 <17.4 mg/dL (N:90 - 180), and C4 < 6 mg/dL (N:10-40). Anti-nuclear antibody (ANA) was slightly positive but anti-neutrophil cytoplasm antibody, rheumatoid factor, anti ds-DNA, anti-streptolysin O titer (239 IU/mL) were negative. Immunoglobulins were normal. Serology analyses for hepatitis A, B and C, HIV, salmonella, brucella, parvovirus, Epstein-Barr virus were all negative. The throat swab culture was negative. Urinalysis revealed nephrotic range proteinuria (55 mg/m^2/h), haematuria and plenty of erythrocyte casts. Abdominal ultrasonography revealed increased echogenity of the kidney parenchyma.

Medical treatment was started for electrolyte imbalance and he was prescribed acetaminophen for leg pain. Liver enzymes ALT and AST were elevated to 774 and 684 U/L, respectively (Figure 1). The increase in liver enzymes and current findings altogether were thought to be compatible with acute hepatitis. Abdominal ultrasound revealed normal liver structure. Other relevant assessments excluded Wilson's disease, autoimmune and hepatotropic virus disease, α1-antitrypsin deficiency, peroxisomal disorders or lysosomal and glycogen storage disorders. Ultrasound-guided renal biopsy was performed and the histopathological examination revealed diffuse thickness of glomerular basement membrane (Figure 2). Peripheral granular immune complex (IgG and C3) deposition was detected by immunofluorescence microscopy (IFM) (Figure 3). Electron microscopy analysis revealed no hump accumulation (Figure 4). This finding is compatible with Type II MPGN. The patient's case, due to clinical and pathological assessment, was considered as a suspect MPGN case. Pulse methylprednisolone (MPZ) was administered 30 mg/day for 3 days and after the administration we observed a significant improvement in clinical and laboratory findings. The patient was prescribed 2 mg/day oral prednisolone and 30 mg/day methylprednisolone once a week, for treatment with outpatient follow-up after his discharge.

Two weeks after discharge the patient was admitted again with complaints of periorbital and scrotal oedema as well as an inability to walk. On physical examination, blood pressure was 130/80 mmHg with weakness in the lower extremities and decreased deep tendon reflexes. BUN was 38 mg/dL, and creatinine 0.89 mg/dL. His proteinuria persisted in the nonnephrotic range. EMG revealed left median and ulnar sensory action potentials of normal latency, low amplitude, normal conduction velocity and normal motor action potential, moderate left sural sensory action potential conduction velocity, low-amplitude and within normal limits. Left tibial and peroneal motor action potential amplitude and conduction velocity were normal to low. Data could not be obtained for left tibial latency. Needle EMG examination could not be maintained because of low cooperation of the patient, and the optimal resting potential

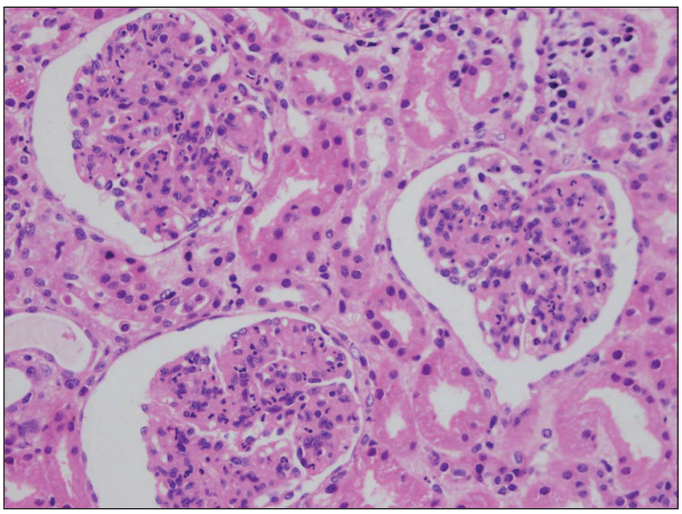

Figure 1: *Serum Creatinine and ALT levels relation with the treatment.*

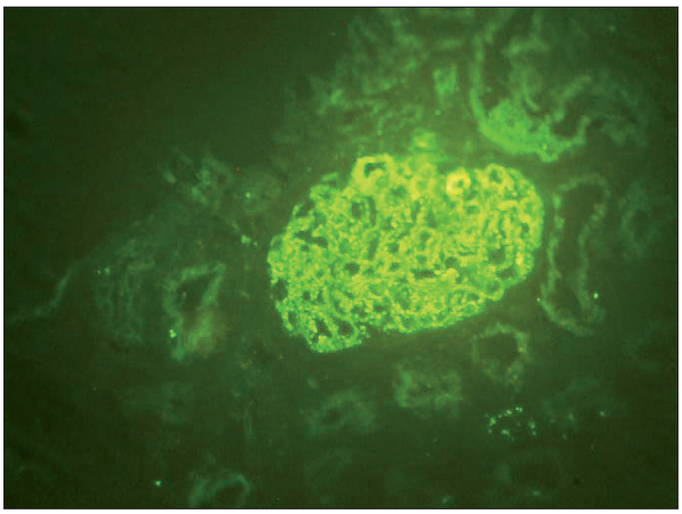

Figure 2: *Lobulations, neutrophilic infiltration, diffuse global thickness of basement membranes were observed in glomeruli (HEx400).*

could not be assessed. Extremity examination for muscles in the left upper and lower needles on the recruitment area showed decreased EMGs with a small number of IP activity. Morphology was assessed as normal IP. These findings directed us towards acute phase motor axonal fiber damage, and thus supported the diagnosis of polyneuropathy.

The patient was assessed for Gullian-Barre Syndrome (GBS). Ganglioside antibodies (GM1, gq1b, GD1B, gt1b, GD1a, GM3, GM2) were reported as negative. The patient was evaluated in terms of Alport Syndrome, and audiometry was reported as normal. Antibody effects on glomerular basement membrane, possibly damaging the myelin sheath, were also considered to be possibly related with the polyneuropathy. Hence, 0.4 mg/day of intravenous immunoglobulin (IVIg) treatment was prescribed for five days. Scrotal oedema was decreased, returning to normal levels of muscle strength and DTRs. The patient could start walking again in the fourth day of the IVIg treatment. The patient showed remission of nephrotic syndrome and polyneuropathy, during his six months of follow-up period.

DISCUSSION

Inflammatory polyneuropathy with nephrotic syndrome is a rare but identified condition. However, it is not yet clear whether it should be considered as a distinct clinical entry or not (1). The association is thought not to be coincidence. Molecular mimicry and common antigens of both the peripheral nervous system and the glomerulus might be involved (3). Alongside with podocytes and myelin, there appears to be biological similarities: one of such is that myelin protein O (PO) is the common protein (3). These circulating antibodies to nerve tissue, as well as kidney, liver and muscle tissues have been previously shown by Van Doorn et al. (2). Some gangliosides expressed in the kidney are of the major ganglioside species of GM3 and GD3. 46 of such gangliosides could be the target molecules in an immune reaction (3). Antiganglioside antibodies were assessed in some cases including the present case, but no specific antiganglioside antibodies-related axonal subtypes were found (5).

Demonstration of hypocomplementemia and complement deposition shown in renal histopathology during the immune attack suggested that these four conditions characterized by a humoral attack would be mediated by complement fixation. Also, the time course and improvement of these four conditions with immunosuppressive treatment (corticosteroid and IVIg) may be due to the same immunopathological mechanisms, such as viral- and neural-derived antigens, being common triggers/. However we could not identify any certain viral infection such as HIV, hepatitis B and C, or an autoimmune disorder with no immunization history. When the patient was admitted with lassitude and pain in the extremity muscle with elevated CK and LDH, diagnosis focused on myopathy and steroid treatment was administered. At the second admission, however, the patient's inability to walk, decrease in DTR during physical examination and EMG findings were finally correlated with polyneuropathy.

Demyelinating and axonal subtypes of GBS-mimicking polyneuropathies were distinguished by EMG findings. This patient had an acute sensorimotor polyneuropathy. Neurological symptoms were mainly motor impairments. In both types there is no difference in terms of the treatment and prognosis.

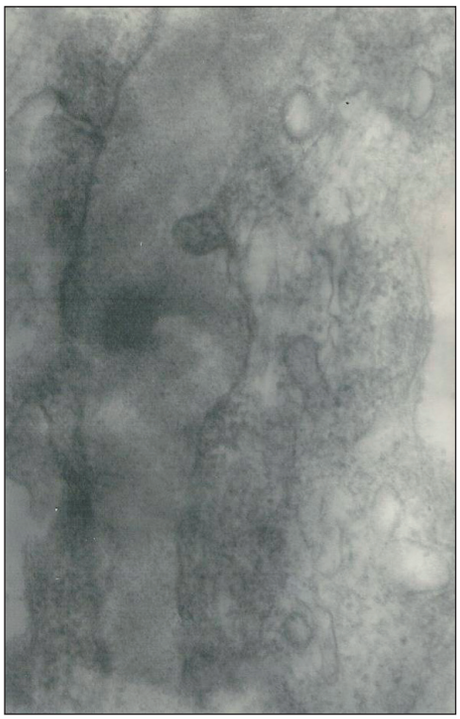

Figure 3: *IgG granular accumulation in peripheral zone (IFMx200).*

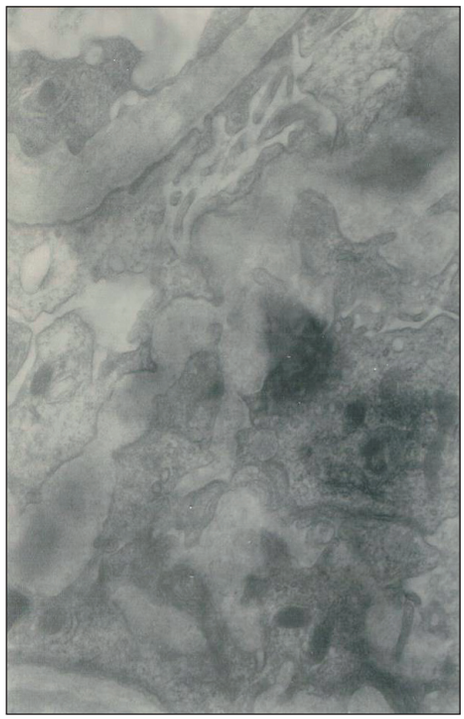

Figure 4: *EM there were not hump accumulation.*

There is no correlation between the symptoms, severity and recurrence of neuropathy and histopathologic diagnosis of nephrotic syndrome. Membraneous glomerulonephritis (6), focal segmental glomerulosclerosis (7), post-infectious glomerulonephritis, and minimal change NS (4,8) were reported in some studies. Majority of cases occurred in men because estrogen or gender-related factors in women are thought to lower morbidity (1). Our case studied was a male patient, consistent with the literature. However, the possible mechanisms may be too obscure. Initial treatment has been recommended with corticosteroids (9) and/or IVIg (10) or plasma exchange but sometimes it can be ineffective or only transiently effective. In our case, the patient had already been taking steroids because of nephrotic proteinuria, so the IVIg was administered for five days at a dose of 0,4 g and methylprednisolone was continued at the dose of 2 mg/day. Polyneuropathy showed gradual improvement and complete recovery on prednisone after 3 weeks of IVIg treatment. Nephrotic syndrome went into remission within a week; serum liver function tests were normalized. Serum complement levels were normalized after 8 weeks of steroid treatment, also. This is why this patient's diagnosis was thought to possibly be postinfectious glomerulonephritis (PIGN). However, histopathological examination of the kidney revealed no subepithelial humps that are characteristics of PIGN. On the other hand, basement membrane thickness was compatible with MPGN. Relapses of neuropathy occurred in half of these cases (1,5) but they had not been intractable or progressive. The patient is still under follow up for nephrotic syndrome.

In conclusion, this case report suggests that the same underlying immunological mechanisms appear in relation with each other. Further studies are needed to elucidate the pathophysiology of the relationship between these immunologically mediated mechanisms so that recurrence of related diseases can be effectively prevented.

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