2009; in females, rates were 8.1% in 1999, 7.1% in 2004, and 6.9% in 2009.[14]

The proportion of patients with a history of systemic steroid administration did not change during the study period. With respect to individual underlying diseases treated by steroid administration, proportions of patients treated for SLE and renal transplantation decreased in both genders. In Japan, SLE patients receiving public financial aid for treatment have been increasing: there were 47 295 patients in 1999, 52 195 in 2004, and 57 253 in 2009.[15] Also, an increase in number of patients with renal transplantation was shown: 158 patients in 1999, 173 in 2004, and 182 in 2009.[16] However, current treatments for SLE and prevention of rejection after renal transplantation have improved and provided steroid-sparing options,[17–19] which are expected to contribute to the significant reduction in the number of steroid-induced ONFH cases. In contrast, the number of patients with pulmonary diseases other than asthma significantly increased. The majority of cases were chronic obstructive pulmonary disorder (COPD) and interstitial pneumonia (IP). These findings are consistent with the increasing trends in COPD and IP documented in Japan.[15,20] Most patients admitted with exacerbation of COPD are likely to be treated with high-dose steroids, although a study has shown that low doses of steroids are not associated with worse outcomes.[21] Because the treatment for IP has been changing towards a steroid-sparing regimen,[22] a decline in ONFH may be observed in the future.

The shift in age distribution in this study population might also influence trends in underlying diseases which needed steroid administration, especially in females. The average ages of females with underlying diseases treated with steroids that showed a significant increase were relatively old: 56 years in other types of collagen disease; 58 years in pulmonary disease; and 53 years in skin disease. In contrast, the average age of females with underlying diseases that showed a significant decline was relatively young: 37 years in SLE and 37 years in renal transplantation. A similar relationship was observed in males.

There are several limitations to this study. First, our findings might be biased because the monitoring system is based solely on data from university hospitals and highly specialized hospitals. However, when we compared our findings with the results of a 2004 nationwide epidemiologic survey in Japan,[5] we did not find any substantial differences between the two studies. The nationwide survey showed a similar distribution of age at diagnosis to this study and a gender ratio of 1.5, which was slightly lower than in the present study. In addition, assessment of potential causative factors in that study found 34% of patients with systemic steroid administration, 47% with habitual alcohol intake, 4% with both factors, and 15% with neither factor among males; in females, 76% of patients had systemic steroid administration, 6% had habitual alcohol intake, 1% had both factors, and 16% had neither. Because ONFH is designated as an intractable disease in Japan, patients are likely to visit or be referred to highly specialized hospitals, which might mean that similar characteristics are reported in both the monitoring system and the nationwide survey. Second, although we collected data on the stage and type of ONFH, we could not assess trends in these characteristics due to the revision of their definitions in 2001. Third, a significant increase in the proportion of patients with skin disease as an underlying disease treated by steroid administration in females was demonstrated, but the details of the disease entity were unknown.

Conclusions

This study confirms that the monitoring system is a useful method for documenting temporal trends in the characteristics of ONFH. Main findings include an increase in the number of patients, a shift to an older age at diagnosis, a decline in the proportion of patients with SLE and renal transplantation, and an increase in the proportion of patients with pulmonary disease (except asthma) as underlying diseases treated by systemic steroid administration. Because our study was a descriptive epidemiologic study, further analytical studies are needed to elucidate the factors associated with these trends.

ONLINE ONLY MATERIALS

eTable 1. Trends in the distribution of demographic data and assessment of potential causative factors according to gender in the 11 hospitals between 1997 and 2011.

eTable 2. Trends in the distribution of underlying diseases for which patients received steroid therapy in the 11 hospitals between 1997 and 2011 in males.

eTable 3. Trends in the distribution of underlying diseases for which patients received steroid therapy in the 11 hospitals between 1997 and 2011 in females.

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Conflicts of interest: None declared.

APPENDIX

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Original Article

Descriptive Epidemiology of Prion Disease in Japan: 1999–2012

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ABSTRACT

Background: Epidemiologic features of prion diseases in Japan, in particular morbidity and mortality, have not been clarified.

Methods: Since 1999, the Research Committee has been conducting surveillance of prion diseases, and the surveillance data were used to assess incident cases of prion diseases. For the observation of fatal cases, vital statistics were used.

Results: Both incidence and mortality rates of prion diseases increased during the 2000s in Japan. However, this increase was observed only in relatively old age groups.

Conclusions: The increased number of patients among old age groups might be due to increased recognition of the diseases. If so, the number of cases should plateau in the near future.

Key words: prion diseases; Creutzfeldt-Jakob syndrome; incidence; mortality; secular trends

INTRODUCTION

In 1996, when the paper indicating the relationship between bovine spongiform encephalopathy (BSE) and the human variant Creutzfeldt-Jakob disease (CJD) was published,[1] full-scale epidemiologic research for prion diseases, such as CJD, Gerstmann-Sträusslar-Scheinker disease (GSS), and fatal familial insomnia (FFI), started in Japan.[2] Since 1999, a nationwide surveillance system for prion diseases has been implemented, and patients with prion diseases have been registered.[3] The epidemiologic features of prion diseases in Japan are summarized as follows[2,3]: (1) the annual incidence rate is about 1 case per 1 million population, which is similar to the worldwide standard; (2) the incidence rate is highest among those aged in their 60s and 70s; and (3) CJD associated with cadaveric dura mater transplantation is more prevalent in Japan than in other countries.

Over the past decade, the number of patients with prion diseases has increased in Japan. While the reason for this increase is unclear, epidemiologists must consider that increased recognition of the disease may lead to a subsequent increase in the number of patients. In other words, whether prevalence has truly increased or whether some other factors have made the number merely seem increased should be clarified. Detailed observation of the epidemiologic features of prion diseases might shed light on this apparent increase in prevalence.

We conducted this descriptive epidemiologic research with two purposes: to clarify the recent epidemiologic features of prion diseases in Japan and to obtain some hints about the cause of increasing incidence of the diseases in Japan.

METHODS

We used two data sets in this study. One was the registry data of prion diseases in Japan obtained through the surveillance system conducted by the Surveillance Committee, which is financially supported by the Ministry of Health, Labour and Welfare of the Japanese government.[3] The system was first implemented in April 1999. There are several routes to obtain information about the existence of potential patients with prion diseases: a mandatory reporting system from

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physicians, the public-aid-for-treatment system, and clinical examinations.

First, since 1999, prion diseases have been designated as reportable diseases by the Prevention of Infectious Diseases and Medical Care for Infectious Patients Act (Act No. 114 of 1998). When a physician diagnoses a patient as having a prion disease, he or she must report the fact to a local public health center.

Second, prion diseases are designated as diseases qualifying for public aid. Patients with one of the designated diseases receive treatment from a hospital with public aid, and he or she is not required to pay any fee. The aid is based on a claim made by the patient or his or her family to a public health center, so information on the patient is obtained when making the claim.

Lastly, the Surveillance Committee conducts human prion protaineous gene analyses at Tohoku University and cerebrospinal fluid analyses (14-3-3 protein and total tau protein) at Nagasaki University. Physicians who suspect that a patient has a prion disease or who want to certify the diagnosis of a prion disease may send blood or cerebrospinal fluid to these universities with a patient's informed consent. The cost is covered by research funds from the national government, and the patient and physician are not responsible for paying any fees.

When the Surveillance Committee obtains information about a potential patient through one of these three routes, one of the committee members, who is a neurologist or a psychiatrist familiar with prion diseases, obtains detailed data about the patient by meeting the patient if possible or using hospital records. Based on the obtained data, the Committee members discuss whether or not the patient has a prion disease, and patients recognized to have a prion disease are registered anonymously.

In the present study, we used only data of registered patients with disease onset from 1999 through 2012. We observed epidemiologic features of prion diseases in Japan calculated standardized morbidity rates by prefecture and secular trends of age-specific incidence rates. As shown in Figure 4, the 2012 data are still incomplete, so patients diagnosed in this year were excluded in observation of time and place.

We also used data on vital statistics in Japan from 1999 through 2012 (http://www.e-stat.go.jp/SG1/estat/GL08020101.do?_toGL08020101_&tstatCode=000001028897&requestSender=dsearch). Since 1999, the statistics presented the numbers of fatal cases with prion diseases (ICD-10th; A81.0 [Creutzfeldt-Jakob disease] + A81.8 [Other atypical virus infections of central nervous system]) by prefecture as an infectious disease as well as the fatal numbers by age and sex. Therefore, we calculated standardized mortality ratios by prefecture in addition to age-specific mortality rates in Japan. For calculating 95% confidence intervals (CIs) of standardized morbidity and mortality ratios, we used the table presented by Schoenberg.[4]

In addition to these analyses, standardized morbidity and mortality ratios—the former of which were based on the surveillance data and the latter of which were based on the vital statistics—were compared with the number of neurologists authorized by the Societas Neurologica Japonoca (http://www.kktcs.co.jp/jsn-senmon/secure/senmon.aspx) per population by prefecture.

The age-specific population for incidence and mortality rates by calendar year was that used in vital statistics, while that for calculation of standardized morbidity and mortality ratios by prefecture was the census population in 2005.

RESULTS

There were 2026 incident cases of prion diseases (854 males and 1172 females) from 1999 through 2012 and 2334 fatal cases (1035 males and 1299 females) from 1999 through 2012 according to vital statistics in Japan. The average annual incidence rate was 1.09 cases per 1 million population (0.95 for males and 1.22 for females, calculated from 1999 through 2011) and average annual mortality rates were 1.32 per 1 million population (1.20 for males and 1.44 for females).

The results below are described according to the three major characteristic headings of descriptive epidemiology: persons, place, and time.[5]

Persons

Table 1 shows the characteristics of 2026 incident patients with prion diseases in Japan during the 14 years from 1999 through 2012. The number of patients by age class was largest in the group aged 70–79 years, followed by those aged 60–69 years. Of the 2026 patients with prion diseases, 77% was sporadic CJD patients.

Place

The standardized morbidity and mortality ratios for each prefecture are shown in Table 2. The standardized morbidity ratios ranged from 0.28 (Shiga Prefecture) to 2.15 (Saga Prefecture), while the ratios for mortality ranged from 0.24 (Tottori Prefecture) to 1.90 (Yamanashi Prefecture). As shown in Figures 1 and 2, no geographical clustering of prevalent prefectures was observed. The correlation coefficient between the morbidity and mortality ratios was 0.53 (95% CI 0.29 to 0.71; Figure 3). We assessed the relationship between the morbidity and mortality of prion diseases and the number of neurologists per population because there is a possibility that shortage of neurological medical services introduces misdiagnosis of prion diseases. However, the correlation coefficient between the standardized morbidity ratio and the number of neurologists was −0.12 (95% CI −0.39 to 0.17), while that for the standardized mortality ratio was −0.09 (95% CI −0.37 to 0.20). The coefficients for the relationship between standardized morbidity and mortality ratios and the number of neurologists per population aged ≥65 years were

Table 1. Demographic characteristics of patients with prion diseases in Japan, 1999–2012

	Whole patients	Sporadic CJD[a]	Variant CJD	CJD with dura mater transplantaion	Familiar prion diseases			Unclassified CJD[c]
					Familiar CJD[b]	GGS	FFI	
Total sample	2026 (100)	1550 (77)	1	83 (4)	298 (15)	84 (4)	4	6
Sex								
Male	854 (42)	636 (41)	1	35 (42)	136 (46)	41 (49)	3	2
Female	1172 (58)	914 (59)		48 (58)	162 (54)	43 (51)	1	4
Total	2026 (100)	1550 (100)	1	83 (100)	298 (100)	84 (100)	4	6
Age at onset (years)								
10–19	3			2 (2)	1 (0)			
20–29	8 (0)			5 (6)	1 (0)	2 (2)		
30–39	29 (1)	12 (1)		7 (8)	1 (0)	9 (11)		
40–49	69 (3)	40 (3)	1	5 (6)	10 (3)	11 (13)	1	1
50–59	304 (15)	212 (14)		20 (24)	30 (10)	40 (48)	2	
60–69	613 (30)	498 (32)		25 (30)	70 (23)	18 (21)	1	1
70–79	738 (36)	590 (38)		17 (20)	123 (41)	4 (5)		4
80–89	245 (12)	186 (12)		2 (2)	57 (19)			
90–99	14	9			5			
Unknown	3	3						
Total	2026 (100)	1550 (100)	1	83 (100)	298 (100)	84 (100)	4	6
Mean	67.9	68.7		57.9	70.7	53.8	54.5	
SD	11.1	9.8		16.2	11.4	10.7	6.4	
Oldest age	94	94		85	93	75	61	
Youngest age	15	30		15	15	22	46	

CJD, Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; GSS, Gerstmann-Sträusler-Scheinker disease; SD, standard deviation.
Percentages are shown in parentheses. Percentages may not add up to exactly 100% because of rounding.
[a]Including CJD without prion protein gene analyses.
[b]Including patients without prion protein gene variation but with family histories of CJD.
[c]Those whose diagnosis has been confirmed as CJD, but whose type of CJD has not been surveyed.

−0.17 (95% CI: −0.44 to 0.12) and −0.00 (95% CI: −0.29 to 0.29), respectively.

Time

Figure 4 shows the annual incidence and mortality cases by year. Because the cases of prion diseases in recent years have not all been discussed by the Committee yet, the numbers of new cases in recent years (specifically 2012) were small. Figures 5 and 6 show the age-specific incidence and mortality rates of prion diseases by year. Although the rates increased among older subjects, those among younger subjects did not increase.

DISCUSSION

In the present study, we described the epidemiologic features of prion diseases in Japan using two data sources—the prion disease surveillance system and vital statistics—from three descriptive epidemiologic viewpoints: persons, place, and time.

The prion disease surveillance system in Japan intends to collect information when a person receives a prion disease. The vital statistics comprise the data when the patient dies. According to the natural history of the disease, which is that patients with prion diseases die within a few years of disease onset, the numbers of incident patients and deceased ones should be similar, although they were not identical because of the time lag between onset and death. We recognized 2026 incident cases and 2334 fatal cases in this study for the observed 14 years. There are several possible explanations for the difference between the two figures (308 cases). First, as mentioned before, a time lag exists between onset and death. Second, the surveillance data were incomplete for recent calendar years (Figure 4). In addition, discrepancies in diagnoses may exist between the two databases. Cases in the surveillance system should be true prion diseases because their diagnoses were based on the discussion of the Surveillance Committee, which consists of neurologists, psychiatrists, and neuropathologists and uses clinical findings and medical records gathered by the committee members, gene analyses, and pathological findings including results of western blot analyses. On the other hand, the vital statistic data consists of death certificate data for which the recorded cause underlying death was a prion disease. Because all physicians are able to create death certificates, some of these might be cases described by physicians who were not experts in prion diseases. These points might be the reasons for the gap between the numbers of incident and fatal cases. Nonetheless, we consider the validity of the two datasets used in this study to be quite high and believe that our findings accurately reflect the true epidemiologic features of prion diseases in Japan.

Table 2. Morbidity, mortality, and other variables concerning prion diseases in Japan, by prefecture

	Population[a] (thousands)	Number of newly diagnosed patients	Number of newly diagnosed patients (1999–2011)[b]	Crude incidence rate (per million population/year)	Standardized morbidity ratio (95% CI)	Number of fatal patients (1999–2012)	Crude mortality rate (per million population/year)	Standardized mortality ratio (95% CI)
Total	127 768	2026	1814	1.09		2334	1.30	
Hokkaido	5628	138	124	1.69	1.47 (1.23–1.76)	106	1.35	0.97 (0.80–1.18)
Aomori	1437	19	16	0.86	0.72 (0.41–1.16)	20	0.99	0.69 (0.42–1.07)
Iwate	1385	19	19	1.06	0.85 (0.51–1.35)	22	1.13	0.75 (0.47–1.14)
Miyagi	2360	44	43	1.40	1.31 (0.95–1.77)	43	1.30	1.01 (0.73–1.37)
Akita	1146	28	28	1.88	1.40 (0.93–2.03)	32	2.00	1.22 (0.84–1.72)
Yamagata	1216	20	20	1.26	1.00 (0.61–1.54)	18	1.06	0.69 (0.41–1.09)
Fukushima	2091	38	35	1.29	1.10 (0.77–1.53)	36	1.23	0.87 (0.61–1.20)
Ibaraki	2975	18	15	0.39	0.36 (0.20–0.59)	35	0.84	0.66 (0.46–0.91)
Tochigi	2017	16	10	0.38	0.36 (0.17–0.66)	40	1.42	1.11 (0.79–1.51)
Gunma	2024	41	39	1.48	1.33 (0.95–1.82)	36	1.27	0.95 (0.67–1.32)
Saitama	7054	67	60	0.65	0.66 (0.50–0.85)	119	1.20	1.04 (0.86–1.24)
Chiba	6056	97	85	1.08	1.05 (0.84–1.30)	100	1.18	0.97 (0.79–1.19)
Tokyo	12 577	166	149	0.91	0.90 (0.76–1.06)	228	1.29	1.08 (0.94–1.23)
Kanagawa	8792	154	134	1.17	1.19 (1.00–1.42)	153	1.24	1.07 (0.91–1.26)
Niigata	2431	51	49	1.55	1.28 (0.94–1.68)	53	1.56	1.06 (0.79–1.39)
Toyama	1112	12	10	0.69	0.57 (0.27–1.05)	18	1.16	0.79 (0.47–1.25)
Ishikawa	1174	38	35	2.29	2.05 (1.43–2.84)	22	1.34	1.00 (0.63–1.51)
Fukui	822	7	6	0.56	0.48 (0.18–1.05)	7	0.61	0.43 (0.17–0.89)
Yamanashi	885	26	23	2.00	1.77 (1.12–2.65)	32	2.58	1.90 (1.30–2.68)
Nagano	2196	21	19	0.67	0.55 (0.33–0.86)	47	1.53	1.04 (0.77–1.39)
Gifu	2107	38	32	1.17	1.04 (0.71–1.46)	38	1.29	0.95 (0.68–1.31)
Shizuoka	3792	71	67	1.36	1.22 (0.95–1.55)	86	1.62	1.21 (0.97–1.51)
Aichi	7255	104	94	1.00	1.01 (0.82–1.23)	121	1.19	1.02 (0.85–1.22)
Mie	1867	35	34	1.40	1.23 (0.85–1.72)	41	1.57	1.15 (0.82–1.56)
Shiga	1380	6	5	0.28	0.28 (0.09–0.65)	24	1.24	1.04 (0.67–1.55)
Kyoto	2648	16	14	0.41	0.37 (0.20–0.63)	40	1.08	0.83 (0.59–1.13)
Osaka	8817	109	101	0.88	0.84 (0.68–1.02)	145	1.17	0.94 (0.80–1.11)
Hyogo	5591	61	54	0.74	0.68 (0.51–0.89)	112	1.43	1.10 (0.91–1.33)
Nara	1421	8	7	0.38	0.34 (0.14–0.70)	22	1.11	0.84 (0.53–1.27)
Wakayama	1036	6	6	0.45	0.36 (0.13–0.78)	14	0.97	0.65 (0.35–1.09)
Tottori	607	6	4	0.51	0.42 (0.11–1.07)	3	0.35	0.24 (0.05–0.70)
Shimane	742	23	21	2.18	1.66 (1.02–2.53)	28	2.69	1.68 (1.12–2.43)
Okayama	1957	32	30	1.18	1.01 (0.68–1.45)	28	1.02	0.73 (0.49–1.06)
Hiroshima	2877	46	41	1.10	0.98 (0.70–1.33)	51	1.27	0.95 (0.71–1.24)
Yamaguchi	1493	35	32	1.65	1.29 (0.88–1.82)	42	2.01	1.30 (0.94–1.76)
Tokushima	810	16	13	1.23	1.00 (0.53–1.70)	9	0.79	0.53 (0.26–1.01)
Kagawa	1012	16	14	1.06	0.89 (0.48–1.49)	20	1.41	0.98 (0.60–1.51)
Ehime	1468	26	25	1.31	1.07 (0.69–1.58)	28	1.36	0.92 (0.61–1.33)
Kochi	796	28	28	2.70	2.10 (1.39–3.04)	23	2.06	1.32 (0.83–1.97)
Fukuoka	5050	120	111	1.69	1.57 (1.30–1.90)	93	1.32	1.03 (0.83–1.26)
Saga	866	29	28	2.49	2.15 (1.43–3.12)	19	1.57	1.12 (0.68–1.75)
Nagasaki	1479	27	25	1.30	1.08 (0.70–1.60)	34	1.64	1.13 (0.78–1.59)
Kumamoto	1842	20	17	0.71	0.60 (0.35–0.95)	42	1.63	1.13 (0.81–1.52)
Oita	1210	27	26	1.65	1.34 (0.87–1.96)	26	1.54	1.02 (0.67–1.51)
Miyazaki	1153	14	13	0.87	0.72 (0.38–1.23)	22	1.36	0.94 (0.59–1.42)
Kagoshima	1753	32	29	1.27	1.04 (0.70–1.50)	39	1.59	1.07 (0.76–1.46)
Okinawa	1362	25	24	1.36	1.55 (1.00–2.32)	16	0.84	0.81 (0.47–1.32)
Unknown		30				1		

CI, confidence interval.
[a]Data from 2005 Census.
[b]Patients whose address was unknown were excluded.

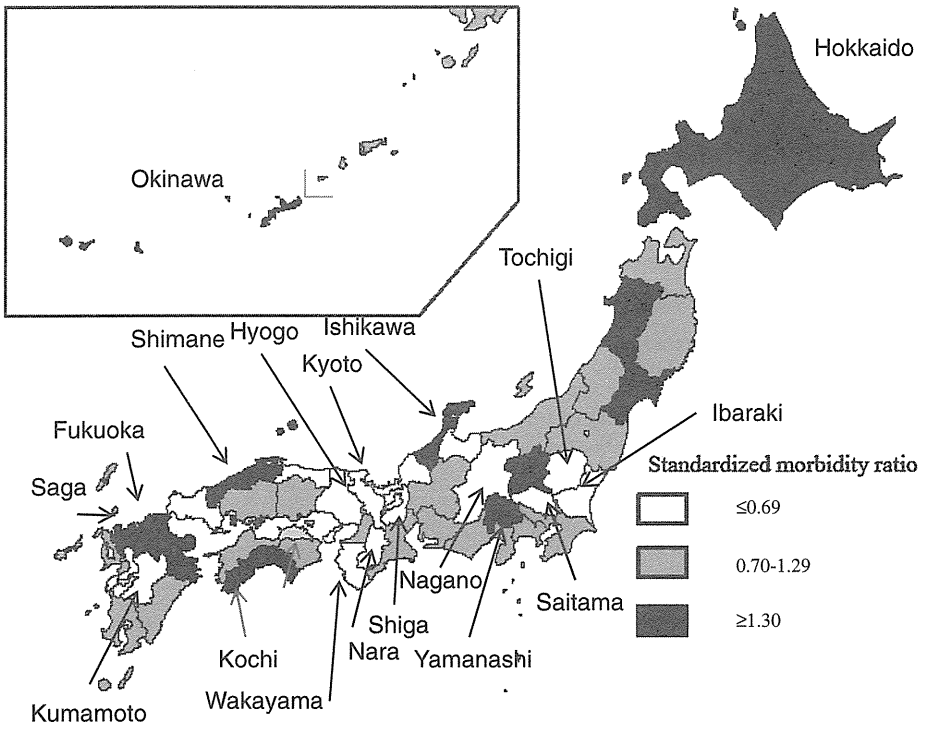

Figure 1. Standardized morbidity ratios of prion diseases in Japan by prefecture, 1999–2011

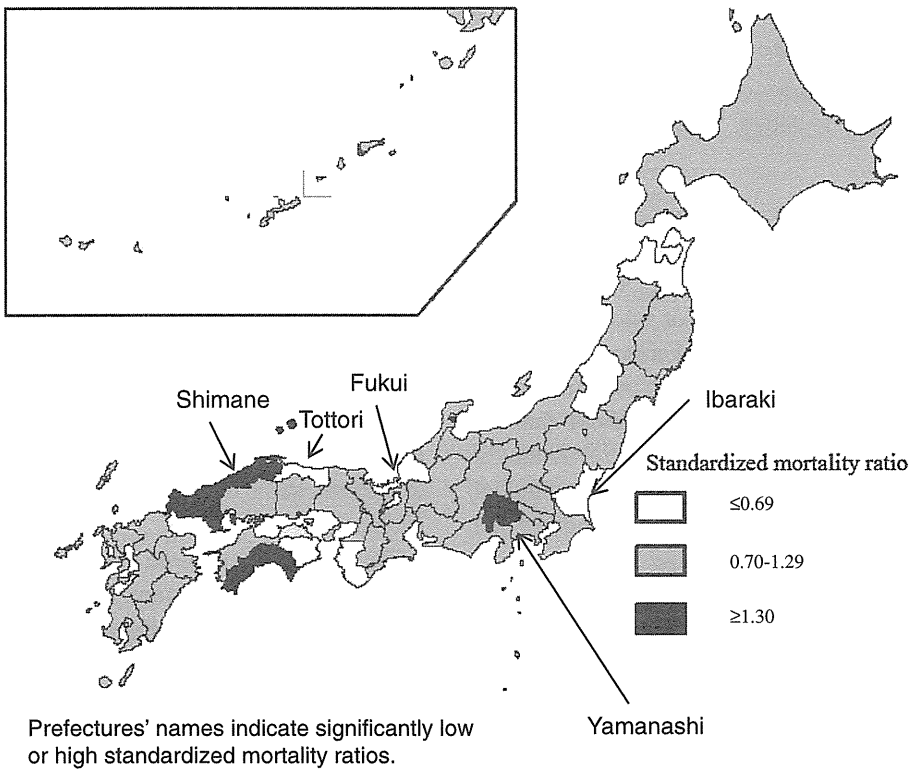

Figure 2. Standardized mortality ratios of prion diseases in Japan by prefecture, 1999–2012

Different epidemiologic aspects from those of prion diseases in European countries and North America[6,7] were observed in Japan in the present study. The proportion of patients with acquired CJD among all prion disease patients was high. Many of them developed CJD following cadaveric dura mater transplantation.[8–12] Currently, we have data of 147 such cases, and detailed epidemiologic features will be presented in another article. On the other hand, we observed

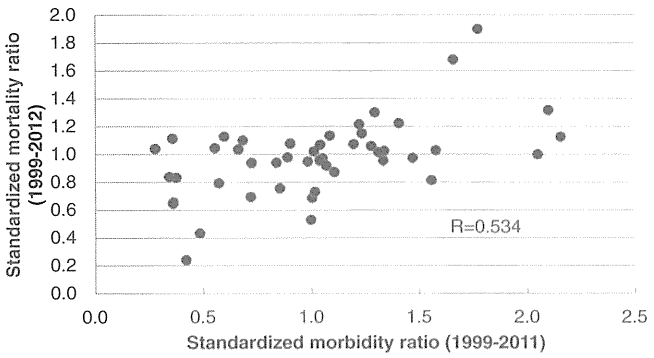

Figure 3. Relationship between standardized morbidity ratios and standardized mortality ratios of prion diseases by prefecture

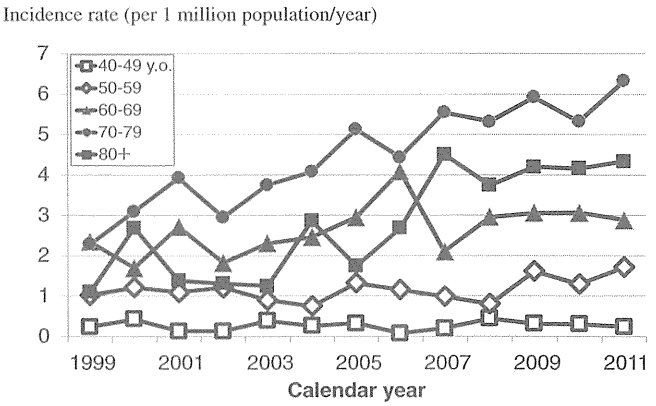

Figure 5. Annual incidence rates of prion diseases in Japan by age

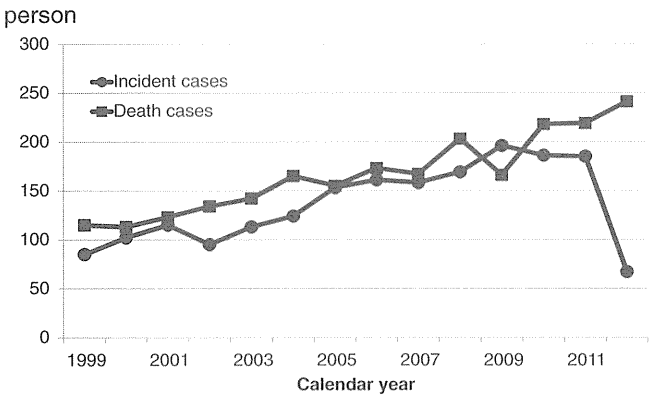

Figure 4. Numbers of incident cases of and deaths from prion diseases in Japan, 1999–2012

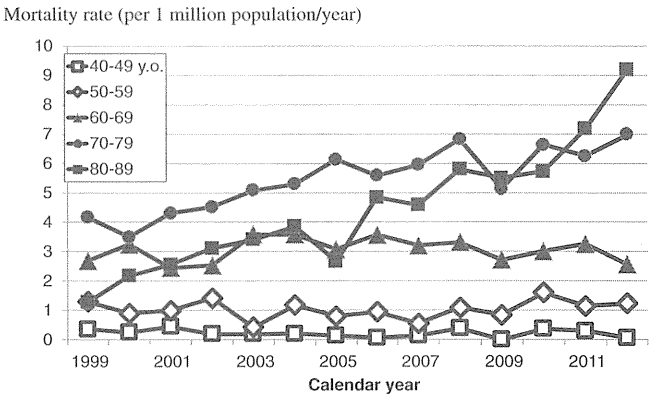

Figure 6. Annual mortality rates of prion diseases in Japan by age

only a single case of acquired prion diseases other than dura-related CJD, which was a case of variant CJD in 2005.[13,14]

Although there was no geographical clustering of prefectures with high incidence rates or mortality rates, some prefectures presented high rates. For example, both incidence and mortality rates were high in Yamanashi prefecture. There have been several articles about familial clustering of prion diseases in this prefecture.[15–19] Of the 23 patients reported in Yamanashi, 57% (13 cases) had familial CJD, although only 15% of prion disease patients had familial CJD in Japan as a whole, as shown in Table 1.

The numbers of incident and fatal patients increased in Japan during the last decade, as shown in Figure 4, although no chronological changes in the number of patients with prion diseases were observed in European countries.[20] The increase in number of fatal cases was reflected in the increase in number of incident cases in our study. As shown in Figures 5 and 6, the increases in numbers of incident and fatal cases were also reflected in the increased number of cases among the elderly. This phenomenon might be due to the substantial network of gene and spinal fluid analytic systems in Japan.

The Surveillance Committee has publicized the system not only to neurologists but also to general physicians. A patient with rapidly progressive dementia dying before diagnosis might be diagnosed with a prion disease through these gene and/or cerebrospinal fluid analyses. If a physician uses these systems, the Surveillance Committee is automatically notified of the existence of a potential patient, starts getting information about the patient, and discusses whether or not the patient has a prion disease. Further dissemination of information about the analytic system might increase the rate of identification of such patients, particularly among older patients.

The number of gene analyses conducted at Tohoku University increased from 132 cases in 1999 to 273 in 2012. Given that relatively young patients (ie, in their 40s or 50s) with rapidly progressing dementia are rare, such patients are typically referred to specialists in dementia (including prion diseases), so any issues with recognition have been negligible. If knowledge of the gene and spinal fluid analyses system is propagated to all physicians in this country, the issue of recognition should be diminished even further, and the chronological increase of the incidence rate should plateau. However, despite this expected plateau in the near future, the number of patients may still increase because of the growing number of old people in Japan.

Selection bias and information bias may have affected this study. The Surveillance Committee has made an effort to obtain information for all patients with prion diseases in Japan, but the database is not complete. Similar selection bias may be present in the vital statistics data as well; those with prion diseases whose deaths were attributed to conditions other than prion diseases would not be counted as prion disease deaths. Information bias may also exist on the vital statistics data; we were unable to clarify the validity of the diagnosis on death certificates, whereas diagnoses obtained through the surveillance system were validated by the Committee members, including neurologists and neuropathologists.

In conclusion, we showed here the epidemiologic features of prion diseases in Japan. Increased recognition of prion diseases may account for the observation of chronological increases in the number of patients with prion diseases, and the increasing trend of numbers of patients might soon plateau.

ONLINE ONLY MATERIAL

Abstract in Japanese.

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Conflicts of interest: None declared.

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ORIGINAL ARTICLE

Sequelae in 145 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms: Survey conducted by the Asian Research Committee on Severe Cutaneous Adverse Reactions (ASCAR)

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ABSTRACT

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a severe adverse drug reaction caused by specific drug. It is characterized by visceral organ involvement and reactivation of various human herpesviruses. Although sporadic reports have documented certain conditions that appear after the resolution of DIHS/DRESS, little information is available on sequelae after resolution of DIHS/DRESS in a large patient population. The Asian Research Committee on Severe Cutaneous Adverse Reactions, comprised of doctors from Japan and Taiwan, conducted a survey on sequelae and deterioration of the underlying disease in patients with DIHS/DRESS. This was achieved by directly interviewing patients who had been followed-up by experts or through a questionnaire mailed to patients. Questions were asked about new onset cardiovascular disease, collagen disease or autoimmune disease, gastrointestinal disease, renal disease, respiratory disease, neoplasms, and other diseases such as herpes zoster and diabetes mellitus, as well as deterioration of the underlying disease. A total of 145 patients were analyzed in this study. The following newly developed diseases after recovery from DIHS/DRESS were observed: Graves' disease (*n* = 2), Hashimoto's disease (*n* = 3), painless thyroiditis (*n* = 2), fulminant type 1 diabetes mellitus (*n* = 5), and infectious diseases (*n* = 7). Several DIHS/DRESS patients with pre-existing renal dysfunction required lifelong hemodialysis. DIHS/DRESS is a condition that increases the risk of new onset of disease. Long-term observation of DIHS/DRESS can provide an opportunity to investigate substantial diseases from onset to the full-blown stage. Patients with DIHS/DRESS require careful long-term follow-up.

Key words: autoimmune thyroiditis, drug reaction with eosinophilia and systemic symptoms, drug-induced hypersensitivity syndrome, fulminant type 1 diabetes mellitus, Graves' disease, Hashimoto's disease.

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INTRODUCTION

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a severe adverse drug reaction caused by specific drugs such as anticonvulsants and allopurinol. It is characterized by visceral organ involvement and reactivation of various human herpesviruses (HHV).[1–9] Sporadic reports have documented the appearance of newly developed diseases after the resolution of DIHS/DRESS, such as autoimmune thyroid disease,[10–13] type 1 diabetes mellitus,[14–17] sclerodermoid graft-versus-host disease-like lesions,[18] and systemic lupus erythematosus.[19] It is likely that DIHS/DRESS is a risk factor for triggering new onset of disease. The newly developed diseases could be recognized as sequelae of DIHS/DRESS. It is also likely that DIHS/DRESS is a risk factor for deterioration of pre-existing disease. However, little information is available on sequelae or deterioration of the underlying disease after resolution of DIHS/DRESS in a large patient population because of the difficulty of long-term follow-up after clinical resolution of DIHS/DRESS and the potential development of sequelae after a disease-free period of several months to years.[20,21] Despite this, it is important to clarify the association of DIHS/DRESS with the development of sequelae or deterioration of pre-existing disease. To investigate the link between DIHS/DRESS and the development of newly onset disease as suggested by previous reports, we surveyed patients from a total of 14 institutions in Japan and Taiwan, and analyzed the presence of sequelae and deterioration of the underlying disease in patients with DIHS/DRESS. Our findings suggest that late-onset complications, characteristic sequelae, and deterioration of pre-existing disease occur in patients with DIHS/DRESS.

PATIENTS AND METHODS

Patients with DIHS/DRESS who were treated in institutions belonging to the Japanese or the Taiwanese Research Committee on Severe Cutaneous Adverse Reaction (SCAR) between 1998 and 2013 were eligible for this study. All patients satisfied the diagnostic criteria for DIHS proposed by the Japanese SCAR group and/or the criteria for DRESS proposed by the international Registry of Severe Cutaneous Adverse Reactions.[22,23] The criteria for DIHS were the presence of a high-grade fever, widespread maculopapular and/or diffuse erythematous eruption, lymphadenopathy, leukocytosis with atypical lymphocytosis and/or eosinophilia, liver dysfunction, and HHV-6 reactivation. Because cases that satisfied the DIHS criteria were recognized as either definite or probable according to the Registry of Severe Cutaneous Adverse Reactions scoring system for DRESS,[24] DIHS and DRESS were recognized as homogenous conditions. The period of observation and follow-up of study patients was more than 6 months (range, 6 months–13 years; median, 4.9 years) after the onset of disease. There were a total of 215 DIHS/DRESS patients who were treated in participating hospitals. In addition to direct interviews conducted with the 44 patients who were regularly followed-up, including those without overt clinical or laboratory findings, a questionnaire was sent to 171 patients who were not undergoing regular follow-up (Fig. 1). The questionnaire asked about cardiovascular disease, collagen disease or autoimmune disease, gastrointestinal disease, ocular disease, renal disease, respiratory disease, tumor/cancer, and other diseases such as herpes zoster and diabetes mellitus (Table 1). Responses were obtained from a total of 158 patients. Patients who had died before initiation of the survey were excluded. This study was approved by the institutional review board of each participating institution.

RESULTS

Patient characteristics

The questionnaire response rate was 66.7%. Of the 145 DIHS/DRESS patients analyzed, 59 were men and 86 were women. The mean age at onset of DIHS/DRESS was 51.0 ± 18.8 years (range, 6–86 years). The culprit drugs were allopurinol, anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin, and zonisamide), antibiotics, mexiletine, and sulfa agents (e.g. diaphenylsulfone and salazosufapyridine). The underlying diseases treated by the causative drugs were arrhythmia, cerebral infarction, colitis, convulsion, encephalitis, epilepsy, hyperuricemia, immunoglobulin A nephritis, lupus erythematosus, neuralgia, psychiatric diseases, restless leg syndrome, rheumatoid arthritis, tonsillitis, and vasculitis. In the majority of patients, the culprit drug was discontinued when drug eruption was suspected. The causative drug was identified by the clinical course or using the lymphocyte transformation test and/or patch test. Most patients were treated by systemic corticosteroids, but some patients were managed with supportive therapy alone for dehydration. A 4–8-week treatment of oral corticosteroids was required to achieve complete resolution. In three patients, methylprednisolone pulse therapy (1000 mg/day for 3 days) was administered. One patient received plasmapheresis because of recurrence after systemic corticosteroid treatment. Cyclosporine was given to one patient. Some patients received topical corticosteroids for symptomatic relief.

Outcomes after DIHS/DRESS

Various newly developed diseases were documented after the resolution of DIHS/DRESS, including thyroid diseases, diabetes mellitus, herpes zoster, drug eruption, arthritis, pneumonia, thrombotic infarction, alopecia, systemic lupus erythematosus, and vitiligo (Table 2). Among these diseases, thyroid disease was the most frequent sequela in the present study. Seven of the 145 patients developed autoimmune thyroiditis after the onset of DIHS/DRESS. In patients with autoimmune thyroiditis, two had Graves' disease, three had Hashimoto's disease, and two had painless thyroiditis. Two patients had thyroid dysfunction without antithyroid antibodies. The age at onset of DIHS/DRESS was markedly younger in patients with Graves' disease (mean age, 30.0 years) than those with Hashimoto's disease (mean age, 67.0 years) and painless thyroiditis (mean age, 61.5 years). Five patients were women. Clinical manifestations

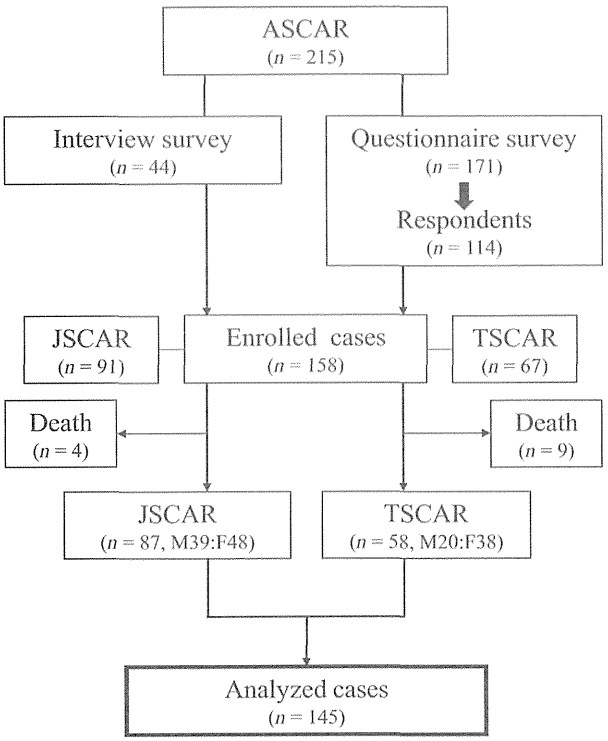

Figure 1. Patient flow diagram. ASCAR, Asian Research Committee on Severe Cutaneous Adverse Reaction; JSCAR, Japanese Research Committee on Severe Cutaneous Adverse Reaction; TSCAR, Taiwanese Research Committee on Severe Cutaneous Adverse Reaction.

Table 1. Interview questionnaire

Do you suffer from following diseases? Have you suffered from following diseases?

1. Ocular disease
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible/☐No)
2. Respiratory disease
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible/☐No)
3. Renal disease
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible/☐No)
4. Gastrointestinal disease
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible/☐No)
5. Cardiovascular disease
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible/☐No)
6. Collagen disease (Ex. Lupus erythematosus)
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible /☐No)
7. Tumor/Cancer (Ex. Lymphoma, gastric cancer)
   - ☐ No
   - ☐ Yes: Please tell the name of disease. _____
   (Relation to the drug eruption:☐Possible/☐No)
8. Other diseases
   - ☐ Herpes zoster
   - ☐ Thyroid disease
   - ☐ Type 1 diabetes mellitus/Type 2 diabetes mellitus
   - ☐ Drug eruption (Please tell the causative drug. _____
   - ☐ Others _____

that led to suspicion of autoimmune thyroiditis were alopecia, palpitation, and hand tremor in two patients with Graves' disease, and general fatigue in one patient with Hashimoto's disease. In the other two patients with Hashimoto's disease, the diagnosis was based on the results of follow-up laboratory examinations in the absence of overt clinical symptoms. In two patients with thyroid dysfunction alone, autoantibodies such as rheumatoid factor and antinuclear antibodies (ANA) were detected. The interval between onset of DIHS/DRESS and the appearance of autoimmune thyroiditis was 2 months to 3 years (Fig. 2).

Besides autoimmune thyroiditis, other autoimmune diseases and conditions such as alopecia, arthritis, systemic lupus erythematosus, and vitiligo were detected. Rheumatoid arthritis appeared with characteristic deformity of the joint more than 10 years after the onset of DIHS/DRESS, which had been managed with supportive therapy alone, and there was no family history of autoimmune disease. Vitiligo appeared in a female patient 4.5 months after the onset of DIHS/DRESS. In this patient, systemic corticosteroids had been given for DIHS/DRESS, but recurrence occurred after tapering the corticosteroids. Therefore, in addition to corticosteroids, cyclosporine was added.

Fulminant type 1 diabetes mellitus (FT1D) is a major concern during the follow-up of DIHS/DRESS because the abrupt onset of FT1D requires prompt intervention. In five patients with FT1D, the mean age at onset of DIHS/DRESS was 56.6 years (range, 21.0–84.0 years). No gender difference in the development of FT1D was observed in this study. FT1D developed within 2 months after the onset of DIHS/DRESS in all patients. The average interval between onset of DIHS/DRESS and the emergence of FT1D was 42.0 days (Fig. 3). Of these five patients, one was positive for anti-insulinoma-associated protein-2. Prompt intervention was initiated in all patients after the diagnosis of FT1D; therefore, no patients died from FT1D.

Table 2. Newly developed disease

Newly developed disease	Number of patients	Age or mean age (years)	Interval†	Published cases
Autoimmune thyroiditis				
Graves' disease	2 (M1:F1)	30.0	2 m, 9 m	Chen *et al.*[20]
Hashimoto's thyroiditis	3 (F)	67.0	6 m–3 yr	Ushigome *et al.*[21]
Painless thyroid disease	2 (M1:F1)	61.5	2 m, 2 yr	
Thyroid dysfunction††	2 (F)	53.0	1 m, NA	
DM				
Fulminant type 1 DM	5 (M3:F2)	56.6	1–2 m	Chiou *et al.*[16], Chen *et al.*[20]
Type 2 DM	1 (F)	64	3 m	
Herpes zoster	5 (M3:F2)	59.6	2 m–3 yr	Ushigome *et al.*[21], Kano *et al.*[26]
Drug eruption	4 (M2:F2)	60.5	2–6 yr	Ushigome *et al.*[21]
Arthritis				
Reactive arthritis	1 (F)	63	3 m	Morito *et al.*[25]
Rheumatoid arthritis	1 (F)	48	10 yr	
Arthralgia	1 (F)	67	11 m	
Pneumonia	2 (M)	70.5	8 m, 1.5 yr	Ushigome *et al.*[21]
Thrombotic infarction‡	2 (M)	63.5	2 m	Hashizume *et al.*[27]
Alopecia§	1 (F)	45	4 m	Ushigome *et al.*[21]
Systemic lupus erythematosus¶	1 (M)	36	3.5 yr	Aota *et al.*[19]
Vitiligo	1 (F)	45	4.5 m	

†Between the onset of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, and the detection of newly developed diseases. ‡Inferior vena cava and cerebral blood vessel, respectively. §No thyroid disease. ¶After the onset of subacute necrotizing lymphadenitis. ††Thyroid dysfunction cannot be included as autoimmune thyroiditis because it may develop as a prior condition. Therefore, this is in parentheses.DM, diabetes mellitus; F, female; M, male; m, month; NA, not available; yr, year.

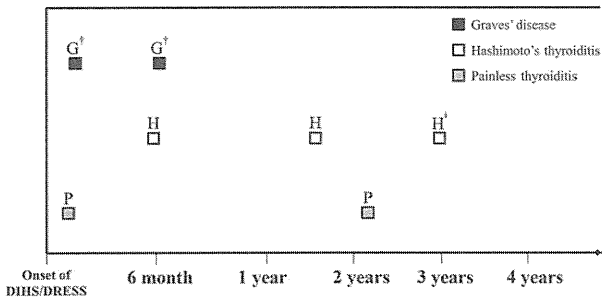

Figure 2. Detection of autoimmune thyroiditis. DIHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; G, Graves' disease; H, Hashimoto's thyroiditis; P, painless thyroiditis; †Reported by Chen *et al.*[20] ‡Reported by Ushigome *et al.*[21]

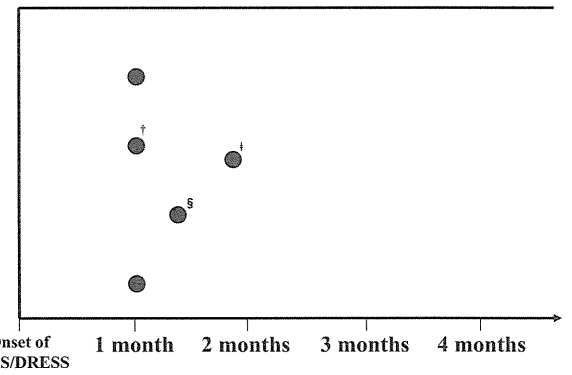

Figure 3. Onset of fulminant type 1 diabetes mellitus. DIHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. †Anti-insulinoma-associated protein-2 was detected. ‡Reported by Chiou *et al.*[16] §Reported by Chen *et al.*[20]

In most patients, DIHS/DRESS was treated with systemic corticosteroids.

Several manifestations related to viral reactivations were detected in this study. Herpes zoster appeared in five patients. Herpes zoster lesions developed within 3.5 months after the onset of DIHS/DRESS in three of the five patients; they developed 3 years after onset in one patient; and the interval was unclear in the other. Infarction in a cerebral lesion and a limb was documented in one patient each approximately 2 months after the onset of DIHS/DRESS. Both patients were diagnosed with thrombotic infarction, and cytomegalovirus reactivation was detected in this period in both. Pneumonia was detected in two patients, and the infectious agent was *Cryptococcus* in one patient and undetermined in the other. Some of the cases described above have been previously described elsewhere.[19–21,25–27]

Alterations in the underlying disease were observed as a result of the commencement of hemodialysis (HD) in patients with renal disease, autoimmune hemolytic anemia in a patient with systemic lupus erythematosus, and resolution of restless leg syndrome. With respect to deterioration of the underlying disease, four patients with renal disease required lifelong HD. The mean age at onset of DIHS/DRESS in these four patients was 55.0 years (range, 24.0–79.0 years). The causative drugs of DIHS/DRESS were allopurinol (n = 2) and diaphenylsulfone

(n = 1); the causative drug was unknown in one patient. The interval between the onset of DIHS/DRESS and commencement of HD ranged from 0.5 month to 5 years. Even a young patient with immunoglobulin A nephritis developed irreversible renal insufficiency after DIHS/DRESS. Autoimmune hemolytic anemia occurred in a patient with systemic lupus erythematosus. Surprisingly, the recalcitrant symptoms of restless leg syndrome disappeared 3 months after the onset of DIHS/DRESS; DIHS/DRESS had been managed with supportive therapy alone in this patient (Table 3).

DISCUSSION

The development of sequelae such as autoimmune thyroiditis and FT1D after several months or years has been described in many reports.[10–17] However, previous similar studies with a small sample size may have been affected by sampling bias and thus might not be representative of the outcome of DIHS/DRESS. In this study, the relatively larger number of patients from 14 institutions in two countries provided findings that are more reliable than those of previous reports. In addition, DIHS/DRESS was diagnosed by experts on drug reactions in this study. Therefore, the evaluation of patients was accurate. The present study revealed that DIHS/DRESS could lead to the occurrence of various sequelae, many of which may have been overlooked had the follow-up survey of patients not been performed by dermatologists and other experts. However, this survey does have a limitation: patients who have a newly developed disease or who have manifested clinical symptoms tend to respond to this kind of medical questionnaire. Furthermore, the follow-up intervals of each patient were not defined in order to obtain short- and long-term sequelae. Therefore, the diverse differences in observation periods among patients precluded comparisons between incidences of newly developed diseases in this survey and those in the general population. In addition, family history, detailed laboratory analysis and viral reactivation, and detailed treatment were not analyzed.

In this study, various newly developed diseases after DIHS/DRESS were documented. They include autoimmune diseases and autoimmune-related diseases, FT1D, and infectious diseases. With regard to autoimmune diseases, six patients (four from Japan and two from Taiwan) developed autoimmune diseases, such as autoimmune thyroiditis, reactive arthritis, and systemic lupus erythematosus, after recovery from DIHS/DRESS;[19–21,25] these patients were included in the present study. In this survey, autoimmune thyroiditis, including Graves' disease, Hashimoto's disease and painless thyroiditis, was the most common disease after recovery from DIHS/DRESS, with a prevalence of 4.8% (7/145). Together with previous studies,[10–13,18] the present results suggest an association between DIHS/DRESS and the appearance of autoimmune thyroiditis. A female predominance in patients with autoimmune thyroiditis after DIHS/DRESS was similar to that observed in the general population. Graves' disease was detected in patients who were younger than those with other autoimmune thyroid diseases such as Hashimoto's disease and painless thyroiditis, a trend similar to that observed in the general population. The interval between the onset of DIHS/DRESS and autoimmune thyroiditis ranged from 2 months to 2 years. In view of our previous study showing that autoantibodies such as antithyroid peroxidase and antithyroglobulin antibodies were detected without any clinical manifestations of thyroiditis after the clinical resolution of DIHS/DRESS,[21] it is likely that the production of antithyroid antibodies might precede the clinical appearance of autoimmune thyroiditis in patients with DIHS/DRESS. Considering that autoimmune thyroiditis, in particular Hashimoto's disease, has been frequently linked to genetic background, family history should have been examined in this survey.

Brown *et al.* documented the coexistence of autoimmune thyroiditis and autoimmune FT1D in a patient with DRESS. In this case, various autoantibodies, including anti-glutamic acid decarboxylase, antithyroid peroxidase, antithyroglobulin, ANA, and anti-Sjögren's syndrome A, were detected.[11] Therefore, the possibility of overlapping autoimmune diseases was raised. In addition, a recent report described the concurrent development of FT1D and Hashimoto's disease at the onset of DIHS/DRESS, characterized by the presence of antithyroglobulin antibodies, ANA, and anti-Sjögren's syndrome A antibodies with the absence of glutamic acid decarboxylase and islet cell antibodies.[28] In the present study, a case of rheumatoid arthri-

Table 3. Alteration of underlying disease

Alteration of underlying disease	Underlying disease	Number of patient (M:F)	Age or mean age (years)	Interval†	Published cases
Onset					
Autoimmune hemolytic anemia	SLE	1 (F)	35	2 m	Chen *et al.*[20]
Deterioration					
Induction of hemodialysis	CRI	2 (M1:F1)	65.5	0.5 m, 2.5 yr	Chen *et al.*[20]
	IgA nephritis	1 (M)	24	5 yr	
	Renal disease	1 (F)	65	1 yr	
Resolution					
Symptoms	Restless leg syndrome	1 (M)	72	3 m	

†Between the onset of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, and alteration of underlying disease. CRI, chronic renal insufficiency; IgA, immunoglobulin A; m, month; SLE, systemic lupus erythematosus; yr, year.

tis was seen. In this patient, the appearance of autoimmune antibodies, such as antithyroid peroxidase, antithyroglobulin antibodies, and ANA, was observed without any clinical symptoms 3 years after the onset of DIHS/DRESS, and bone deformity developed 10 years later, after the disappearance of these antithyroid antibodies. These findings indicate that several autoimmune diseases can occur concurrently or sequentially in patients with DIHS/DRESS.

It is unclear why autoimmune diseases develop in patients with DIHS/DRESS. Considering the viral involvement in the development of autoimmune diseases, several articles have reported that herpesvirus infections might contribute to the occurrence of autoimmune thyroiditis. Descamps suggested a possible association between HHV-6 reactivation and autoimmune thyroid disease because the presence of HHV-6 in the thyroid was significantly higher in Hashimoto's thyroiditis than in controls.[29] Based on the observed discrepancy between the viral reactivation period and the onset of autoimmune thyroiditis, the host immune response may also play a pivotal role in the appearance of autoimmune thyroid disease. From an immunological perspective, our previous study showed that the number of fully functional $CD4^+CD25^+FoxP3^+$ regulatory T (Treg) cells is markedly increased in the acute stage of DIHS/DRESS compared with other drug reactions, which contributed to viral reactivation. These Treg cells lost their ability to inhibit cytokine production and proliferation of effector T cells, which coincided with their contraction upon clinical resolution of DIHS/DRESS.[9,30,31] This functional defect of Treg cells might be responsible for the emergence of autoimmunity. In addition, it is likely that drug eruption in four patients after recovery from DIHS/DRESS might be associated with this functional defect of Treg cells.

FT1D is a subtype of diabetes mellitus characterized by an abrupt onset, absence of islet-related autoantibodies, and nearly complete destruction of pancreatic β-cells. FT1D and autoimmune type 1 diabetes mellitus have been linked to DIHS/DRESS.[11,14–17] In particular, many articles reported that FT1D can occur in association with DIHS/DRESS.[11,14–17] Although one patient had islet cell antibodies in the present study, all diagnosed cases had features that were compatible with FT1D. In this current survey, the prevalence of FT1D was 3.45% (5/145). Previous reports and our present results strongly suggest that DIHS/DRESS could trigger the development of FT1D. The mean interval between the onset of DIHS/DRESS and FT1D was 42.0 days in the present study. This interval was comparable with the finding of an interval of 39.9 days in a previous article.[17] Although we are unable to provide a satisfactory explanation for the development of FT1D, a strong association between HLA-B62 and FT1D in Japanese patients with mexiletine-induced DIHS/DRESS has been demonstrated.[17] Based on this finding, it is worthwhile to investigate the contribution of genetic susceptibility to the development of FT1D on a large scale, including in Taiwanese patients with DIHS/DRESS. Factors that predict the development of FT1D were not found in this study.

Infectious diseases such as herpes zoster and cryptococcal pneumonia were observed after the resolution of DIHS/DRESS.[21,26] Accumulating evidence suggests that various herpesviruses reactivate during the course of DIHS/DRESS, but varicella zoster virus reactivations have rarely been reported during the course of the disease. Because herpes zoster is frequently observed without any relationship to the underlying disease, it is very difficult to determine whether there is any association between herpes zoster and the preceding DIHS/DRESS. However, considering that two patients developed herpes zoster after dose reduction of systemic corticosteroids,[26] herpes zoster is likely one of the manifestations of immune reconstruction inflammatory syndrome in the setting of DIHS/DRESS.[32] The occurrence of cryptococcal pneumonia might also be regarded as a manifestation of the immune reconstruction syndrome in this setting. Interestingly, two patients had thrombotic infarction at the same time, approximately 2 months after the onset of DIHS/DRESS.[27] Given that reactivation of cytomegalovirus was detected at this time and the characteristic intranuclear inclusion body of cytomegalovirus is frequently observed in endothelial cells,[33] it is likely that the onset of thrombotic disease in the two patients was not coincidental but might have been caused by cytomegalovirus reactivation. It seems that these conditions might have been overlooked in previous cases of DIHS/DRESS.

Four patients with pre-existing renal dysfunction due to chronic renal insufficiency and immunoglobulin A nephritis required HD within 5 years after the onset of DIHS/DRESS. Although it is extremely difficult to determine whether deterioration was related to the prior occurrence of DIHS/DRESS, DIHS/DRESS could increase the risk of progression to renal failure in the setting of prior renal function disturbance. Further special attention needs to be given to this possibility.

In conclusion, our results indicate that DIHS/DRESS might contribute to the new onset of diseases after recovery from DIHS/DRESS. DIHS/DRESS is a condition that provides an invaluable opportunity to observe newly developed disease from their initiation to the full-blown stage. Patients with DIHS/DRESS require careful long-term follow-up.

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REVIEW ARTICLE

Japanese guidelines for the management of pemphigus

Committee for Guidelines for the Management of Pemphigus Disease
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ABSTRACT

The Committee for Guidelines for the Management of Pemphigus was organized as one element of the Japanese Dermatological Association (JDA) and the Ministry of Health, Labour, and Welfare (MHLW) Research Project on Measures for Research Committee for Intractable Skin Disease. Pemphigus has been defined as a group of intractable autoimmune blistering diseases caused by anti-desmoglein 1 and/or anti-desmoglein 3 IgG autoantibodies by the MHLW. The diagnosis of this condition and the criteria for assessing its severity are based on suggestions from the MHLW Research Group. The clinical practice guidelines presented here are those that are currently recommended in Japan. However, symptoms and complications can vary widely among individual pemphigus patients, so not all therapies will be required to be in complete agreement with these guidelines.

Key words: **autoantibody, desmoglein, diagnosis, therapy.**

INTRODUCTION

Definitions

Pemphigus is defined as a group of autoimmune blistering diseases that cause lesions in the skin and mucous membranes. From a histopathological perspective, the epidermis undergoes acantholysis, in which the cell–cell adhesion between adjacent keratinocytes are impaired, resulting in the formation of blisters. From an immunological perspective, pemphigus is characterized by the *in vivo* deposition of immunoglobulin (Ig)G on cell surfaces of keratinocytes in the epidermis, or of the detection of such autoantibodies in the circulation. The pemphigus antigen is desmoglein (Dsg), a cadherin-type cell–cell adhesion molecule found in desmosomes.

Pemphigus can be broadly classified into three major forms: (i) pemphigus vulgaris; (ii) pemphigus foliaceus; and (iii) others. The other known forms include paraneoplastic pemphigus; pemphigus vegetans, which is a subtype of pemphigus vulgaris; pemphigus erythematosus or Senear–Usher syndrome, which is a subtype of pemphigus foliaceus; herpetiform pemphigus; and drug-induced pemphigus.

Epidemiology

According to the Ministry of Health, Labor and Welfare (MHLW) Research Project on Measures for Intractable Diseases, applications for public financial aid for treatment were received from 3504 pemphigus patients in 2004 and 4085 pemphigus patients in 2007. The MHLW has a registration system of intractable diseases including pemphigus. We obtained the 2004 clinical database from the MHLW, which contained 2503 patients with pemphigus (input rate, 71%).

The sex ratio of the patients (male : female) was 1:1.5, making the condition slightly more common in women. The disease most frequently afflicted patients in the 60–69-year age group. Disease onset of pemphigus was peak in those aged 50–59 years. The most common disease type was pemphigus vulgaris (65%), followed by pemphigus foliaceus (23%), pemphigus erythematosus (6%), pemphigus vegetans (2%) and unknown disease type (4%). These conditions were classified as mild (74%), moderate (20.4%) or severe (5.0%), using Severity Criteria I from the MHLW Research Group for Rare Intractable Skin Diseases (Table 2). New applicants made up 10% of all applicants, and the ratio of relatively severe cases was higher among these new applicants (mild, 34.2%; moderate, 45.2%; severe, 20.6%) than among all patients.

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Pathophysiology

The basic pathophysiology of blister formation in pemphigus is the inhibition of adhesive function of Dsg by IgG autoantibodies, which leads to the loss of cell–cell adhesion of keratinocytes with resultant blister formation. The pemphigus vulgaris antigen is Dsg3, and the pemphigus foliaceus antigen is Dsg1. Pemphigus vulgaris can be further classified as mucosal-dominant or mucocutaneous. Ordinarily, only anti-Dsg3 IgG antibodies are detected in mucosal-dominant pemphigus vulgaris, while both anti-Dsg3 and anti-Dsg1 IgG antibodies are detected in mucocutaneous pemphigus vulgaris. Only anti-Dsg1 IgG antibodies are detected in pemphigus foliaceus.

The diversity of blister formation sites in pemphigus is explained by the Dsg compensation theory, which suggests that intercellular adhesion is compensated when two or more types of Dsg isoform are expressed in the same cell. Within the epidermis, Dsg3 is strongly expressed in the lower epidermis, and particularly in the basal and parabasal cell layers. Dsg1 is expressed in all layers of the epidermis, and particularly strongly expressed in the upper layers. However, within the oral mucosa or esophagus Dsg3 is strongly expressed in the whole epithelial layer and Dsg1 is weakly expressed in all layers except for the basal cell layer. In pemphigus foliaceus, where only anti-Dsg1 IgG antibody is found in the serum, in the skin, blisters are induced in the upper layer of the epidermis where there is no Dsg3-mediated compensation for the adhesive function. However, Dsg3 is strongly expressed in all layers of the mucosa, so Dsg3 compensates for the Dsg1 interference with the adhesion function. As a result, no apparent erosions develop in oral mucosa. In mucosal-dominant pemphigus vulgaris, where only anti-Dsg3 antibodies are found in the serum, Dsg1 is expressed in all layers of the epidermis. Thus, Dsg1 compensates for antibody-mediated inhibition of the Dsg3 adhesion function. Blisters do not form, or they form only locally in the skin. In oral mucosa, in contrast, Dsg1 is expressed in low levels and cannot compensate for the lost Dsg3 adhesion function, so erosions are formed. Similarly, in cases of mucocutaneous pemphigus vulgaris, the serum contains anti-Dsg1 antibody as well as anti-Dsg3 antibody, so function is inhibited both for Dsg3 and for Dsg1. In this condition, blisters and erosions can develop extensively in both the skin and the mucosa.

Regarding the mechanisms of blister formation in pemphigus, at least two theories are well accepted. One is the direct inhibition of Dsg adhesion or steric hindrance by IgG autoantibodies. The other is the involvement of intracellular signal transduction induced by IgG binding to Dsg. Phosphorylation of Dsg or anchoring proteins causes Dsg internalization into the cells from the surface of the cell membranes, which leads to reduced levels of Dsg on the cell membrane.

Paraneoplastic pemphigus is an autoimmune skin condition in which IgG autoantibodies to Dsg and plakin molecules are present. This disease is associated with a malignant or benign neoplasm (generally, a lymphoproliferative disorder) that is characterized by serious mucosal lesions, primarily erosive, and a variety of skin lesions. Characteristically, not only humoral immunity but also cellular immunity is involved in damage to the mucosal epithelium as well as to the skin.

Clinical symptoms and histopathological findings

Pemphigus vulgaris. This is the most common form of pemphigus. The most characteristic clinical findings in pemphigus vulgaris are painful refractory erosions and ulcers in the oral mucosa. Initial symptoms generally involve the oral mucosa, and in severe cases can lead to insufficient food intake. In addition to the oral mucosa, this form of pemphigus can also affect the stratified squamous epithelium in areas such as the lips, pharynx, larynx, esophagus, eyelid conjunctiva and vagina. In approximately half of patients, the condition is not limited to the oral mucosa, but also involves the skin, with the development of flaccid bullae and erosions. The blisters rupture easily, and produce erosion of the overlying epidermis that is attached to the perimeter of the blister. Such erosions are often painful, and adjoining erosions tend to coalesce to form a large eroded surface. The most frequent sites for blistering are the head, axilla, inguinal area, upper back and buttocks, where pressure is applied, and this condition spreads readily. Even in areas that appear normal, if pressure is applied, the skin may be detached to reveal erosion (Nikolsky's sign). Pemphigus vulgaris can be divided into two categories based on the clinical symptoms: (i) mucosal-dominant type in which mucosal lesions are the primary symptom, and skin blisters and erosions may be localized if present; and (ii) mucocutaneous cases in which there is widespread involvement of both the mucous membrane and the skin.

Biopsy specimens should be obtained from new vesicles or margins of vesicles. The cell–cell adhesion of keratinocytes is lost, and the blister formation is seen between basal and parabasal layers as suprabasilar acantholysis. Within the vesicles, acantholytic cells can be seen. The attachment is damaged between the basal cells and their neighboring cells, but the connection to the basement membrane is retained, resulting in what is termed a "row of tombstones" appearance.

Pemphigus foliaceus. Clinically, this condition is characterized by scaly crusted erosion, often on an erythematous base on the skin. The erythema is most commonly seen as small red spots, up to the size of a fingernail plate. Rarely, the erythema extends over a large local area and becomes erythroderma. Seborrheic regions such as the head, face, chest and back are most frequently affected. Pemphigus foliaceus almost never produces mucosal lesions in areas such as the oral cavity. Nikolsky's sign can also be detected.

The cell–cell adhesion of keratinocytes is lost, and blister formation can be noted in the upper layer of the epidermis, from the subcorneal layer to the granular layer. Blisters must be checked carefully, because the acantholytic cells are not numerous within the blisters, and can be easily missed.

Paraneoplastic pemphigus. The most common clinical symptom of this condition is the presence of refractory lesions within the oral cavity. Paraneoplastic pemphigus is