Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients

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Although uremia is well known as the most common cause of pruritus, the mechanisms of pruritus in chronic hemodialysis patients remain unclear. The purpose was to characterize uremic pruritus in more detail and to investigate whether severe pruritus is a marker for poor prognosis. A total of 1773 adult hemodialysis patients were studied. A questionnaire was given to each patient to assess the intensity and frequency, as well as pruritus-related sleep disturbance. We analyzed the relationship between clinical and laboratory data and the severity of pruritus in hemodialysis patients and followed them for 24 months prospectively. In total, 453 patients had severe pruritus with a visual analogue scale (VAS) score more than or equal to 7.0. Among them, more than 70% complained of sleep disturbance, whereas the majority of patients with a VAS score of less than 7.0 had no sleep disturbance. Male gender, high levels of blood urea nitrogen, β2-microglobulin (β2MG), hypercalcemia, and hyperphosphatemia were identified as independent risk factors for the development of severe pruritus, whereas a low level of calcium and intact-parathyroid hormone were associated with reduced risk. During the follow-up, 171 (9.64%) patients died. The prognosis of patients with severe pruritus was significantly worse than the others. Moreover, severe pruritus was independently associated with death even after adjusting for other clinical factors including diabetes mellitus, age, β2MG, and albumin. Severe uremic pruritus caused by multiple factors, not only affects the quality of life but may also be associated with poor outcome in chronic hemodialysis patients.

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Pruritus has been well recognized as a common and sometimes unbearable complication in patients with chronic renal failure.[1–3] Although the association between chronic renal failure and skin itching has been recognized for more than a century, the molecular basis of pruritus in chronic renal failure remains an elusive problem, mainly because of its subjective and capricious nature and the strong influence of psychological factors.

There is no confirmed evidence that uremic pruritus can be caused by a single factor,[4,5] whereas many metabolic factors have been implicated in the pathogenesis of itching, for example, hypercalcemia, hyperphosphatemia, secondary hyperparathyroidism, and hypermagnesemia.[6,7] It has been reported that higher dialysis efficacy with a good nutritional state reduces the prevalence and degree of pruritus in hemodialyzed patients.[8] In addition to affecting the quality of life and sleep, uremic pruritus has been reported to be a marker of poor outcome in patients on long-term hemodialysis.[9] However, the prognostic significance of uremic pruritus has not been examined in Japanese patients. Because many of the previous clinical studies on uremic pruritus have been performed on a small number of patients and the involvement of multiple confounding factors has not been fully evaluated, the impact of uremic pruritus on survival of hemodialysis patients is yet to be confirmed.

To clarify the risk factors for the development of severe uremic pruritus, we investigated the relationship between clinical and laboratory data and the development of severe uremic pruritus in a large number of patients undergoing chronic hemodialysis. This study also investigated the prognostic significance of uremic pruritus for survival of Japanese patients undergoing chronic hemodialysis treatment by prospective observation for 24 months.

RESULTS

In total, 1773 patients were included in the analyses. Figure 1 shows the distribution of patients with each range of visual analogue scale (VAS) scores, subjectively assessed for skin itching of the patients. In all, 1292 (72.9%) of the 1773 had VAS score of at least more than 1.0. The patients were stratified into three groups as described in the Patients and

Methods. The validity of this simple stratification method was evaluated by subsequent analyses and by survival analysis. Table 1 shows the distribution of the categorized frequencies of skin itching, sleep disturbances due to itching, as well as antipruritic treatments used in each group of patients. It was obvious that the intensity of the itching was strongly associated with the frequency ($\chi^2 = 266.669$, $P < 0.0001$). In patients with severe pruritus, about 80% complained of itching at least more than a few times a day (grade 4 or 5), and more than 70% of them complained of sleep disturbance, ranging from grade 2 to 4, whereas the majority of patients in the other groups had no sleep disturbance ($\chi^2 = 254.974$, $P < 0.0001$). The frequencies of any kind of antipruritic treatment in each group were also strongly correlated with the stratified intensity of pruritus. The mean values of grades of frequency and sleep disturbance were also compared using the Kruskal–Wallis H statistic among the three groups. Both frequency (Figure 2a) and sleep disturbance (Figure 2b) were significantly different across groups (a, $P < 0.0001$; b, $P < 0.0001$), clearly indicating that the increased intensity of pruritus is associated with the frequency of skin scratching episodes and sleep disturbance, leading to a decline in the quality of life.

Table 2 shows the demographic and laboratory data of the study subjects and comparisons among groups with each grade of uremic pruritus intensity at the study entry. The group with severe pruritus had a significantly higher proportion of male gender, longer duration of dialysis, as well as higher levels of serum creatinine, blood urea nitrogen

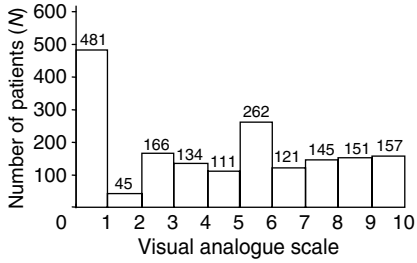

Figure 1 | Number of patients in each range of VAS scores for intensity of uremic pruritus.

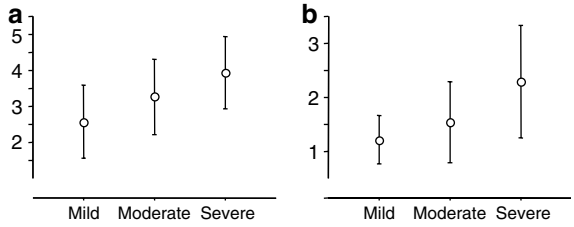

Figure 2 | The (mean ± s.d.) values of grades of frequency and sleep disturbance were compared using the Kruskal–Wallis H statistic among the three groups. Both grades for **(a)** frequency of skin scratching episode and **(b)** sleep disturbance due to skin itching were significantly different across groups (a, $P < 0.0001$; b, $P < 0.0001$).

Table 1 | Frequencies of skin itching, sleep disturbances due to itching, and anti-pruritic treatment in each group of patients

		Pruritus grade			Among three groups		Between severe vs others	
	All patients *N*=1773	Mild (VAS < 4.0) *N*=826	Moderate (VAS 4.0–6.9) *N*=494	Severe (VAS > 7.0) *N*=453	*P*-value	χ^2	*P*-value	χ^2
Frequency								
Less than once a week	63 (5.54)	28 (12.50)	23 (4.79)	12 (2.77)				
Less than once every few days	235 (20.67)	93 (41.52)	100 (20.83)	42 (9.70)				
More than once a day	230 (20.23)	59 (26.34)	132 (27.50)	39 (9.01)				
More than a few times a day	419 (36.85)	36 (16.07)	175 (36.46)	208 (48.04)				
Total restlessness	190 (16.71)	8 (3.57)	50 (10.42)	132 (30.48)	<0.0001	266.669	<0.0001	198.247
Number of answers	1137 (100)	224 (100)	480 (100)	433 (100)				
Sleep disturbance								
No sleep disturbance	592 (51.57)	186 (79.49)	284 (59.17)	122 (28.11)				
Waking up less than a few times a night	322 (28.05)	45 (19.23)	143 (29.79)	134 (30.88)				
Waking up more than a few times a night	156 (13.59)	3 (1.28)	43 (8.96)	110 (25.34)				
Sleeplessness	78 (6.79)	0 (0.00)	10 (2.08)	68 (15.67)	<0.0001	254.974	<0.0001	225.626
Number of answers	1148 (100)	234 (100)	480 (100)	434 (100)				
Anti-pruritic treatment								
Antipruritic lotions	718 (40.50)	106 (12.83)	285 (57.69)	327 (72.19)	<0.0001	511.722	<0.0001	244.788
Antihistamines	220 (12.41)	24 (2.91)	67 (13.56)	129 (28.48)	<0.0001	176.849	<0.0001	139.913
Sedatives	75 (4.23)	3 (0.36)	26 (5.23)	46 (10.12)	<0.0001	71.036	<0.0001	52.474
Ultraviolet therapy	4 (0.23)	0 (0.00)	1 (0.20)	3 (0.66)	0.0574	5.716	0.0235	5.135

VAS, visual analogue scale; (), %.

Table 2 | Demographics and laboratory data of the study population and comparisons among groups with each grade of uremic pruritus

	All patients N=1773	Pruritus grade			Among three groups		Between Severe vs Others	
		Mild N=826	Moderate N=494	Severe N=453	P-value	χ^2	P-value	χ^2
Gender (male %)	58.9	52.8	62.3	66.4	<0.0001	25.849	0.0001	14.489
Age (*year*)	60.2±12.8	60.5±13.3	60.1±12.5	59.8±12.3	0.4411		0.2345	
BMI (kg/m^2)	21.18±2.79	20.94±2.63	21.32±2.77	21.51±3.09	0.0916		0.0654	
Duration of dialysis (months)	123.6±90.1	118.8±88.7	122.7±92.1	133.0±90.0	0.0048		0.0014	
Diabetes mellitus (%)	18.9	19.7	19.2	16.8	0.4052	1.807	0.1312	2.278
History of parathyroidectomy	72	32	23	17	0.7344	0.633	0.7020	0.146
Serum creatinine (mg/dl)	11.0±2.6	10.7±2.7	11.2±2.4	11.4±2.7	0.0001		0.0010	
BUN (mg/dl)	70.7±16.1	69.3±16.2	71.6±15.7	72.3±16.3	0.0008		0.0060	
Hematocrit (%)	30.3±4.4	30.2±4.3	30.5±4.4	30.3±4.6	0.7378		0.9039	
Total protein (g/dl)	6.4±0.6	6.4±0.7	6.4±0.6	6.4±0.6	0.5627		0.5486	
Albumin (g/dl)	4.01±0.52	4.01±0.57	3.99±0.47	4.01±0.49	0.3302		0.6948	
β2-microglobulin (mg/dl)	29.3±8.7	28.6±8.7	29.0±7.8	30.7±9.3	0.0018		0.0006	
K_t/V[a]	1.21±0.26	1.23±0.28	1.20±0.27	1.19±0.22	0.0957		0.1180	
CRP[a] (mg/dl)	0.65±1.4	0.65±1.34	0.57±1.12	0.75±1.75	0.0517		0.0180	
Intact-PTH (pg/ml)	209.4±228.3	192.2±215.7	203.6±226.9	246.5±247.8	<0.0001		<0.0001	
Calcium (mg/dl)	8.73±1.35	8.55±1.43	8.86±1.24	8.94±1.28	0.0001		0.0005	
Phosphate (mg/dl)	5.62±1.47	5.41±1.40	5.71±1.44	5.91±1.58	0.0001		<0.0001	
EPO users (%)	74.1	79.3	69.4	68.2	0.0378	6.552	0.1346	2.238
EPO dose (U/week)	4278 3151	4506 3018	3954 3147	4153 3423	0.2973		0.7133	
Blood pressure (mm Hg)								
Systolic	151.0±25.4	150.7±26.0	151.3±24.3	151.4±25.5	0.7235		0.5147	
Diastolic	83.1±40.1	83.1±40.4	81.5±23.0	84.7±52.3	0.8598		0.6391	

Values are mean±s.d.
VAS, visual analogue scale; BUN, blood urea nitrogen; PTH, parathyroid hormone; BMI, body mass index; CRP, C-reactive protein; EPO, erythropoietin.
[a]Data of Kt/V and CRP are for 547 and 331 patients, respectively.

(BUN), β2-microglobulin (β2MG), intact-parathyroid hormone (i-PTH), calcium, phosphate, and serum C-reactive protein levels (CRP than the other groups, while there was no significant difference among the three groups for age, body mass index, incidence of diabetes mellitus, hematocrit, history of parathyroidectomy, total protein, albumin, K_t/V, and blood pressure. The frequency of erythropoietin users in the group with mild pruritus was significantly higher than that of the other groups ($P=0.0105$), whereas the weekly dose of erythropoietin was not significantly different among the three groups, as was the type of dialysis membrane (data not shown).

The multiple logistic regression analysis was used to test the significance of confounding factors for the development of severe uremic pruritus. As shown in Table 3, the final logistic regression model showed increased odds ratio for males of 1.514 (95% confidence interval (CI), 1.175–1.950; $P=0.0013$), BUN ($\geqslant$81.3 mg/dl) of 1.422 (95% CI, 1.028–1.967; $P=0.0036$), β2MG ($\geqslant$34.1 mg/dl) of 1.647 (95% CI, 1.198–2.264; $P=0.0021$), calcium ($\geqslant$9.5 mg/dl) of 1.431 (95% CI, 1.053–1.945; $P=0.0220$), and phosphate ($\geqslant$6.6 mg/dl) of 1.650 (95% CI, 1.200–2.269; $P=0.0021$). On the other hand, low levels of calcium ($\leqslant$8.1 mg/dl) and i-PTH ($\leqslant$200 pg/ml) were associated with reduced risk for severe pruritus (odds ratio for low calcium = 0.639; 95% CI, 0.457–0.893; $P=0.0087$; odds ratio for low i-PTH = 0.565; 95% CI, 0.414–0.772; $P=0.0003$, respectively). Age, diabetes mellitus, duration of dialysis, level of creatine, hematocrit,

Table 3 | Multiple logistic regression analysis for severe uremic pruritus (VAS$\geqslant$7.0)

Variables	χ^2	P-value	Odds ratio	95% CI
Gender				
Female		Referent		
Male	10.300	0.0013	1.514	1.175, 1.950
BUN (mg/dl)				
$\leqslant$60.0	1.553	0.2126	1.237	0.885, 1.728
>60.0, <81.2		Referent		
$\geqslant$81.3	4.513	0.0036	1.422	1.028, 1.967
β2MG (mg/dl)				
<23.6	0.048	0.8263	0.965	0.701, 1.329
23.6, <34.1		Referent		
$\geqslant$34.1	9.456	0.0021	1.647	1.198, 2.264
Intact-PTH (pg/ml)				
<200	12.899	0.0003	0.565	0.414, 0.772
$\geqslant$200, <400		Referent		
$\geqslant$400	0.178	0.6732	0.916	0.608, 1.379
Calcium (mg/dl)				
$\leqslant$8.1	6.893	0.0087	0.639	0.457, 0.893
>8.1, <9.5		Referent		
$\geqslant$9.5	5.242	0.0220	1.431	1.053, 1.945
Phosphate (mg/dl)				
$\leqslant$4.6	0.068	0.7945	0.956	0.685, 1.335
>4.7, <6.6		Referent		
$\geqslant$6.6	9.486	0.0021	1.650	1.200, 2.269

VAS, visual analogue scale; BUN, blood urea nitrogen; PTH, parathyroid hormone; β2MG, β2-microglobulin.

Table 4 | Causes of death in each group

Cause of death	Over all	Pruritus grade		
		Mild	Moderate	Severe
Cardiac	51 (29.8)	22 (30.6)	16 (42.1)	13 (21.3)
Infection	28 (16.4)	9 (12.5)	5 (13.2)	14 (23.0)
Cerebrovascular	27 (15.8)	13 (18.1)	5 (13.2)	9 (14.8)
Withdrawal	13 (7.6)	5 (6.9)	3 (7.9)	5 (8.2)
Sudden death	6 (3.5)	3 (4.2)	1 (2.6)	2 (3.3)
Others	46 (26.9)	20 (27.8)	8 (21.1)	18 (29.5)
Total death	171	72	38	61

(), %; the total percentage may not be 100% because of rounding.

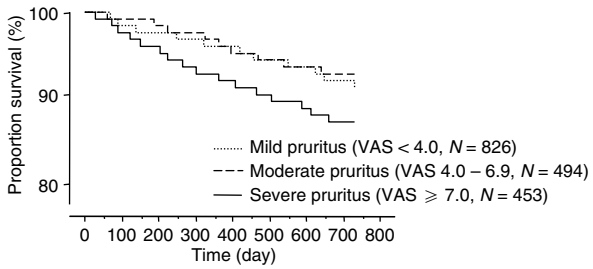

Figure 3 | Kaplan–Meier analysis for the survival of patients. The prognosis of patients with severe uremic pruritus was significantly worse than those of the others (log rank test, $\chi^2 = 14.426$; $P = 0.0001$).

albumin, K_t/V, and blood pressure were not recognized as independent risk factors for severe uremic pruritus in this model.

Next, to investigate whether severe uremic pruritus has an impact on death, the patients were prospectively followed up until death or for 24 months. During the follow-up, 171 of the 1773 patients (9.64%) died. The causes of death are listed in Table 4. There was no significant difference in the cause of death among each group ($\chi^2 = 7.283$, $P = 0.7100$). Death due to infection tended to be more prevalent in patients with severe uremic pruritus compared with other groups, although the difference was not significant.

Figure 3 shows the survival of patients analyzed by the Kaplan–Meier method. The prognosis of patients with severe pruritus was significantly worse than the others (log rank test, $\chi^2 = 14.426$; $P = 0.0001$). To investigate further the significance of severe uremic pruritus as an independent predictive marker for death, the multivariate Cox proportional hazard regression model was used. After forcing severe pruritus (VAS$\geqslant$7.0) in the model, significant variables, other than CRP because of incomplete data, were selected using a stepwise backward procedure so that the maximum likelihood ratio was generated ($\chi^2 = 134.988$; $P < 0.0001$). This model revealed that severe uremic pruritus was an independent predictive factor for death even after adjusting for other clinical risk factors (Table 5, Hazard ratio (HR) for severe pruritus = 1.595; 95% CI, 1.160–2.381; $P = 0.0084$). In this model, diabetes mellitus, age, and low level of albumin were independent risk factors for death, whereas low β2MG was protective. In the 331 patients in whom CRP values were available, survival rates analyzed by the Kaplan–Meier method was lower in patients with CRP levels above the 75 percentile (>0.51 mg/dl) (log rank test, $\chi^2 = 18.602$; $P < 0.0001$).

Table 5 | Cox proportional hazard model to test the significance of clinical covariates and uremic pruritus as predictors of death

Variable	*P*-value	HR	95% CI
Severe pruritus			
VAS > 7.0	0.0084	1.595	1.160, 2.381
Diabetes mellitus	0.0047	1.711	1.179, 2.485
Age (years)	<0.0001	1.053	1.037, 1.069
β2MG (mg/dl)			
⩽23.6	0.0287	0.588	0.365, 0.946
>23.6, <34.1	Referent		
⩾34.1	0.4468	1.163	0.788, 1.714
Alb (g/dl)			
⩽3.7	0.0003	2.097	1.400, 3.141
>3.7, <4.4	Referent		
⩾4.4	0.0340	0.552	0.318, 0.956

HR, Hazard ratio; CI, confidence interval; MG, microglobulin; Alb, albumin.

DISCUSSION

Uremic pruritus remains a frequent and tormenting problem in patients with end-stage renal disease, mainly because of the lack of knowledge of the underlying pathophysiological mechanisms. In the present study, a large number of adult patients undergoing chronic hemodialysis treatment, at least for more than 24 months, were analyzed in order to clarify the risk factors for the development of severe uremic pruritus. To our knowledge, this is the largest study population used to characterize the multiple confounding factors for severe uremic pruritus. We stratified patients into three groups according to the intensity of their skin itching, which was subjectively estimated by VAS scores. The scoring method for the intensity of pruritus employed in the present study was simple compared to the detailed scoring system of previous studies.[10,11] However, the validity of the stratification in this study was confirmed by the subsequent analyses, which tested the relationship between the intensity and the frequency of skin scratching episodes, its influence on sleep disturbance, as well as its relationship to the necessity of treatments, indicating that the stratified intensity of pruritus is significantly associated with a fall in the quality of life. Since pruritus is affected by seasonal changes, we conducted the study in a spring season, which corresponds to the average temperature and humidity in Niigata prefecture.

The result of the logistic regression analysis revealed that the development of severe uremic pruritus is associated with multiple clinical factors. Male gender, high pre-dialysis level of BUN, high levels of β2MG, calcium, and phosphate, as well as i-PTH were independently associated with the development of severe uremic pruritus. All these factors have already been reported in previous studies,[1,4,6,8,12,13] although their relative impacts have not been fully tested by

multivariate analysis in a large population. The duration of dialysis was longer in the patients with severe pruritus when simply compared, but it was not selected as an independent factor in the multivariate logistic regression model. This may be because the longer duration of dialysis was correlated with other significant risk factors such as the high levels of BUN, β2MG, and i-PTH. In fact, significant correlations were observed between dialysis duration and these factors in our patients (data not shown).

The mean level of BUN was significantly higher in patients with severe pruritus when simply compared with those of other groups, and the multiple logistic regression analysis indicated that a high level of BUN was a significant risk factor for severe uremic pruritus. This may indicate that a substantial proportion of patients with severe uremic pruritus are in an underdialysis state, although K_t/V was no different among groups, when simply compared. K_t/V does not quantify the removal of mid- and large-sized molecules which may be responsible for uremic pruritus.[14] There is also a possibility that severe uremic pruritus is associated with a hypercatabolic state; however, we could not analyze the relation between protein catabolic rate and pruritus because we lacked the data of interdialytic urinary urea nitrogen excretion in patients with urine output. Nonetheless, the significantly higher CRP levels in patients with severe pruritus support the latest possibility. To establish a definitive link between a high level of BUN and uremic pruritus, further investigations with precise assessments of the nutritional state of every patient, using other markers such as subjective global nutritional assessment (SGNA), measuring several anthropometric markers, plasma insulin, insulin growth factor-1, are needed.[15]

In addition to hyperparathyroidism, divalent-ion abnormalities, and a high level of BUN, the data indicated that a high level of β2MG is independently associated with the development of severe uremic pruritus. While it has been revealed that the β2MG content in skin tissue increases with the duration of dialysis,[16] there is no evidence for a direct cause-and-effect relationship between β2MG and pruritus. Although it has been established that β2MG is a major component of dialysis-associated amyloidosis,[17] it is not likely that uremic pruritus is directly caused by amyloidosis, because the incidence of accumulation of β2MG amyloid fibrils in tissues other than joints and juxta-articular structures is extremely low.[18] If anything, there is a possibility that increased accumulation of middle-molecular weight molecules, which are unknown so far and reflected by the high level of B2MG, is a pruritogenic factor in hemodialysis patients. Recently, two new hypotheses for the underlying pathophysiological mechanisms of uremic pruritus have been proposed, the immuno-hypothesis and opioid hypothesis.[19] Mettang *et al.* have suggested that numerous factors including IL-2, TNF-α, and CD4 cells are probably involved in the pathogenesis of uremic pruritus. Therefore, the increased level of β2MG in patients with severe uremic pruritus may indicate that a condition which promotes the production or accumulation of IL-2 or TNF-α and activation of CD4 cells also promotes the development of pruritus.

The important and interesting finding of the present study is that the prognosis of patients with severe uremic pruritus was significantly poorer than that of other groups, and that the impact of uremic pruritus was independent even after adjusting for other significant clinical risk factors for death. The mechanism by which severe uremic pruritus had a significant impact on survival is unknown. It may be related to a chronic subclinical inflammation as suggested by the significantly higher CRP levels in patients with severe pruritus. In our study, patients with higher CRP had a lower survival rate. Unfortunately, we could not conduct further analysis to prove this relation because CRP was not routinely measured in all of our patients. Chronic inflammation has been increasingly recognized as a poor survival factor in chronic hemodialysis patients.[15,20,21] The causes of death in patients with severe uremic pruritus were no different from those in other patient groups. The mortality rate of about 10% during 2-year observation in this study was compatible with other reports in Japanese hemodialysis patients. We could not accurately measure drug dosage or continuous duration of medical therapies such as ACE inhibitors, active Vitamin D, phosphate binders, or HMG-CoA reductase inhibitors during the clinical course in this study. The presence of uremic neuropathy, and whether it has any relation with the severity of pruritus and poor outcome, was also not checked in our study. It has been suggested that somatic and autonomic dysfunction may be related to uremic pruritus.[22] Further investigation with a longer duration of observation and fixed medical protocol is necessary to clarify the mechanism by which severe uremic pruritus was accompanied with poor outcome.

In conclusion, this is the largest population-based study with quantitative analysis of uremic pruritus in chronic hemodialysis patients. Our study indicated that severe uremic pruritus is an independent predictor of poor outcome, and that the etiology of uremic pruritus is multiple. Therefore, we recommend individualized treatment to prevent the development of severe pruritus, which may consequently improve the outcome of patients undergoing chronic hemodialysis therapy.

MATERIALS AND METHODS

Study subjects

In the year 2000, a total of 3840 adult patients underwent chronic hemodialysis treatment at 41 institutions in Niigata Prefecture, Japan. Among them, 1773 patients, who did consent to participate in this study, were recruited from March to May 2000, while patients with a history of pruritus or dermatologic disease antedating renal failure were excluded. Also, patients with systemic diseases such as malignancy, cholestatic liver disease, and those with psychiatric disorders or non-compliance to hemodialysis treatment were excluded. The patient's mean age was 60.2 ± 12.8 years (range; 20–92) and mean duration of hemodialysis was 123.6 ± 90.1 months (range; 24–408). The underlying renal diseases were chronic glomerulonephritis ($N = 1052$), diabetic nephropathy ($N = 332$),

polycystic kidney disease ($N=73$), nephrosclerosis ($N=95$), chronic pyelonephritis ($N=30$), other diseases ($N=172$), and unknown ($N=19$). All patients gave written informed consent before enrollment in the study.

Estimation of pruritus, analysis of clinical data, and follow-up

At the study entry, a questionnaire was given to each patient to assess the intensity and frequency of pruritus, as well as its influence on the quality of sleep. Each patient estimated his or her current skin itching intensity using a VAS (0 = no pruritus to 10 = unbearable pruritus). Frequency of itching was categorized into five grades as follows: 1, scratching episodes less than once a week; 2, more than once a week but less than once a day; 3, more than once a day; 4, more than a few times a day; 5, total restlessness. Sleep disturbance was categorized as follows: 1, no sleep disturbance (no episodes of waking up because of itching); 2, waking up, but less than a few times a night, due to skin itching; 3, waking up more than a few times a night; 4, sleeplessness due to skin itching.

Clinical characteristics including age, sex, body weight, height, blood pressure, duration of dialysis (in months), type of dialysis membrane, prior history of parathyroidectomy, erythropoietin and antipruritic treatments at the time of study entry were recorded. Laboratory data including levels of serum creatinine (mg/dl), BUN (mg/dl), albumin (g/dl), hematocrit (%), β2MG (μg/l), i-PTH (pg/ml), calcium (mg/dl), and phosphate (mg/dl) before the dialysis session were measured. Dialysis adequacy expressed as K_t/V values, estimated by the method described by Daugirdas,[23] and CRP levels (mg/dl) were only available in 547 and 331 patients, respectively.

In all institutions, hemodialysis was conducted using high-flux dialysis membranes, such as polymethylmethacrylate, poly-acrylonitrile, polysulfone, and triacetate with bicarbonate as a dialysis buffer. Water purified by reverse osmosis was used as the dialysate in all patients.

To test the significance of severe pruritus as a predictive risk factor for death, all patients were prospectively followed up until death, or May 1, 2002. Causes of death were classified as cerebrovascular, infection, cardiac, dialysis withdrawal, sudden death, and others. Dialysis withdrawal-associated deaths were noted in patients who were unable to undergo regular dialysis because of severe malnutrition or unstable hemodynamic condition.

Statistical analysis

Statview 5.0 statistical software (Abacus Concepts, Inc. Berkeley, CA, USA) was used for the analyses on a Macintosh G4 computer. The χ^2 analysis was used when comparing categorical variables between the groups. Continuous variables were compared using the Mann–Whitney U-test or Kruskal–Wallis analysis of variance. All tests were two-sided. A P-value less than 0.05 was considered significant. The patients were stratified into three groups according to the itching intensity as follows: group 1, patients with no or mild pruritus, whose VAS scores were less than 4.0 ($N=826$); group 2, those with moderate pruritus, whose VAS were 4.0–6.9 ($N=494$); and group 3, those with severe pruritus, whose VAS were equal or more than 7.0 ($N=453$). Odds ratio with 95% CI for the development of severe pruritus (VAS score $\geqslant$7.0) in association with potential confounding variables (sex, age, the duration of dialysis, and the presence or absence of diabetes mellitus) were calculated on the basis of univariate and multiple logistic-regression analysis. In this analysis, the levels of serum creatinine, BUN, hematocrit, calcium, phosphate, and CRP were stratified into three groups by interquartile range, so that patients were stratified into lower than 25 percentile, 25–75 percentile, or higher than 75 percentile groups. All possible predictor variables were used in a logistic regression model with severe pruritus as the dependent variable. Then, the model was simplified in a stepwise fashion by removing variables which had a P-value of greater than 0.05.

The Kaplan–Meier method and the Cox proportional hazard regression model were used to test the impact of severe pruritus on the survival of patients. In the Cox proportional model, significant variables were selected using a stepwise backward procedure after forcing severe pruritus (VAS$\geqslant$7.0) in the model so that the maximum likelihood ratio was generated.

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