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Generalized Pustular Psoriasis in Japan: Two Distinct Groups Formed by Differences in Symptoms and Genetic Background

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A multi-center study for investigating generalized pustular psoriasis was carried out in Japan in order to clarify the prevalence, the etiology, and the standard therapy. Through questionnaires, 541 cases of patients with generalized pustular psoriasis and related disorders were collected, and the history, the precipitating factors, the symptoms and the laboratory findings were analyzed from medical records. The statistic analysis revealed that 902 ($\pm$102.2) patients with generalized pustular psoriasis were expected at the time, and that the prevalence of generalized pustular psoriasis in Japan was 7.46/million. Of 541 patients with generalized pustular psoriasis, 208 cases had the recurrent episodes of symptoms with generalized pustules which had been referred to von Zumbusch type pustular psoriasis or to the acute form of generalized pustular psoriasis. Two hundred and eight patients were further subdivided into two groups: one with a preceding history of ordinary psoriasis (pso$^+$ generalized pustular psoriasis; 65 cases) and another without a psoriasis history (pso$^-$ generalized pustular psoriasis; 143 cases). Subdivision into the two groups defined that the onset of pustular outbreak was earlier in the pso$^-$ generalized pustular psoriasis group. It was also pointed out that the precipitating factors were different, as the pso$^-$ generalized pustular psoriasis group was more frequently affected after infections, and that the pso$^+$ generalized pustular psoriasis group was more frequently affected by preceding corticosteroid therapy.

HLA analysis of 92 cases with von Zumbusch type generalized pustular psoriasis confirmed that A2, B14, B35 phenotypes were weakly correlated, and when 92 cases were subdivided into the two groups, the pso$^+$ generalized pustular psoriasis group revealed a statistically significant correlation with A1 ($p<0.01$), B37($p<0.02$) and DRw10 ($p<0.05$), which was closely related with psoriasis vulgaris patients in Japan. Both clinical surveillance and genetic analysis have disclosed the heterogeneity of von Zumbusch type generalized pustular psoriasis, as there exist two types; one is closely related to psoriasis and the other not.

Key words: HLA; epidemiology.

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Generalized pustular psoriasis (GPP) was first proposed by von Zumbusch in 1910 (1), describing a man who, after many years of uneventful discoid psoriasis, began to suffer from recurrent episodes of a different nature, characterized by the development of bright erythema and edema, which then became studded with multiple pustules. The eruption was at times almost universal and was constantly accompanied by fever and signs of toxicity. At first these episodes appeared to be produced by pyrogallic acid applications but they later recurred without obvious cause. Since the first description by von Zumbusch, a number of publications have added many cases and have tried to clarify the etiology, diagnostic criteria, and classification of this syndrome. However, the pathogenesis of GPP remains uncertain, and even the classification of GPP has not been fully agreed on yet because of its heterogeneous features.

Among the various classification systems of GPP, Baker's five subdivisions (2) have been most helpful in understanding the variable and heterogeneous features of GPP: acute, of pregnancy, infantile and juvenile, circinate, and localized (not hands and feet). Baker's classification was based on the epidemiologic study by Baker & Ryan (3), who reported 24 of their own cases plus 80 others, in which information was obtained through questionnaires sent to dermatologists in Great Britain. In the recent literature, Zelickson & Muller (4) have proposed to classify GPP into four subgroups, based on their own 63 cases: acute (von Zumbusch), subacute annular, chronic (acral), and mixed.

Recently, a multi-center study of GPP was carried out by the Research Committee for Rare and Intractable Diseases sponsored by the Ministry of Health and Welfare of Japan in order to clarify the prevalence, the etiology, and the standard therapy of this severe, sometimes life-threatening skin disease in Japan. The purpose of this study is not only to evaluate the heterogeneity of the clinical features but also to add new information regarding genetic background (HLA analysis) through large series of patients who were reported to the Research Committee in questionnaires.

MATERIAL AND METHODS

Multi-center study

A multi-center study was designed by the Research Committee for Rare and Intractable Diseases, as previously reported (5). Questionnaires were sent to 575 community center hospitals throughout Japan, asking for the details of patients with GPP and related disorders, who visited these hospitals during 1983–1989. The diagnosis of GPP depended on the dermatologists at each hospital.

Questionnaire

From the medical records of each hospital, the family history, the age of onset, the presence of ordinary psoriasis before the pustular outbreak and during the quiescent period, the precipitating factors, associated symptoms and laboratory findings, pattern of generalized flare (distribution, mucous membrane involvement), biopsy results, recurrence frequency, and, finally, treatments and prognosis were reported from 196 hospitals through questionnaires. There were 541 well-documented cases with GPP and related disorders; these were

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listed, as in Table I, according to the diagnoses which were made by each dermatologist.

Subdivision of GPP

Two hundred and eight cases were reported as GPP of von Zumbusch (including infantile cases). They were subdivided into two groups according to the presence or absence of a history of ordinary psoriasis. Each item of the questionnaire was compared between the two groups, and symptom differences were statistically analyzed by the χ^2 test.

HLA analysis

Among 208 cases of GPP of von Zumbusch, 92 cases were subjected to HLA analysis (HLA-A, B, C, and DR) by the NIH standard method. The results were statistically analyzed by the χ^2 test, between normal population, psoriasis vulgaris patients, and the two subgroups of GPP of von Zumbusch.

RESULTS

Prevalence of GPP in Japan

The prevalence of GPP was calculated by the method previously described (5). The expected number of patients with GPP and related disorders was 902($\pm$102.2) in Japan, and the expected prevalence was 7.46/million at the time. The number per year was estimated to be 16.5 cases.

Subdivision of GPP into two groups

From questionnaires, 208 cases (88 males, 120 females) were recorded as von Zumbusch type GPP, including infantile cases. Marked differences were found in the age distribution of the onset of GPP and in the precipitating factors of pustular outbreak, when GPP was subdivided into two groups according to the presence or the absence of a history of ordinary psoriasis (pso$^+$ GPP, with a history of ordinary psoriasis, 65/208; pso$^-$GPP, without a history of ordinary psoriasis, 143/208). In the pso$^-$GPP group, the age of onset was most frequently observed to be under 9 years (30/143 cases, 21.0%), and the average was 32 years. On the other hand, the pustular outbreak after ordinary psoriasis was most frequent in the third decade, and the average was at 37 years of age among the pso$^+$GPP group (Fig. 1). Since the onset of preceding ordinary psoriasis was at 31 years of age on average, the time between the onset of ordinary psoriasis and the pustular outbreak was estimated to be 6 years.

Table I. *Cases of pustular psoriasis in Japan*

Disease	Number of patients (male/female)
von Zumbusch (acute & infantile and juvenile)	208 (88/120)
Impetigo herpetiformis	19 (0/19)
Annular and circinate	9 (3/6)
Generalized form of acrodermatitis continua, Hallopeau	10 (6/4)
Subcorneal pustulosis (Sneddon-Wilkinson)	56 (25/31)
Generalized form of palmoplantar pustulosis	23 (11/12)
Acute pustular bacterid (Tan)	2 (0/2)
Psoriasis with pustules	
Generalized	98 (53/45)
Localized	81 (50/31)
Others	35 (12/23)

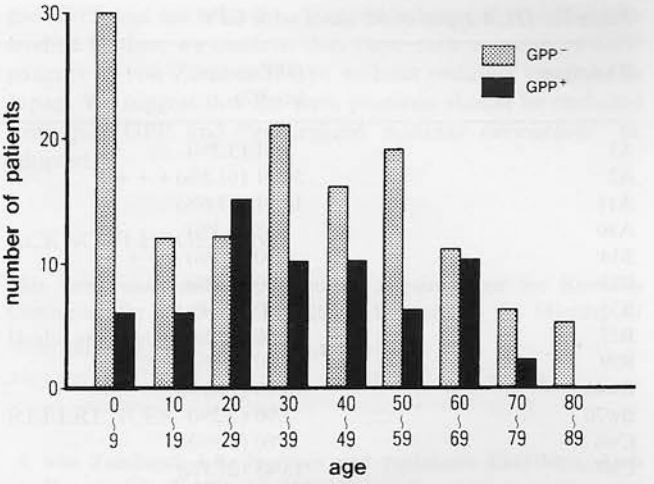

Fig. 1. Age distribution as to GPP onset. GPP$^-$: Patients without a preceding history of ordinary psoriasis. GPP$^+$: Patients with a preceding history of ordinary psoriasis.

A distinctive difference was also observed among the precipitating factors. Both topical and systemic corticosteroids were found to affect the GPP flare more frequently in pso$^+$GPP (topical; 27.7%, systemic; 15.4%) than in pso$^-$GPP (topical; 12.6%, systemic; 7.0%). Infections were also one of the important precipitating factors; however, only a small difference was observed (pso$^-$GPP; 23.1%, pso$^+$GPP; 30.8%). There were no differences in other precipitating factors, including pregnancy, menstruation, or drugs.

Skin and mucous membrane lesions during the generalized flares were similar in the two groups. Flexural sites and mucous membranes were slightly more affected in pso$^-$GPP than in pso$^+$GPP (Fig. 2). However, a greater difference was observed in the skin lesions during the quiescent period. Although ordinary psoriatic lesions were recorded in 51.7% of the pso$^+$GPP group, the 66.2% of the pso$^-$GPP group revealed no skin lesions or some erythematous patches during the quiescent period. Analysis of associated symptoms, including high fever, elevated CRP, elevated erythrocyte sedimentation rate, leukocytosis, and hypocalcemia, revealed no differences between the two groups. Joint symptoms were reported in 29.8% of all cases; however, no differences were observed between the two groups as to the occurrence of joint symptoms. The presence of Kogoj's spongiform pustules in the biopsy results did not reveal any differences (pso$^-$GPP; 89.6%, pso$^+$GPP; 86.8%).

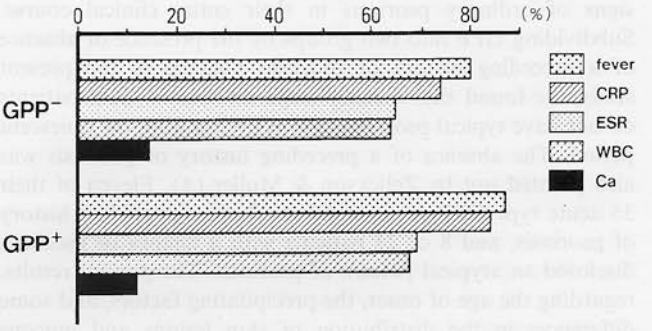

Fig. 2. Accompanying symptoms of GPP$^-$ and GPP$^+$.

Table II. *HLA types of 92 cases with GPP*

HLA type	GPP ($n=92$)	Psoriasis vulgaris ($n=113$)	Healthy control ($n=472$)
A1	3/91 (3.3%)	9/113 (8.0%)	6/472 (1.3%)
A2	56/91 (61.5%)+++		192/472 (40.7%)
A11	16/91 (17.6%)		81/472 (17.02%)
A30	1/48 (2.1%)		2/425 (0.5%)
B14	2/90 (2.2%)+++		0/472 (0.0%)
B27	1/90 (1.1%)		2/472 (0.4%)
B35	22/90 (24.4%)+		73/472 (15.5%)
B37	2/48 (4.2%)	11/113 (9.7%)****	6/437 (1.4%)
B39	6/90 (6.7%)	25/113 (22.1%)****	34/472 (7.2%)
Bw46	10/90 (11.1%)	28/113 (24.8%)****	44/437 (10.1%)
Bw70	2/90 (2.2%)		6/333 (1.8%)
Cw6	2/80 (2.5%)	10/64 (15.6%)****	8/425 (1.9%)
Cw7	13/48 (27.1%)	38/113 (33.6%)*	104/437 (23.8%)
Cw11	2/11 (18.2%)	27/113 (23.9%)****	44/437 (10.1%)
DR4	29/53 (54.7%)		192/461 (41.6%)
DRw10	1/32 (3.1%)	7/113 (6.2%)****	4/461 (0.9%)

*: <0.05,
****: $p<0.001$
+: $p<0.05$ (corrected $p>0.05$)
+++: $p<0.01$ (corrected $p>0.05$)
++++: $p<0.001$ (corrected $p>0.05$)

HLA types between the two groups (Tables II & III)

Among all GPP patients examined in the present study ($n=92$), A2, B14, and B35 were found at higher frequencies than in the healthy Japanese controls (statistically not significant by corrected p). When the pso$^-$GPP and pso$^+$GPP groups were subdivided, the pso$^+$GPP group revealed higher frequencies than the Japanese controls (6) (statistically significant) of A1($p<0.01$), B37($p<0.02$) and DRw10($p<0.05$), which were closely related with psoriasis vulgaris patients in Japanese (6,7).

DISCUSSION

GPP is conventionally classified into the five subdivisions proposed by Baker (2), and it has long been accepted that GPP is a part of the psoriasis spectrum. We agree that a close relationship between GPP and psoriasis vulgaris does exist, since patients with GPP may go through phases of psoriasis vulgaris and both diseases are characterized by similar histopathological features, in which neutrophilic invasion into the epidermis plays a key role. However, there is still some controversy, due to the presence of patients who lack any signs of ordinary psoriasis in their entire clinical course. Subdividing GPP into two groups by the presence or absence of a preceding history of psoriasis vulgaris in the present study, we found that a fairly large number of GPP patients do not have typical psoriasis lesions even during the quiescent period. The absence of a preceding history of psoriasis was also pointed out by Zelickson & Muller (4). Eleven of their 35 acute type GPP patients did not have a preceding history of psoriasis, and 8 of 24 patients with a history of psoriasis disclosed an atypical pattern of psoriasis. The present results, regarding the age of onset, the precipitating factors, and some differences in the distribution of skin lesions and mucous membrane involvement during pustular flares, may indicate that the acute type of GPP (von Zumbusch) can be further subdivided into one which is a part of the psoriasis spectrum and another which is not.

Table III. *Comparison of HLA types between the pso$^-$GPP group and pso$^+$GPP group (pso$^-$GPP: without a preceding history of ordinary psoriasis, pso$^+$GPP: with ordinary psoriasis)*

HLA types	pso$^-$GPP ($n=55$)	pso$^+$GPP ($n=37$)
A1	0/54 (0.0%)	3/37 (8.1%)***
A2	31/54 (57.4%)++	25/37 (67.6%)+++
A11	12/54 (22.2%)	4/37 (10.8%)
A30	1/24 (4.2%)	0/24 (0.0%)
B14	1/54 (1.9%)+++	1/36 (2.8%)++++
B27	0/54 (0.0%)	1/36 (2.8%)
B35	12/54 (22.2%)	10/36 (27.8%)
B37	0/24 (0.0%)	2/24 (8.3%)**
B39	5/54 (9.3%)	1/36 (2.8%)
Bw46	4/54 (7.4%)	6/36 (16.7%)
Bw70	0/54 (0.0%)	2/36 (5.6%)
Cw6	0/49 (0.0%)	2/31 (6.5%)
Cw7	7/24 (29.2%)	6/24 (25.0%)
Cw11	1/8 (12.5%)	1/3 (33.3%)
DR4	18/30 (60.0%)+	11/23 (47.8%)
DRw10	0/17 (0.0%)	1/15 (6.7%)*

*: $p<0.05$
**: $p<0.02$
***: $p<0.01$
+: $p<0.05$ (corrected $p>0.05$)
++: $p<0.02$ (corrected $p>0.05$)
+++: $p<0.01$ (corrected $p>0.05$)
++++: $p<0.001$ (corrected $p>0.05$)

It was reported that GPP is positively correlated with HLA B27, and that the association of GPP with polyarthritis may

partly explain this finding (8,9). However, others have reported that there is no correlation of particular HLA antigens in GPP (6). Our data of 92 cases is the largest analysis of HLA antigens of GPP to date (6,8,9,10). Even if there exist racial differences, we may come to the conclusion that the pso$^+$GPP group with a preceding history of ordinary psoriasis is closely associated with psoriasis vulgaris, exhibiting similar HLA antigens (A1, B37, DRw10), and that the pso$^-$GPP group without a preceding history of ordinary psoriasis may not be within the spectrum of psoriasis.

A group of cases with pustular dermatoses different from GPP was designated as acute generalized exanthematous pustulosis (AGEP) by Beylot and Roujeau et al. (11,12). They have reported cases in whom generalized pustules develop in an acute course with mild general symptoms, such as joint pain. The skin symptom of AGEP is usually self-limiting, with short duration. They also emphasized the fact that in AGEP, drugs were most frequently suspected as a causative factor. In the present study, we found that drugs were suspected in only 3 cases of 143 pso$^-$GPP patients as a causative factor. Although it cannot be completely denied that the pso$^-$GPP group may include some cases of a single episodic pustulosis induced by drugs, pso$^-$GPP is distinct from AGEP and from pustular drug eruptions because of the absence of drug intake in the majority of cases.

A group of pustular dermatoses which is not related to ordinary psoriasis is also referred to as impetigo herpetiformis. Since the first description by von Hebra (13), who reported 5 cases with generalized pustules during the third trimester of pregnancy, a wide variety of cases have been reported as impetigo herpetiformis. Because of the heterogeneous features in those cases, the criterion of impetigo herpetiformis has long been debated, especially the identity of this unique skin disorder. In Baker's classification, GPP of pregnancy was adopted instead of impetigo herpetiformis for the patients in whom pustules appear during pregnancy and menstruation. Others use impetigo herpetiformis for GPP patients without a preceding history of psoriasis, as in Lever's textbook (14): 'the disease starts suddenly without any preceding lesions of psoriasis as an extensive eruption of pustules on an erythematous base'. In this context, the pso$^-$GPP proposed in the present study must be most comparable with impetigo herpetiformis. However, we consider that the term impetigo herpetiformis should be reserved only for the cases in whom disturbed hormonal circumstances such as pregnancy and menstruation have been proved to play an important role in the pathogenesis of pustularization; therefore, such cases were excluded from 208 cases of von Zumbusch type and were classified as impetigo herpetiformis in the present study. Although the entity of pso$^-$GPP and the criterion of impetigo herpetiformis must be studied further, we confirm that there exist a group of GPP patients of von Zumbusch type without ordinary psoriasis in Japan. We suggest that the term psoriasis should be excluded from pso$^-$GPP and "generalized pustular dermatosis" be adopted.

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