Calciphylaxis確実例臨床データ

対応calciphylaxis症例番号	37	43	44	46	47	48	49	50
発症時年齢	32歳4ヶ月	65歳9ヶ月	46歳6ヶ月	57歳1ヶ月	64歳4ヶ月	57歳10ヶ月	40歳	58歳
発症時透析歴	15年4ヶ月	13年3ヶ月	19年6ヶ月	8ヶ月	2年10ヶ月	13年10ヶ月	10年6ヶ月	11年
性別	男	女	女	女	女	女	男	男
透析導入原疾患	慢性腎炎	腎硬化症	慢性腎炎	薬剤性	糖尿病	慢性腎炎	慢性腎炎	慢性腎炎
ワルファリン（有・無）	無	有	無	無	有	不明	有	無
活性型ビタミンD（有・無）	有	有	無	有	無	不明	不明	有
血清総蛋白濃度	7.8	6.0	6.5	5.3	6.9	4.9	不明	5.3
血清アルブミン濃度	3.1	3.4	4.2	3.4	3.2	2.2	不明	2.5
血清カルシウム濃度	8.5	9.5	10.0	8.3	10.2	8.0	不明	9.1
補正カルシウム濃度	9.4	10.1	10.0	8.9	11.0	9.8		10.6
血清リン濃度	3.8	5.1	2.6	9.5	3.9	1.1	不明	2.8
intact PTH濃度	63.3	777.0	未	130.0	1480.0	未	不明	628.0
Al-P活性	260.0	161.0	301.0	722.0	300.0	418.0	不明	249.0
空腹時血糖	96.0	未	未	105.0	94.0	166.0	不明	163.0
血清総コレステロール	157.0	175.0	244.0	223.0	244.0	未	不明	未

Calciphylaxis確実例臨床データ

対応calciphylaxis症例番号	52	57	64	66
発症時年齢	64歳7ヶ月	47歳6ヶ月	68歳5ヶ月	75歳
発症時透析歴	26年7ヶ月	18年6ヶ月	4年2ヶ月	4年
性別	女	男	男	男
透析導入原疾患	血管炎	糖尿病	慢性腎炎	慢性腎炎
ワルファリン（有・無）	有	不明	有	無
活性型ビタミンD（有・無）	有	不明	無	有
血清総蛋白濃度	5.2	7.3	6.3	6.2
血清アルブミン濃度	2.4	3.9	3.7	2.8
血清カルシウム濃度	9.1	10.0	10.1	9.5
補正カルシウム濃度	10.7	10.1	10.4	10.7
血清リン濃度	5.4	8.8	4.7	6.1
intact PTH濃度	161.0	129.0	188.0	323.0
Al-P活性	526.0	317.0	198.0	434.0
空腹時血糖	88.0	未	未	101.0
血清総コレステロール	未	163.0	183.0	84.0

対照例臨床データ

対応calciphylaxis症例番号	1	1	2	2	3	3	6	6	7
発症時年齢（年、月）	57, 5	51, 10	52, 6	53	63, 3	65, 7	43, 9	37	55
発症時透析歴（年、月）	3, 4	0, 9	5, 3	4, 6	1, 0	1, 2	1, 9	0, 11	7
性別	男	男	男	男	女	男	男	男	男
透析導入原疾患	糖尿病	糖尿病	慢性腎炎	慢性腎炎	糖尿病	慢性腎炎	糖尿病	慢性腎炎	慢性腎炎
ワルファリン（有・無）	無	無	無	無	無	無	無	無	無
活性型ビタミンD（有・無）	無	有	有	無	無	有	無	有	無
血清総蛋白濃度	6.7	6.2	7.2	6.5	7.2	6.4	7.4	7.2	6.2
血清アルブミン濃度	4.1	4	4.1	4.5	3.9	3.9	4.2	4.6	4
血清カルシウム濃度	8.6	8.9	9.1	10.1	9.1	8.5	8.7	8.6	9.4
補正カルシウム濃度	8.6	8.9	9.1	10.1	9.2	8.6	8.7	8.6	9.4
血清リン濃度	5.7	4.3	7	8.1	5	7.4	3.2	7.3	6.8
intact PTH濃度	173	72	654	100.8	238	258	80	51.9	287
Al-P活性	109	168	238	141	269	237	149	129	149
空腹時血糖	151	152	82	97	114	100	112	85	124
血清総コレステロール	182	182	157	142	163	136	233	160	119

対照例臨床データ

対応calciphylaxis症例番号	7	10	10	13	13	15	15	18	18
発症時年齢（年、月）	54, 3	69, 4	73, 7	65, 9	66, 6	58, 10	61, 1	52, 6	50, 9
発症時透析歴（年、月）	7, 0	1ヶ月	2ヶ月	10, 3	10, 1	1, 4	1, 4	14, 9	15,1
性別	男	女	男	男	女	女	女	女	女
透析導入原疾患	慢性腎炎	PKD	糖尿病	糖尿病	慢性腎炎	腎炎	糖尿病	慢性腎炎	慢性腎炎
ワルファリン（有・無）	無	無	無	無	無	無	無	無	無
活性型ビタミンD（有・無）	有	無	無	無	有	有	有	無	有
血清総蛋白濃度	6.9	6.8	5.9	6.4	7	6.5	6.6	6.6	7.2
血清アルブミン濃度	4.2	3.6	3.4	3.5	4.1	3.8	3.5	4.2	4.5
血清カルシウム濃度	10.2	9.2	8.5	7.7	8.3	9	8.7	9.3	9.1
補正カルシウム濃度	10.2	9.6	9.1	8.2	8.3	9.2	9.2	9.3	9.1
血清リン濃度	3.8	5.2	3.9	5	6.1	5.8	5.9	6.1	4.8
intact PTH濃度	482	未	108	322	337	433	646	315	197
Al-P活性	207	205	212	382	263	133	360	335	608
空腹時血糖	102	163	190	133	128		160	98	67
血清総コレステロール	134	193	151	164	148	140	130	195	184

対照例臨床データ

対応calciphylaxis症例番号	21	21	26	26	27	27	28	28	29
発症時年齢（年、月）	69, 1	66, 11	66, 2	67, 5	52, 3	65, 2	59, 11	62, 1	74, 1
発症時透析歴（年、月）	7, 1	7, 1	4, 11	5, 1	20	19, 3	15, 9	15, 9	12, 1
性別	男	女	男	男	女	女	女	男	男
透析導入原疾患	糖尿病	慢性腎炎	腎硬化症	糖尿病	CGN	慢性腎炎	腎炎	慢性腎炎	糖尿病
ワルファリン（有・無）	無	無	無	無	有	有	無	無	無
活性型ビタミンD（有・無）	無	有	有	有	無	無	有	有	有
血清総蛋白濃度	6.2	6.6	7	6.6	6.8	7.6	6.1	6.8	6.2
血清アルブミン濃度	3.9	3.9	3.8	3.9	4.3	3.5	3.9	4.1	3.4
血清カルシウム濃度	8.4	9.1	8.7	9.1	9.7	8.8	10.1	9.2	8.4
補正カルシウム濃度	8.5	9.2	8.9	9.2	9.7	9.3	10.2	9.2	9
血清リン濃度	4.8	5.3	7.8	5.3	5.4	4.9	5.1	6.6	4.7
intact PTH濃度	191	234	295	234	36	482	106	294	189
Al-P活性	282	193	233	193	151	364	170	165	252
空腹時血糖	153	83		83	未	111		89	138
血清総コレステロール	175	177	178	177	220	155	232	154	169

対照例臨床データ

対応calciphylaxis症例番号	1	1	2	2	3	3	6	6	7
発症時年齢（年、月）	57,5	51,10	52,6	53	63,3	65,7	43,9	37	55
発症時透析歴（年、月）	3,4	0,9	5,3	4,6	1,0	1,2	1,9	0,11	7
性別	男	男	男	男	女	男	男	男	男
透析導入原疾患	糖尿病	糖尿病	慢性腎炎	慢性腎炎	糖尿病	慢性腎炎	糖尿病	慢性腎炎	慢性腎炎
ワルファリン（有・無）	無	無	無	無	無	無	無	無	無
活性型ビタミンD（有・無）	無	有	有	無	無	有	無	有	無
血清総蛋白濃度	6.7	6.2	7.2	6.5	7.2	6.4	7.4	7.2	6.2
血清アルブミン濃度	4.1	4	4.1	4.5	3.9	3.9	4.2	4.6	4
血清カルシウム濃度	8.6	8.9	9.1	10.1	9.1	8.5	8.7	8.6	9.4
補正カルシウム濃度	8.6	8.9	9.1	10.1	9.2	8.6	8.7	8.6	9.4
血清リン濃度	5.7	4.3	7	8.1	5	7.4	3.2	7.3	6.8
intact PTH濃度	173	72	654	100.8	238	258	80	51.9	287
Al-P活性	109	168	238	141	269	237	149	129	149
空腹時血糖	151	152	82	97	114	100	112	85	124
血清総コレステロール	182	182	157	142	163	136	233	160	119

対照例臨床データ

対応calciphylaxis症例番号	44	44	46	46	47	47	48	48	49
発症時年齢（年、月）	46	45, 5	57	57, 11	64, 2	64, 3	58, 2	56, 8	45, 6
発症時透析歴（年、月）	18	20, 8	0, 8	0, 7	2, 11	2, 9	14, 1	13, 10	12, 3
性別	男	男	男	男	男	女	女	女	女
透析導入原疾患	慢性腎炎	慢性腎炎	慢性腎炎	PKD	腎硬化症	糖尿病	腎炎	慢性腎炎	慢性腎炎
ワルファリン（有・無）	無	無	無	無	無	無	有	無	無
活性型ビタミンD（有・無）	有	有	無	無	有	有	無	有	無
血清総蛋白濃度	6.8	7.3	7.3	6.9	6.2	7.3	5.8	6.9	6.6
血清アルブミン濃度	3.96	3.8	4	4	3.7	3.8	3.8	4.1	3.8
血清カルシウム濃度	10.3	9.6	8.1	8.7	8.3	9.6	10.5	8.9	10.9
補正カルシウム濃度	10.34	9.8	8.1	8.7	8.6	9.8	10.7	8.9	11.1
血清リン濃度	5.8	6.9	6.7	7.3	4.2	6.9	5	5.7	5
intact PTH濃度	243	276	95	385	309	276	720	122	10
Al-P活性	331	167	783	250	238	167	295	467	146
空腹時血糖	122	97	93	138		97		79	82
血清総コレステロール	119	108	179	114	156	108	184	170	150

対照例臨床データ

対応calciphylaxis症例番号	49	50	50	52	52	57	57	64	64
発症時年齢（年、月）	39, 4	58, 9	58, 10	63, 3	64, 7	48	48, 6	69,1	67, 8
発症時透析歴（年、月）	10,8	11, 3	11, 0	26, 7	26, 1	19	18, 5	4, 2	4, 4
性別	女	男	男	男	女	女	男	男	男
透析導入原疾患	慢性腎炎	慢性腎炎	糖尿病	CGN	慢性腎炎	慢性腎炎	慢性腎炎	腎炎疑	糖尿病
ワルファリン（有・無）	無	無	無	無	無	無	無	無	無
活性型ビタミンD（有・無）	有	無	無	有	有	無	有	有	有
血清総蛋白濃度	6.6	6.6	6.5	6.9	6.7	6.4	6.7	6.5	7.4
血清アルブミン濃度	4.1	4.1	3.8	3.8	3.7	4.3	3.9	4	4.1
血清カルシウム濃度	10.3	9.4	8.5	9.8	8.8	8.7	9.9	9.8	8.8
補正カルシウム濃度	10.3	9.4	8.7	10	9.1	8.7	10	9.8	8.8
血清リン濃度	5.8	4.4	4.9	4	7.9	5.9	6	5.4	4.4
intact PTH濃度	351	36	166	490	480	79.6	416	65	228
Al-P活性	140	178	259	650	378	299	432	212	249
空腹時血糖	99	153	99	未	107	95	80	115	206
血清総コレステロール	156	235	140	191	169	209	172	166	98

対照例臨床データ

対応calciphylaxis症例番号	66	66
発症時年齢（年、月）	75, 1	76, 1
発症時透析歴（年、月）	3, 8	4, 0
性別	男	女
透析導入原疾患	腎硬化症	糖尿病
ワルファリン（有・無）	無	無
活性型ビタミンD（有・無）	無	有
血清総蛋白濃度	6.1	7.1
血清アルブミン濃度	3.7	3.7
血清カルシウム濃度	9.3	8.6
補正カルシウム濃度	9.6	8.9
血清リン濃度	7.3	5.1
intact PTH濃度	76	328
Al-P活性	142	288
空腹時血糖	134	81
血清総コレステロール	223	223

研究成果の刊行に関する一覧表
雑誌

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A case–control study of calciphylaxis in Japanese end-stage renal disease patients

Matsuhiko Hayashi[1], Ichiro Takamatsu[1], Yoshihiko Kanno[1], Tadashi Yoshida[1], Takayuki Abe[2] and Yuji Sato[2]; for the Japanese Calciphylaxis Study Group

[1]Apheresis and Dialysis Center, School of Medicine, Keio University, Tokyo, Japan and [2]Center for Clinical Research, School of Medicine, Keio University, Tokyo, Japan

Correspondence and offprint requests to: Matsuhiko Hayashi; E-mail: matuhiko@z3.keio.jp

Abstract

Background. Calciphylaxis, also called calcific uremic arteriolopathy, is a rare and often fatal complication of end-stage renal disease and is characterized by painful skin ulceration, necrosis, medial calcification and intimal proliferation of small arteries. Studies in western countries have reported incidences ranging from 1 to 4% in chronic hemodialysis patients. Since no systematic studies of calciphylaxis have ever been performed in Japan, we conducted a nationwide survey and a case–control study to identify the characteristics of calciphylaxis in the Japanese dialysis population.

Methods. Firstly, we sent a questionnaire to 3760 hemodialysis centers in Japan, asking whether calciphylaxis cases had been encountered in the past, and detailed clinical data regarding each case were then collected from the centers. In addition, two control dialysis patients matched for age and duration of hemodialysis to each calciphylaxis case were identified at the participating centers, and their data were analyzed to identify risk factors for calciphylaxis.

Results. Responses to the questionnaire were obtained from 1838 centers (48.3%), and 151 centers reported that a total of 249 cases had been encountered. Sixty-four centers agreed to participate in the case–control study, and detailed clinical data in regard to 67 cases were obtained. In 28 of the 67 cases, a definite diagnosis of calciphylaxis was made by our study group based on the clinical characteristics and skin biopsy findings. A univariate logistic regression model comparing them with 56-matched controls identified warfarin therapy [odds ratio (OR) 11.4, 95% confidence interval (CI)] 2.7–48.1, P = 0.0009], each 1 g/dL decline in serum albumin level (OR 19.8, 95% CI 4.4–89.5, P = 0.0001), each 100 mg/dL increment in plasma glucose level (OR 3.74, 95% CI 1.08–12.9, P = 0.037) and each 1 mg/dL increment in adjusted serum calcium level (OR 3.2, 95% CI 1.63–6.30, P = 0.0008) at the time of diagnosis as significantly associated with calciphylaxis, but no significant associations were found with female gender, vitamin D analog therapy, serum phosphate level, adjusted calcium–phosphate products or serum alkaline–phosphatase level. Warfarin therapy and lower serum albumin levels were still significant risk factors after a multivariate logistic regression model analysis.

Conclusion. The results of this study showed that warfarin therapy and lower serum albumin levels are significant and strong risk factors for the development of calciphylaxis in chronic hemodialysis patients in Japan.

Keywords: albumin; calciphylaxis; hemodialysis; warfarin

Introduction

Calciphylaxis, also called calcific uremic arteriolopathy, is a rare and often fatal complication of end-stage renal disease [1–3]. Calciphylaxis is clinically characterized by painful skin ulceration and necrosis. Pathological examination of biopsied skin shows medial calcification and intimal proliferation of small arteries. Selye et al. [4] were the first to use the term 'calciphylaxis', applying it to a condition they observed in rodents, and defining it as 'a condition of hypersensitivity in which, during a critical period after sensitization by a systemic calcifying factor, treatment with certain challengers causes an acute, local calcification followed by inflammation and sclerosis'. A few years after their report, a syndrome of peripheral ischemic tissue necrosis and cutaneous ulceration was reported in uremic patients [5], and because of its resemblance to the skin lesion of the rodent model described by Selye, it was termed calciphylaxis. The characteristic histological features of calciphylaxis in humans are medial calcification and intimal proliferation in small arteries, and although they are clearly different from the characteristic histological features in the rodent model, the term calciphylaxis is being still used [3]. The term calcific uremic arteriolopathy may be more appropriate [2], but calciphylaxis has often been reported in patients who were not uremic.

Previous studies in western countries have reported incidences of calciphylaxis ranging from 1 to 4% in chronic hemodialysis patients [2]. Several risk factors have been suggested, including female gender, obesity, diabetes mellitus, elevated serum phosphate levels, hypercalcemia, hyperparathyroidism, low serum albumin levels and warfarin therapy. Sporadic cases of calciphylaxis have also been reported in Japan, and although its prevalence seems to be very low, no systematic surveys have ever been conducted. We conducted the present study to identify the characteristics of Japanese calciphylaxis patients and to identify risk factors for calciphylaxis in Japanese hemodialysis patients.

Materials and methods

Study population

Nationwide survey and cases. Firstly, we conducted a nationwide survey to recruit calciphylaxis patients by mailing a questionnaire containing the following questions to all 3760 hemodialysis centers that are institutional members of the Japanese Society of Dialysis and Transplantation:

Q1. Has a patient with calciphylaxis ever been encountered at your center?
If answer is 'no', go to Q5.
Q2. What was the total number of calciphylaxis patients encountered at your center? What was the gender of the patients?
Q3. Please state the number of the calciphylaxis patients in each of the following age ranges.
Under 20, 21–30, 31–40, 41–50, 51–60, 61–70, >71.
Q4. Does your center wish to participate in our case–control study?
Q5. Do you know about calciphylaxis (please circle one of the following answers)?
Yes, very well; yes, well; yes, but only the name of the disease; no.
Responses to the questionnaire were received from 1838 (48.3%) of the centers and 64 of them agreed to participate in the case–control study. Clinical data regarding each of the calciphylaxis cases were collected by the study group.

Controls. The controls were selected from the patients undergoing hemodialysis at Keio University Hospital, Saitama Social Insurance Hospital, Yoyogi Station Clinic, Yoshizawa Clinic, Tokorozawa Jin Clinic and Inagi Municipal Hospital. Two controls matched for age (within ±2 years) and duration of hemodialysis (within ±20%) were selected for each case. The control patients were alive at the time of the survey.

Data collection

The clinical records of all cases and controls were reviewed retrospectively, and the following demographic and medical data were abstracted from them: age, gender, primary cause of the end-stage renal disease, total period of hemodialysis and whether the subject was being treated with warfarin, vitamin D or a vitamin D analog currently or at the time of diagnosis of calciphylaxis. A summary of the clinical course of each subject (sites affected, histological features, management of the skin lesions and main therapy) was recorded. Whenever histological slides of skin biopsy specimens were available, they were sent to the study group to be scanned and recorded with a Virtual Slide System (Olympus Co., Ltd, Tokyo, Japan). The slides were used to make a diagnosis by pathologists in our study group. The final diagnosis of calciphylaxis by the core members of the study group was based on the presence of painful purpura, characteristic skin lesions and typical pathological findings in the biopsy specimen, i.e. medial calcification and intimal hyperplasia of small arteries.

The following data, which were recorded at the time of the diagnosis of calciphylaxis at each hemodialysis center, were collected: serum albumin level, serum calcium level, serum phosphate level, serum intact parathyroid hormone level, serum alkaline phosphatase level, total cholesterol concentration and plasma glucose level. The data listed above were also collected for each of the control cases.

Statistical analysis

The following formula was used to calculate the serum adjusted Ca concentration (mg/dL): [measured Ca concentration (mg/dL) + 4.0] − serum albumin concentration (g/dL). Discrete variables at baseline were compared by chi-square tests, and normally distributed continuous variables were compared by Student's t-tests.

The risk factors for developing calciphylaxis were identified by performing univariate and multivariate logistic regression analyses. The covariates included in the multivariate models were chosen from the factors identified as significant by using the univariate model. Two-sided P-values <0.05 were considered statistically significant. All data were analyzed using IBM SPSS Statistics 18 software (IBM corporation).

Results

Responses to the questionnaire were obtained from 1838 (48.3%) of the 3760 centers. The responses revealed that a case of calciphylaxis had been encountered at 151 of the centers in the past, and the age and gender distributions of the cases are shown in Table 1. A total of 249 cases had been encountered, and their gender distribution did not differ significantly from that of the total dialysis population in Japan. According to the results of the Wilcoxon rank sum test, the age range of the calciphylaxis patients was significantly lower than the age range of hemodialysis patients in Japan as a whole. Sixty-four of the 151 centers at which a case of calciphylaxis had been encountered agreed to participate in our case–control study, and they sent the clinical data listed above in the 'Materials and methods' section to our study group. The 1687 centers that replied to the questionnaire but at which no cases of calciphylaxis had been encountered answered Q5 (Do you know about calciphylaxis?) as follows: yes, very well, 6.4%; yes, well, 30.3%; yes, but only the name of the disease, 37.7%; no, 28.0%.

These results indicated that only 40% of the physicians who answered the questionnaire at each of the hemodialysis centers knew any more about calciphylaxis than the name of the disease.

Clinical data regarding 67 cases were sent to the study group and analyzed, but 39 of the cases were excluded because of the uncertainty about the diagnosis. The remaining 28 cases were identified as definite cases of calciphylaxis, and their clinical records were used in the case–control study. Data regarding the control cases were then collected from the hemodialysis centers named in the 'Materials and methods' section above. As shown in Table 2, the ages and duration of hemodialysis of the cases and controls were well matched, and the gender distribution of the two groups was not significantly different. The albumin levels were significantly lower, the adjusted calcium concentrations were significantly higher and warfarin therapy was significantly more common in the calciphylaxis cases.

Table 3 shows the results of the univariate logistic analysis. They showed that warfarin therapy [odds ratio (OR)] 11.4, 95% confidence interval (CI) 2.7–48.1, P = 0.0009], each 1 g/dL decline in serum albumin level (OR 19.8, 95% CI 4.4–89.5, P = 0.0001), each 100 mg/dL increment in plasma glucose level (OR 3.74, 95% CI 1.08–12.9, P = 0.037) and each 1 mg/dL increment in adjusted serum calcium level (OR 3.2, 95% CI 1.63–6.30, P = 0.0008) at

Table 1. Age and gender distribution of the controls and cases

Gender ratio and age (years)	All dialysis patients in Japan (as of 31 December 2008) [6]	Calciphylaxis cases
Gender (F/M)	104 252/167 446	89/160
<20	213 (0.08%)	2 (0.8%)
21–30	1421 (0.52%)	4 (1.61%)
31–40	7898 (2.91%)	17 (6.83%)
41–50	20 273 (7.46%)	35 (14.06%)
51–60	52 417 (19.29%)	59 (23.69%)
61–70	81 312 (29.93%)	77 (30.92%)
>71	108 134 (39.80%)	53 (21.29%)

Table 2. Clinical characteristics of the definite calciphylaxis cases and the control patients[a]

	Controls	Cases
Gender	M: 34, F: 22	M: 12, F: 16
Age (years)	58.4 ± 11.1	58.4 ± 10.9
History of dialysis (months)	108.6 ± 85.5	107.5 ± 86.9
Warfarin therapy	4/56 (3/44)	10/22***
Vitamin D therapy	32/56 (25/42)	13/21
Albumin (g/dL)	3.9 ± 0.3	3.2 ± 0.7***
Adjusted Ca (mg/dL)	9.3 ± 0.7	10.0 ± 1.0***
Inorganic phosphate (mg/dL)	5.7 ± 1.2	5.7 ± 2.6
Intact PTH (pg/mL)	246 ± 166	310 ± 358
Alkaline phosphatase (IU/L)	254 ± 133	307 ± 138
Plasma glucose (mg/dL)	118 ± 36	146 ± 60
Total cholesterol (mg/dL)	165 ± 33	163 ± 46
Diabetic nephropathy	18/56	11/28

[a]Values are means ± SD. No record of warfarin therapy was obtained in six cases, and no record of vitamin D analog therapy was obtained in seven cases. Number in parenthesis presents the results of corresponding controls to the cases with medication record.
***$P < 0.001$ in comparison with the controls.

Table 3. Results of using the univariate logistic regression model to identify predictors of calciphylaxis among the parameters measured at the time the diagnosis of calciphylaxis was made[a]

	P-value	OR (95% CI)
Female gender	0.124	2.06 (0.82–5.28)
Warfarin therapy	0.0009	11.4 (2.7–48.1)
Vitamin D therapy	0.960	1.03 (0.39–2.73)
Serum albumin (for each 1 g/dL decline)	0.0001	19.8 (4.4–89.5)
Adjusted Ca (for each 1 mg/dL increment)	0.0008	3.20 (1.63–6.30)
Inorganic phosphate (mg/dL)	0.888	1.02 (0.78–1.33)
Intact PTH (pg/mL)	0.312	1.00 (1.00–1.00)
Alkaline phosphatase (IU/L)	0.117	1.00 (1.00–1.00)
Plasma glucose (for each 100 mg/dL increment)	0.037	3.74 (1.08–12.9)
Total cholesterol (mg/dL)	0.830	1.00 (0.98–1.01)
Diabetic nephropathy	0.517	1.37 (0.53–3.51)

[a]Only 22 cases and their corresponding matched controls were used in the analysis in regard to warfarin therapy. Only 21 cases and their corresponding matched controls were used in the analysis in regard to vitamin D analog therapy.

Table 4. Results of using the multivariate logistic regression model to identify predictors of calciphylaxis at the time the diagnosis of calciphylaxis was made

	P-value	OR (95% CI)
Warfarin therapy	0.013	10.1 (1.63–62.7)
Serum albumin (for each 1 g/dL decline)	0.003	12.7 (2.35–68.6)
Plasma glucose (for each 100 mg/dL increment)	0.309	0.99 (0.97–1.01)

the time of diagnosis were significantly associated with calciphylaxis. On the other hand, there were no significant associations with the previously reported risk factors: female gender, vitamin D analog therapy, serum phosphate level, adjusted calcium–phosphate products or serum alkaline–phosphatase level.

Table 4 shows the adjusted relative risk of calciphylaxis associated with possible risk factors at the time calciphylaxis was diagnosed at each center. Warfarin therapy was still significantly associated, and there was a 10.1-fold higher risk of calciphylaxis. Each 1.0 g/dL decline in the serum albumin level at the time of diagnosis increased the risk of calciphylaxis by 12.7-fold, but the serum glucose level was not a significant risk factor according to the multivariate analysis. Since the calculation of adjusted calcium concentration includes the serum albumin concentration, it was not simultaneously included in the multivariate analysis with the serum albumin concentration. When the adjusted calcium concentration instead of the albumin concentration was used in the multivariate logistic analysis, the adjusted calcium concentration was also found not to be a significant risk factor either.

Discussion

The results of this case–control study identified risk factors for calciphylaxis in Japanese hemodialysis patients. In the univariate logistic analysis, warfarin therapy, lower serum albumin levels, higher adjusted calcium concentrations and higher glucose levels were identified as significant risk factors for developing calciphylaxis. In the multivariate logistic analysis, warfarin therapy and lower serum albumin levels were identified as risk factors, but glucose levels and adjusted calcium concentrations were not.

As stated in the introduction, calciphylaxis was first reported by Selye and defined as a systemic hypersensitivity reaction analogous to the allergic reaction (anaphylaxis) [4]. A case of calcifying panniculitis with renal failure was reported as calciphylaxis in 1968 and that case was accompanied by the presence of large painful lumps in the fat of the thighs and knees, over which the skin rapidly became necrotic. Since the patient also had hyperparathyroidism, the authors speculated that the skin lesions were caused by sensitization to parathyroid hormone (PTH) [5]. Other early case reports of calciphylaxis also speculated that hypersensitivity to PTH played a major role in the development of the skin lesions [7–9]. After these reports, it became evident from the pathological findings that

calciphylaxis in humans is not the same as in the rodent model [1–3]. Furthermore, cases of calciphylaxis without hyperparathyroidism have been reported in both patients with and without renal failure. Since calciphylaxis in humans is now thought to be different from the calciphylaxis in Selye's rodent model, 'calcific uremic arteriolopathy' has been proposed as a more suitable name for the disease. However, since cases of 'calciphylaxis' without uremia have been reported, we chose to use the term calciphylaxis in this paper.

The prevalence of calciphylaxis in western countries has been reported to vary from 1 to 4% [2], and its prevalence in Japan seems to be much lower. In the present study, we conducted a nationwide questionnaire survey, and about half of the Japanese hemodialysis centers responded to the questionnaire. Assuming that the diagnoses made at the centers were correct, 249 cases of calciphylaxis had been encountered at the centers. We also found reports of 72 sporadic cases in the Japanese literature in the past decade. If we assume that all of these calciphylaxis cases in our survey and the literature were seen within 10 years, the prevalence rate of calciphylaxis in Japan should be less than three cases per 10 000 hemodialysis patients/year. This rate is much lower than the previously reported prevalence rates in western countries. However, in our study, only about half of the hemodialysis centers (1838 centers) responded and a total of 249 potential cases had been encountered at 151 centers. We suspect that the centers that responded were more interested in calciphylaxis. In addition, since ~60% of nephrologists in Japan do not know the disease itself, it is highly likely that calciphylaxis is being overlooked. Based on these results, we speculate that this prevalence rate from our assumptions which are discussed on the above section may underestimate the prevalence rate of calciphylaxis in Japan.

In the present study, we were able to collect 67 cases by conducting a nationwide survey, and the clinical records of 28 definite cases were used for our case–control study. Several risk factors for calciphylaxis in end-stage renal disease patients have been identified in case–control studies in Europe and North America. In 1999, data from 9 calciphylaxis patients were compared with data obtained from a cross-sectional survey of 347 hemodialysis patients [10]. The results of that study showed body mass index (BMI), serum albumin concentration, serum calcium concentration and inorganic phosphate concentration to be significant risk factors for calciphylaxis, and it is interesting that all nine patients were Caucasian. A study by Mazhar et al. [11] revealed female gender and erythropoietin therapy to be significant risk factors in addition to the serum albumin level and calcium–phosphate metabolism disturbances. Fine et al. [12] conducted a prospective observational study of 36 calciphylaxis patients at a single hemodialysis unit in Canada and reported finding that peritoneal dialysis, calcium carbonate administration, vitamin D analog therapy and diabetes mellitus were all significant risk factors in addition to female gender and phosphate and calcium metabolism disturbances. The prevalence rate of calciphylaxis in their report was 4.5/100 patient-years and much higher than in other reports. However, the report from the same facility in 2008 revealed that the high incidence was attrib-

utable to iatrogenic factors [13]. The serum ionized calcium concentration had been used as a marker of calcium metabolism at that facility, and the method of measurement was inappropriate. Because of the inappropriate method and resulting incorrect calcium concentrations, excessive doses of vitamin D analog and calcium salts were administered and presumably induced severe hypercalcemia in the patients. After correcting the method used to monitor calcium metabolism, the prevalence rate decreased dramatically. A case–control study of 47 calciphylaxis patients conducted at the Mayo Clinic was reported in 2007, and it identified BMI [14], steroid use, liver disease, calcium–phosphate product and serum aluminum concentration as significant risk factors for calciphylaxis in end-stage renal disease. In the present study, lower serum albumin levels and higher adjusted calcium concentrations were identified as risk factors by the univariate logistic analysis, the same as in previous studies, whereas adjusted calcium concentrations were found not to be a significant risk factor by the multivariate logistic analysis. Since there were no significant differences in PTH levels and vitamin D therapy between the controls and the cases, the hypercalcemia may have been induced by other factors. In the present study, we asked if the patient had been treated with vitamin D or vitamin D analog but not the dose, and we have no data on medication with calcium-containing salts. It is possible that the therapeutic set point for calcium was higher in the hemodialysis center where the calciphylaxis patients received their medication and that the doses of vitamin D and calcium-containing salt were higher in the calciphylaxis cases.

Warfarin therapy was also identified as a highly significant risk factor for calciphylaxis in our study. It has been suggested that warfarin may play an important role in the development of calciphylaxis by causing changes in the coagulation pathway and vitamin K-dependent bone metabolism, although none of the previous case–control studies mentioned above identified warfarin therapy as a significant risk factor. It was recently reported that warfarin therapy might facilitate vascular calcification in dialysis patients [15] and that warfarin therapy increases the incidence of stroke [16]. However, they were observational studies, and a prospective controlled study will be necessary to determine the usefulness of warfarin therapy in dialysis patients.

Data regarding BMI, dialysis quality (kt/V) and residual renal function, which are considered possible risk factors for the development of calciphylaxis, were not collected in our study. Since our study was based on nationwide surveillance, we chose not to send a complicated data sheet and decided instead to collect the minimum information necessary regarding the calciphylaxis cases to facilitate participation by the hemodialysis centers in our study. In order to collect more detailed information on calciphylaxis, we have inaugurated a Japanese calciphylaxis registry and are going to continue to register for at least 5 years. We hope the registry will make it possible to analyze additional risk factors that were not included in the present study.

In conclusion, the prevalence of calciphylaxis in Japan seems to be much lower than in western countries, suggesting that the incidence of calciphylaxis may vary with racial and geographic factors, although the exact prevalence of

calciphylaxis in chronic hemodialysis patients in Japan cannot be estimated due to the study design. Our study identified warfarin therapy and lower serum albumin concentrations as significant and strong risk factors for the development of calciphylaxis.

The results presented in this paper have not been published previously in whole or part, except in abstract format, while parts of this manuscript were presented in abstract form at the 48th congress of ERA-EDTA, Prague, 2011.

The Core Members of the Japanese Calciphylaxis Study Group are: Takashi Akiba (Tokyo Women's Medical University), Masashi Fukagawa (Tokai University School of Medicine), Akinori Hashiguchi (Keio University), Tatsuo Hosoya (The Jikei University School of Medicine), Akiko Itai (IMMD, Inc.), Tetsuya Kawamura (The Jikei University School of Medicine), Hidetomo Nakamoto (Saitama Medical University), Yuji Sato (Keio University), Takashi Shigematsu (Wakayama Medical University), Masaru Tanaka (Tokyo Women's Medical University Medical Center East), Akihiro Umezawa (National Center for Child Health and Development).

The Members of Case–Control Study Group in the Japanese Calciphylaxis Study Group are Fusae Deguchi (Yoyogi Station Clinic), Kyoko Fujita (Tsurugi Hospital), Tomohiro Furukawa (Kawasaki Ekimae Clinic), Kazuhiro Harada (Kasaoka Daiichi Hospital), Soichiro Haraguchi (Sasebo Kyosai Hospital), Nobuyuki Hayahara (Sakakibara Clinic), Makoto Higuchi, (Shinshu University Hospital) Hideki Hirakata (Japanese Red Cross, Fukuoka Hospital), Hirokazu Honda (Showa University School of Medicine), Masakazu Imamura (Kuma Clinic), Tsutomu Inoue (Saitama Medical University), Nobuo Itagaki (PL Hospital), Nobuo Kato (Fukuyama Clinic), Yoshio Kimura (Kimura Internal Medicine Clinic), Takeshi Kihara (Showakai Hospital), Tomoyuki Kita (Sakai Rumi Clinic), Shinya Kobayashi (Miyanosawa Urological Clinic), Yutaka Koda (Koda Medical and Dialysis Clinic), Akira Konohana (Yokohamashi Nanbu Hospital), Korenaga Hideki (Kenwakai Otemachi Hospital), Masahiro Iyori (Inagi Municipal Hospital), Junichi Kuramoto (Jinomori Clinic), Yumi Matsumura (Graduate School of Medicine Kyoto University), Chiaki Miishima (Miishima Clinic), Yoichi Mishige (Imamura Bun-in Hospital), Yuichi Nakazato (Saitama Social Insurance Hospital), Masahiro Naruse (Tamana First Clinic), Akio Ohta (St Marianna University School of Medicine), Yoshihiko Otsubo (Tenjinkai Shin-Koga Clinic), Toshihiro Sakurai (Horie Hospital), Isoji Sasagawa (Yamagata Tokushukai Hospital), Tamaki Sasaki (Kawasaki Medical School), Tetsuo Shoji (Osaka City University Graduate School of Medicine), Junichi Suga (Maple Nephro-Clinic), Toshiyuki Takahashi (Miyaji Clinic), Kenmei Takaichi (Toranomon Hospital Kidney Center), Masahito Tamura (University of Occupational and Environmental Health), Shigeru Tanaka (Hamanomachi Hospital), Tetsuya Taniguchi (Social Insurance Kamata General Hospital), Kazuhiko Tsuruya (Graduate School of Medical Sciences, Kyusyu University), Terukazu Yokota (Hakuryuko Hospital), Naoko Yokota-Ikeda (Miyazaki Prefectural Miyazaki Hospital), Noriaki Yorioka (Hiroshima University), Kunihiko Yoshiya (Hara Genito-urinary Hospital), Mamoru Yoshizawa (Yoshizawa Clinic).

(See related article by Brandenburg *et al.* Calciphylaxis in CKD and beyond. *Nephrol Dial Transplant* 2012;27: 1314–1318.)

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