

Fibrin Degradation Products Are a Useful Marker for the Risk of Encapsulating Peritoneal Sclerosis

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Encapsulating peritoneal sclerosis (EPS) is the most serious fatal complication of peritoneal dialysis (PD). Previous studies have indicated the importance of PD duration in the risk of EPS. Pathologic factors may include proliferative neoangiogenesis of the peritoneum and peritoneal hyperpermeability to macromolecules. Because the main component of EPS capsules is fibrin, early detection of the appearance of fibrin may contribute to preventing EPS. For this purpose, measurement of fibrin degradation products (FDPs) in peritoneal effluent may be useful. We therefore examined the relationship between FDP levels and the development of EPS, and the effect of steroid administration.

Our study included 237 patients who had undergone PD between January 2002 and April 2006. Mean duration of PD in these patients was 418.4 ± 32.2 months (range: 1–149.8 months). The fast peritoneal equilibration test (PET) was performed every 6 months, and simultaneously, we determined the FDP level in the effluent of the 4-hour PET dwell (eFDP). Patients with rapidly increasing eFDP levels were administered prednisolone therapy.

We obtained eFDP levels a total of 1335 times in 237 patients. The mean eFDP level was 9.0 ± 12.1 ng/mL (range: 0–137.9 ng/mL), and we found that eFDP was correlated with the dialysate-to-plasma ratio of creatinine (D/P Cr) on PET, but not with duration of PD. In 16 patients, eFDP was greater than 40 ng/mL, and D/P Cr on PET ranged from 0.50 to 0.93. In 7 of these 16 patients, the administration of 5–30 mg of prednisolone daily reduced the eFDP level, but not to a normal level, and 1 of the 16 developed EPS.

Effluent FDP in a useful marker for the risk of EPS. Our results suggest that intensive prednisolone

therapy for patients with high eFDP may forestall EPS development.

Key words

Fibrin degradation products, encapsulating peritoneal sclerosis, risk factors

Introduction

Encapsulating peritoneal sclerosis (EPS) is the most serious fatal complication of peritoneal dialysis (PD). A 4-year prospective multicenter study in Japan showed that the incidence of EPS is 2.5% among all patients, and 0.7%, 2.1%, and 5.9% among patients with, respectively, a 5-, 8-, and 10-year history of PD (1). Thus, the incidence increases with the duration of PD, indicating the importance of PD duration as a risk factor.

Neoangiogenesis in the peritoneum and increased permeability to macromolecules have been postulated as pathogenetic factors. Exposure of the peritoneum to bioincompatible dialysis solutions causes low-grade inflammation, which presumably stimulates the exudation of inflammatory mediators and coagulation–fibrinolysis factors into the peritoneal cavity, resulting in subsequent fibrin deposition on the peritoneal surface, leading to the development of EPS. The main component of the capsules covering the intestine is fibrin. Because fibrin deposition begins before the onset of EPS, its early detection may prevent EPS development.

In the present study, we examined the relationship between fibrin degradation products (FDPs) and EPS development, and we evaluated the effect of steroid administration in the patients with high effluent FDP (eFDP) levels.

Patients and methods

Our study included 237 patients who had undergone PD between January 2002 and April 2006 (55 with and

182 without diabetes). Mean age in the group was 59.6 ± 13.6 years, and mean PD duration was 18.4 ± 32.2 months (range: 1 – 149.8 months). The fast peritoneal equilibration test (PET) was performed every 6 months, and simultaneously, eFDP was determined in the effluent from the 4-hour PET dwell. The β_2 -microglobulin (β_2 MG) level was determined in overnight effluent before the fast PET.

A latex photometric immunoassay was used to measure the eFDP. A latex agglutination immunoassay was used to measure β_2 MG in blood and effluent.

Data are expressed as mean \pm standard deviation. Statistical analyses were carried out using the paired-sample *t*-test, with $p < 0.05$ being regarded as significant.

Results

The eFDP level in a 4-hour dwell on PET was determined 1335 times in 237 PD patients. The mean eFDP level was 9.0 ± 12.1 ng/mL (range: 0–137.9 ng/mL). No correlation was found between duration of PD and the dialysate-to-plasma ratio of creatinine (D/P Cr) in the PET or the eFDP level. The eFDP level was positively correlated with the D/P Cr on PET (Figure 1), an indicator of peritoneal permeability to micromolecules. When the patients were categorized into the usual 4 groups by PET D/P Cr results, the mean eFDP levels in the low, low-average, high-average, and high transport groups were 4 ± 4.8 ng/mL, 6 ± 6.9 ng/mL, 11.8 ± 12.7 ng/mL, and 20.7 ± 25.2 ng/mL respectively. The eFDP levels in the latter 3 transport groups were significantly higher than the level in the low transport group (Figure 2). Similarly, eFDP was positively correlated with D/P β_2 MG, an indicator of peritoneal permeability to macromolecules.

Levels of eFDP higher than 40 ng/mL were observed in 16 patients. Prednisolone was administered to 7 patients whose eFDP levels rose rapidly. The mean dialysis duration in those patients was 79 ± 64.1 months, the mean peak eFDP level was 68.8 ± 44.9 ng/mL, and the mean D/P Cr at that time was 0.83 ± 0.08 . The initial dose of prednisolone was 5 – 30 mg daily (mean: 16.4 ± 10.3 mg). Levels of eFDP decreased to 20.6 ± 13 ng/mL from 68.7 ± 44.9 ng/mL, and the D/P Cr decreased to 0.74 ± 0.04 from 0.83 ± 0.03 (Figure 3).

In a patient with a PD duration of 149.8 months, the eFDP level increased rapidly. Because this patient's eFDP level rose markedly to 132.9 ng/mL, prednisolone was administered, producing a fall in the eFDP.

However, this patient developed EPS and underwent surgery (Figure 4).

Discussion

Encapsulating peritoneal sclerosis is the most serious fatal complication of PD. Its incidence is considered to be 2.5%, but the incidence increases with dialysis duration and has been reported to be 0.7%, 2.1%, and 5.9% at 5, 8, and 10 years of dialysis respectively. The mortality rate is high, at 37.5%, and that rate markedly increases with the duration of dialysis: 0%, 8.3%, 28.6%, 61.5%, and 100% at 5, 8, 10, 15, and more than 15 years of dialysis respectively (1). Treatments include steroids, tamoxifen, and surgical enterolysis, none of which

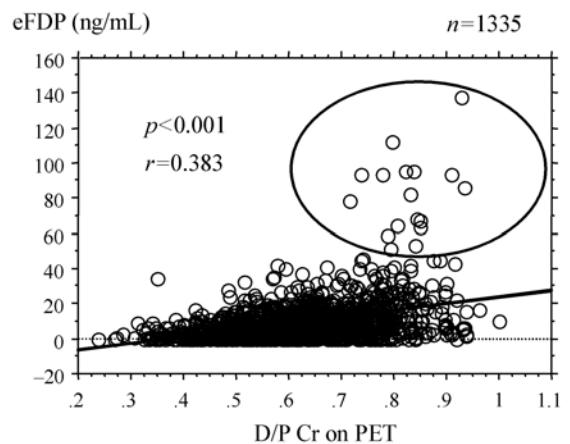


FIGURE 1 Correlation between dialysate-to-plasma ratio (D/P) of creatinine (Cr) and effluent fibrin degradation products (eFDP). PET = peritoneal equilibration test.

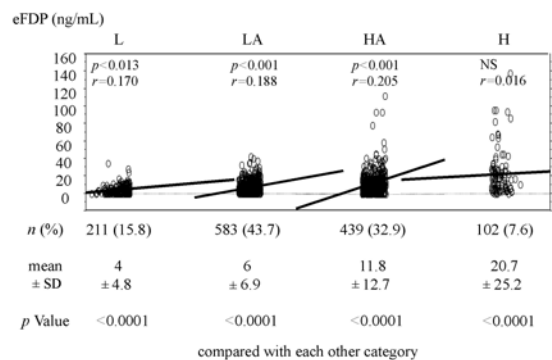


FIGURE 2 Level of effluent fibrin degradation products (eFDP) by peritoneal equilibration test (PET) category. L = low; LA = low average; HA = high average; H = high; NS = nonsignificant; SD = standard deviation.

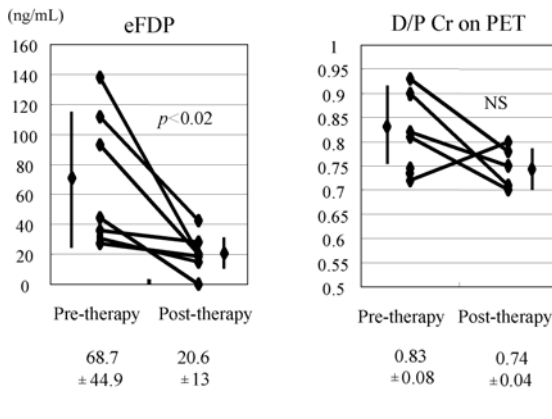


FIGURE 3 The effect of steroid administration on effluent fibrin degradation products (eFDP) and dialysate-to-plasma ratio (D/P) of creatinine (Cr). PET = peritoneal equilibration test; NS = nonsignificant.

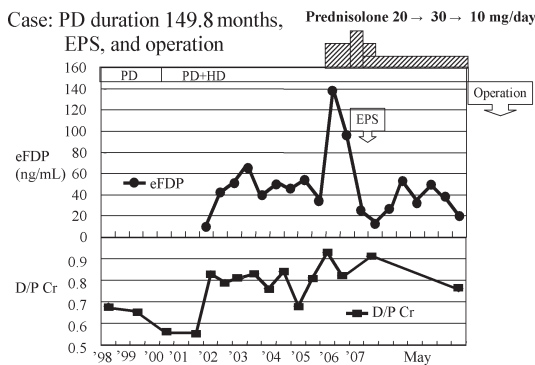


FIGURE 4 A case of progression to encapsulating peritoneal sclerosis (EPS). PD = peritoneal dialysis; HD = hemodialysis; eFDP = effluent fibrin degradation products; D/P Cr = dialysate-to-plasma ratio of creatinine.

achieves a sufficient therapeutic effect, suggesting limitations in the treatment of EPS. Therefore, it is important to identify predictors of EPS and to establish effective therapeutic methods.

Dobbie (2) reported that bioincompatible dialysis solutions causes low-grade peritoneal serositis, which increases the transfer of coagulation factors into the peritoneal cavity, resulting in a hypercoagulable state leading to fibrin generation with increased fibrinolysis—that is, a high-FDP state. In addition, continuous exposure to bioincompatible dialysis solutions causes increased peritoneal permeability, resulting in the

transfer of coagulation factors into the peritoneal cavity, leading to a high-FDP state (3–5).

The D/P Cr on PET is a marker of peritoneal permeability to micromolecules and reflects peritoneal neoangiogenesis. Yamamoto *et al.* reported a significantly higher PET D/P Cr in patients who developed EPS after withdrawal from PD, indicating that a high transport membrane is a risk factor for EPS (6,7). Histologically, peritoneal neoangiogenesis is observed in EPS patients in association with high D/P Cr.

In the present study, eFDP levels were positively correlated with the PET D/P-Cr and D/P β 2MG, indicating that a high eFDP is a risk factor for EPS, just as a high-transport membrane is.

The main component of the capsules covering the intestine is fibrin. We speculate that the exudation of inflammatory mediators and coagulation–fibrinolysis factors into the peritoneal cavity results in fibrin deposition on the peritoneal surface, leading to the development of EPS. Because this fibrin deposition begins before the onset of EPS, its early detection may permit prevention of EPS development. Studies have reported patients in whom levels of FDP and interleukin-6 in the dialysis effluent both rose, but fell after prednisolone administration (8,9).

We administered prednisolone to 7 patients whose eFDP levels rose rapidly, and we found that eFDP levels fell in all of those patients. However, in 1 patient, although prednisolone administration reduced the eFDP level, it did not reduce it to the earlier level. This patient developed EPS. Because this patient was undergoing long-term PD and showing a persistently high eFDP level, we speculated that capsule formation had occurred. Even in long-term PD patients, eFDP levels in the mid-range decreased when prednisolone was administered soon after an increase, and EPS did not develop.

The level of eFDP is a useful marker for the risk of EPS. Our results suggest that positive prednisolone therapy for patients with a high eFDP level may forestall EPS development.

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