Successful treatment by mycophenolate mofetil in a patient with focal segmental glomerulosclerosis associated with posterior reversible encephalopathy syndrome

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Abstract It has been reported that cyclosporine A (CsA) treatment may be associated with posterior reversible encephalopathy syndrome. We report a 16-year-old man who exhibited nephrotic syndrome and posterior reversible encephalopathy syndrome. Intensive antihypertensive therapy restored him to consciousness. Renal biopsy revealed that he suffered from focal segmental glomerulosclerosis. Although he was treated with prednisolone and low-density lipoprotein apheresis therapy, his proteinuria remained at high level. Then, mycophenolate mofetil (MMF) with less influence on vessel endothelium compared with CsA and tacrolimus was administered. Soon after, he reached remission of nephrotic syndrome without recurrence of posterior reversible encephalopathy syndrome. This is the first case that a young patient of focal segmental glomerulosclerosis with posterior reversible encephalopathy syndrome achieved a complete remission by MMF treatment without recurrence of posterior reversible encephalopathy syndrome. MMF may

be effective for young patients of focal segmental glomerulosclerosis especially with clinical condition of vascular endothelial damage such as posterior reversible encephalopathy syndrome.

Keywords Focal segmental glomerulosclerosis · Proteinuria · Posterior reversible encephalopathy syndrome · Mycophenolate mofetil

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by headache, seizures, visual and consciousness disturbance [1]. It was first described in 1996 [2]. Although the exact pathogenesis remains unknown, it may occur due to endothelial dysfunction [3].

It often happens that idiopathic nephrotic syndrome (INS) in children is caused by minimal-change nephrotic syndrome (MCNS). In case of steroid resistance, it may be caused by focal segmental glomerulosclerosis (FSGS). Although the calcineurin inhibitor such as cyclosporine A (CsA) is often administered to the patients with steroid-resistant nephrotic syndrome, CsA treatment with the pediatric patient with FSGS has been reported to cause PRES. [4, 5].

Here, we report a young patient of FSGS with PRES who was successfully treated with mycophenolate mofetil (MMF), instead of treatment with CsA.

Case report

The patient in this report was a 16-year-old Japanese man. He had a history of developmental disorder since the age of

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11 years. Abnormal urinalysis was not pointed out until high school. At the age of 16 years, he failed consciousness and was admitted to a hospital. His blood pressure was very high (195/155 mmHg). High-density area was found in subcortical white matter, basal ganglion, cerebellum and brain stem on head magnetic resonance imaging (Fig. 1). At that time, he presented with massive proteinuria (19.3 g/day) and hypoalbuminemia (serum total protein: 6.3 g/dL, serum albumin: 2.2 g/dL). Taken together, he was diagnosed with nephrotic syndrome and PRES. First of all, intensive antihypertensive therapy was started, leading to restoration of consciousness. Regarding massive proteinuria, his primary physician thought that he might suffer from MCNS on the basis of high selectivity index of proteinuria (0.007) and no autoantibody. He was treated with prednisolone of 60 mg/day and diuretic agent. Despite prednisolone administration for 4 weeks (tapering off to 35 mg/day), his proteinuria remained at high level (3.3 g/day). Thus, he was transferred to our hospital.

On admission, the patient's height was 167 cm, body weight was 41 kg, body mass index was 14.7 kg/m², blood pressure was 150/110 mmHg, body temperature was 36.7 °C. His cardiac and pulmonary function appeared

normal and no peripheral edema was found. Laboratory data upon admission are shown in Table 1. Renal biopsy was performed at day 3. Immunofluorescence microscopy showed slight staining of immunoglobulin G and no staining of complement or fibrinogen. In histopathological observation, mesangial, endocapillary and extracapillary proliferation were not found. Segmental glomerulosclerosis in perihilar lesion was observed in two glomeruli out of 26 glomeruli (Fig. 2). In electron microscopic observation, foot process effacement was partly observed in podocytes without any glomerular endothelial or basement membrane abnormalities (Fig. 2). Given these observations, this patient was diagnosed as FSGS.

We considered the adoption of immunosuppressive therapy for him. Since immunosuppressive drugs such as calcineurin inhibitors might affect vessel endothelium possibly leading to the recurrence of PRES, we decided at first to start low-density lipoprotein apheresis (LDL-A) therapy. LDL-A was performed six times (day 14, 16, 21, 23, 28 and 30), followed by prednisolone (35 mg/day). His proteinuria still remained at high level (1.8 g/day) at day 34. Therefore, we decided to administer MMF with less influence on vessel endothelium compared with CsA and

Fig. 1 Head MRI (diffusion-weighted image). High-density area was found in subcortical white matter (a), basal ganglion (b), cerebellum (c) and brain stem (d)

Table 1 Laboratory data on admission

Blood cell count				Urinalysis	
WBC	11570/ μ L	Na	138 mEq/L	Specific gravity	1.004
RBC	588×10^4 / μ L	K	4.4 mEq/L	PH	7.0
Hb	17.2 g/dL	Cl	101 mEq/L	Protein	2+
Ht	52.2 %	Ca	8.2 mg/dL	Occult blood	–
Plt	26.7×10^4 / μ L	P	2.1 mg/dL	Glucose	–
Blood chemistry		HbA1c	5.0 %	RBC	1.3/HPF
TP	5.7 g/dL	CRP	0.02 mg/dL	WBC	0.4/HPF
Alb	3.3 g/dL	Serological test		Cast	
AST	19 IU/L	IgG	330 mg/dL	Hyaline	30–49/WF
ALT	29 IU/L	IgA	212 mg/dL	Granular	3/WF
T-Cho	293 mg/dL	IgM	33 mg/dL	Epithelial	7/WF
LDL-Cho	153 mg/dL	C3	105 mg/dL	Fatty	30–49/WF
HDL-Cho	99 mg/dL	C4	31 mg/dL	NAG	4.7 U/L
UA	4.4 mg/dL	CH50	49 U/mL	β_2 M	4.8 mg/L
BUN	17.4 mg/dL	ANA	<5.0	U-protein	2.8 g/day
Cr	1.12 mg/dL			24hCcr	53.6 ml/min

WBC white blood cell, RBC red blood cell, Hb hemoglobin, Ht hematocrit, Plt platelet, TP total protein, Alb albumin, AST aspartate aminotransferase, ALT alanine aminotransferase, T-Cho total cholesterol, LDL-Cho low-density lipoprotein cholesterol, HDL-Cho high-density lipoprotein cholesterol, UA uric acid, BUN blood urea nitrogen, Cr creatinine, Na sodium, K potassium, Cl chloride, Ca calcium, P phosphorus, HbA1c hemoglobin A1c, CRP cross-reactive protein, IgG immunoglobulin G, IgA immunoglobulin A, IgM immunoglobulin M, C3 complement C3, C4 complement C4, CH50 hemolytic complement, ANA antinuclear antibody, NAG N-acetyl- β -glucosaminidase, β_2 M β_2 microglobulin, U-protein urinary-protein, 24hCcr 24-h endogenous creatinine clearance

tacrolimus and could be effective for FSGS. MMF at the dosage of 500 mg/day was introduced at day 34. He developed no side effect including leukocytopenia, diarrhea, infection or renal disorder. We escalated the dosage up to 1000 mg/day at day 37. (The dosage of prednisolone decreased to 30 mg/day at day 30.) His proteinuria decreased to 1.0 g/day at day 55 and 0.3 g/day at day 83.

Over the next 1 year, we reduced prednisolone and MMF, respectively, to maintain the current patient in clinical remission of nephrotic syndrome (maintenance therapy: prednisolone 5 mg/day only).

Discussion

Here, we report the first case of a young patient of FSGS with PRES who was successfully treated with MMF. Although he was treated with high dosage of prednisolone under a proper blood pressure control following LDL-A therapy, his proteinuria remained high. Thereafter, an addition of MMF on the treatment led to a complete remission.

PRES is a syndrome characterized by headache, seizures, visual and consciousness disturbance which was first described in 1996 [1, 2]. It may occur due to vascular endothelial dysfunction caused by hypertensive

encephalopathy, renal insufficiency, or immunosuppressant [3, 6]. Regarding the patients with nephrotic syndrome, PRES often occurs at the time of moderate to severe nephrotic state [7]. It was reported that the patient with nephrotic syndrome developed PRES [8–10].

In children, the most frequent type of INS is the MCNS. The treatment for INS is aimed at inducing remission, preventing relapses and avoiding side effects. Minimal-change disease is responsive to immunosuppressive therapy. The conventional treatment consists of glucocorticosteroids and the most widely used derivative is prednisone. Initial treatment should be intensive, for example, prednisone for 12 weeks [11]. Treatment response is usually good. Up to 90 % of patients with MCNS achieve complete remission (in adult) [12, 13].

It sometimes happens that INS in children is caused by the FSGS. FSGS, clinical-pathologic syndrome of severe proteinuria associated with focal and segmental sclerotic glomerular lesions, is one of the most difficult and enigmatic diseases in nephrology. It can occur as a primary disorder without an identifiable cause or as an illness secondary to a variety of problems. FSGS is characterized by podocyte damage. Dysfunction of the podocyte is a central feature for the pathogenesis of FSGS [14]. Recently, Changli Wei et al. found that a circulating, soluble form of the urokinase receptor (suPAR) can activate podocyte

Fig. 2 Light microscopic analysis (**a–d**) and electron microscopy analysis (**e**). **a** Segmental glomerulosclerosis in perihilar lesion was observed (an *asterisk*). Periodic acid-Schiff stain. (Original magnification, $\times 400$). **b** Condensation of glomerular basement membrane was observed (an *asterisk*). Periodic acid silver methenamine stain. (Original magnification, $\times 400$). **c** No accumulation of amyloid was

observed. Congo red stain. (Original magnification, $\times 400$). **d** Minimal tubulointerstitial injury was observed. Masson trichrome stain. (Original magnification, $\times 100$). **e** A partial effacement of podocyte foot process (*arrows*) was observed. Glomerular endothelial or basement membrane abnormalities were not found. (Original magnification, $\times 2760$)

beta3 integrin, leading to FSGS pathology, which provides new insight into this disease and may have important clinical implications [15], although more recent report did not support the role of suPAR in FSGS [16, 17].

Treatment response with glucocorticosteroid for FSGS is sometimes poor. There is no proven therapy for steroid-

resistant cases [18]. FSGS with steroid resistance is often treated by immunosuppressive drugs such as CsA, mizoribine, and cyclophosphamide. LDL-A is also effective therapeutic tool for FSGS [19]. Regarding treatment with our patient, the patient was diagnosed as FSGS by renal biopsy. Since clinical course under prednisolone treatment

fails to reach remission in our case, we next performed LDL-A therapy. However, the treatment response was still not enough. Finally, we considered the introduction of treatment with immunosuppressive drugs. It has been reported that calcineurin inhibitors such as CsA and tacrolimus can cause vascular endothelial damage [20]. It has also been reported that a pediatric patient with FSGS developed PRES after CsA administration [4, 5]. Thus, we hesitated to administer these drugs. It has been reported that MMF is effective for FSGS patients [21–23]. Several uncontrolled trials of FSGS patients treated with MMF have shown response rates of over 40 % [24]. Taken together, we decided to start MMF which was less affected to vessel endothelium than others. Two months after introduction of MMF, he reached complete remission without the recurrence of PRES. Calcineurin inhibitor exerts a harmful effect on reproductive function such as low sperm count and poor sperm movement [25]. In this point, MMF is more suitable for young male patient of FSGS.

MMF inhibits purine metabolism by suppressing de novo pathway. This selectively inhibits the proliferation of T- and B-lymphocytes. It has been suggested that mycophenolatic acid, which is the active metabolite of MMF, inhibits the adhesion of leukocytes to endothelial cells by suppressing the expression of endothelial adhesion molecules [26, 27]. Although the therapeutic mechanism of MMF still remains unclear, our patient reached complete remission without recurrence of PRES possibly because of the above mechanism.

In conclusion, our patient with FSGS was successfully treated with MMF without the recurrence of PRES. MMF may be effective for a young patient of FSGS especially with clinical condition of vascular endothelial damage such as PRES.

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