ORIGINAL ARTICLE

Questionnaire-based epidemiological study of hidradenitis suppurativa in Japan revealing characteristics different from those in Western countries

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic relapsing skin disease localized mainly on the apocrine gland-bearing areas. In Japan, HS is yet to be fully understood, and no criteria have been established for its diagnosis or severity assessment. The purpose of this study was to investigate and characterize HS in Japan. We conducted a nationwide questionnaire-based study, in which Japanese diagnostic criteria were proposed. Question items included age, sex, disease duration, past history, family history, smoking status, disease severity scores (Hurley stage, modified Sartorius score and Physician Global Assessment [PGA] score), treatments, comorbidities and prognosis. We analyzed 300 patients (219 males and 81 females) diagnosed with HS based on our criteria. Average disease duration was 92.3 ± 6.82 months. Only 12 (4%) patients had a family history of HS. Disease severity was classified by PGA score (mild, 100 [33.3%]; moderate, 133 [44.3%]; severe, 34 [11.3%]; most severe, 29 [9.7%]) and Hurley stage (I, 69 [23%]; II, 109 [36.3%]; III, 121 [40.3%]). Disease severities based on PGA score and Hurley stage were positively correlated to modified Sartorius score using the Kruskal–Wallis test (P < 0.001, respectively). Patients with diabetes mellitus showed higher PGA scores (χ² = 10.977, P = 0.01185). Presence of axillary lesions related to higher PGA scores (χ² = 8.6378, P = 0.03452). The results in this study and previous studies indicate that Japanese HS patients have different backgrounds from those in Western countries, and are characterized by male predominance, higher incidence of Hurley stages II and III, higher PGA scores in patients with axillary lesions and much fewer familial cases.

Key words: epidemiology, hidradenitis suppurativa, Hurley stage, modified Sartorius score, physician’s global assessment.

INTRODUCTION

Hidradenitis suppurativa (HS) mostly affects the apocrine gland-bearing areas of the body and shows a chronic relapsing course.1 However, the concept of HS is not well recognized in Japan, despite its significant impairment of patient quality of life (QoL). Moreover, because many Japanese HS patients sustain lesions on the buttocks,2 this condition has been called chronic pyoderma of the buttocks, which is categorized as an infectious skin disease. In addition, there were no diagnostic or severity assessment criteria. Although there is a small-scale epidemiological study analyzing 100 Japanese HS patients,2 the features of HS in Japan are not fully understood. The purpose of this study was to investigate the actual picture of HS in Japan by conducting a nationwide questionnaire-based epidemiological survey.

METHODS

Because there were no diagnostic criteria or severity classifications of HS in Japan, we prepared diagnostic criteria (Table 1) for this survey by referring to European criteria proposed in the second congress organized by the Hidradenitis Suppurativa Foundation.3 Although histopathology is not essential in the European criteria, histopathological elements were included in this study as diagnostic aids to confirm the diagnosis of HS by excluding other diseases, because the concept of HS is still not well-recognized in Japan. A questionnaire-based study was performed by sending questionnaires to the 670 hospitals/facilities that are providing dermatological training under the certification of the Japanese Dermatological Association. The propriety of the participation in this research and the patient number were verified by the first questionnaire. A secondary
I: Diagnostic criteria: there are symptoms in one or more anatomical regions such as the axillae, groin, buttocks, anogenital area and others.

1) Repeated appearance of abscess or drainage
2) Scar or nodule
3) Draining fistula

→If patients have exhibited in only one anatomical region, two or more out of three items ([1]–[3]) are required to be met. If patients have symptoms in two regions, one or more out of three items is/are required to be met for diagnosis.

*Infection and malignancy must be excluded.

II: Diagnostic aids (histopathological findings)

1) Keratotic plug and infiltration of leukocytes in hair follicles
2) Draining fistula or sinus tract in the dermis

### Table 1. Diagnostic criteria of hidradenitis suppurativa in this study

| Total | No. of patients |
|-------|----------------|
| Male  | 219 (mean age: 44.5 ± 15.50 years) |
| Female| 81 (mean age: 36.4 ± 13.63 years) |

### Table 2. Backgrounds of the patients

| No. of patients | Total 300 |
|-----------------|----------|
| Male            | 219      |
| Female          | 81       |

### Table 3. Histopathological examination

| No. of patients | Squamous cell carcinoma |
|-----------------|-------------------------|
| Unknown         | 123 (48.3%)             |
| Yes             | 143 (51.7%)             |

### Table 4. Physician Global Assessment

| No. of patients | Mild 100 (33.3%) |
|-----------------|------------------|
| Moderate        | 133 (44.3%)      |
| Severe          | 34 (11.3%)       |
| Most severe     | 29 (9.7%)        |

### Table 5. Hurley stage

| No. of patients | I 69 (23.0%) |
|-----------------|-------------|
| II              | 109 (36.3%) |
| III             | 121 (40.3%) |

RESULTS

The first questionnaire was sent to 670 institutions, 178 of which responded. Of these, 78 institutions agreed to participate in the study using a secondary questionnaire. The other respondents did not participate in the second survey because they had no HS patients. Twenty-one institutions were not able to provide data because they did not follow the HS patients at the time of second survey. A total of 300 patients’ data from 57 institutions were collected for statistical analysis. All patients met the diagnostic criteria. One hundred and fifty-seven patients had a family history. Smoking histories were unknown for the remaining patients. There was no correlation between the MSS and smoking history (\(P = 0.1277\)). One case (0.33%) with family history suffered from secondary squamous cell carcinoma (SCC) of the buttock.

We next examined the correlation between PGA score, Hurley stage and MSS. The numbers of patients classified as PGA scores (\(\chi^2 = 10.977, P = 0.01185\)) and Hurley stage in 17 (5.6%). Among them, only diabetes mellitus was correlated with higher PGA scores (\(\chi^2 = 10.977, P = 0.01185\)). One hundred and twenty-three patients (41%) had a history of smoking, while 85 (28.3%) had no smoking history. Smoking histories were unknown for the remaining patients. There was no correlation between the MSS and smoking history (\(\chi^2 = 5.6894, P = 0.1277\)). One case (0.33%) with family history suffered from secondary squamous cell carcinoma (SCC) of the buttock.

We next examined the correlation between PGA score, Hurley stage and MSS. The numbers of patients classified as PGA scores mild, moderate, severe and very severe were 100 (33.3%), 133 (44.3%), 34 (11.3%) and 29 (9.7%), respectively. The PGA scores for severe and very severe showed statistically significant correlation with MSS by Kruskal-Wallis test \((P < 0.001; \text{Table 3, Fig. 1})\). Multiple comparisons by Steel-Dwass test showed significant correlation with MSS by Kruskal-Wallis test \((P < 0.001; \text{Table 3, Fig. 1})\).
Dwass test revealed significant difference between each group ($P < 0.001$, respectively; data not shown). There were 69 patients (23%) with Hurley stage I, 109 (36.3%) with stage II and 121 (40.3%) with stage III, and there was a statistically significant correlation with MSS by using the Kruskal–Wallis test ($P < 0.001$; Table 3, Fig. 2). Multiple comparisons by Steel–Dwass test demonstrated a significant difference between each group ($P < 0.001$, respectively; data not shown).

Although the difference was not statistically significant by the Mann–Whitney U-test, there was a tendency that the scores of MSS were higher in patients with a family history (data not shown). We also investigated whether disease duration was related to disease severity, and found that patients with disease duration of more than 5 years showed higher PGA scores ($\chi^2 = 28.688$, $P < 0.001$; Table 4).

Affected anatomical locations in Japanese HS patients are summarized in Table 5. Buttocks, axillae and groin were affected in 54.0%, 26.6% and 14.3%, respectively. The incidences of the lesions on the axillae, groin and buttock were 49 (22.4%), 19 (8.7%) and 162 (66.2%) of the 219 male patients, respectively, and 31 (38.3%), 24 (29.6%) and 17 (21.0%) of the 81 female patients, respectively. Interestingly, the presence or absence of lesions on the axillae, groin or buttocks was associated with sex ($P < 0.001$, respectively; Table 5). The number of affected anatomical sites in each patient was also investigated based on the presence or absence of the lesion(s) on three anatomical sites: axillae, buttocks and groin (Table 6). The majority of the patients (188/300; 62.7%) had only one affected anatomical site. Patients suffering from lesions in two and three anatomical sites were 29 (9.7%) and 12 (4.0%) of the 300 patients, respectively. There was no relationship between the number of affected sites and sex ($\chi^2 = 2.367$, $P = 0.102$). Then, we examined whether there were any associations between the disease severity and affected region(s). Patients with lesion(s) in the axillae had higher PGA scores ($\chi^2 = 8.6378$, $P = 0.03452$; Table 7). There were no significant differences for lesions on the buttocks ($\chi^2 = 2.9012$, $P = 0.4071$; data not shown) and groin ($\chi^2 = 0.60793$, $P = 0.8946$; data not shown).

Table 8 shows the relationship between the Hurley stage and the treatments. One hundred and twenty-two patients (40.6%) were administrated topical antimicrobials, among which nadifloxacin was the most frequently prescribed. On the

| Hurley stage | Case (n) | Modified Sartorius score, median (IQR) |
|-------------|---------|--------------------------------------|
| I           | 69      | 5 (4–10)                             |
| II          | 109     | 16 (11–22.5)                         |
| III         | 121     | 54 (34.5–102.5)                      |
| PGA         |         |                                      |
| Mild        | 100     | 10.5 (5–20)                          |
| Moderate    | 133     | 18.5 (11–35.5)                       |
| Severe      | 34      | 67 (40.75–113.5)                     |
| Most severe | 29      | 161 (83–254)                         |

IQR, interquartile range; PGA, Physician Global Assessment.

Figure 1. Correlation between the modified Sartorius score and Physician Global Assessment (PGA). The PGA score correlated with the modified Sartorius score ($P < 0.001$; Kruskal–Wallis test).

Table 4. Association between PGA score and disease duration

| Disease duration | Mild | Moderate | Severe | Most severe | Unknown | Total |
|------------------|------|----------|--------|-------------|---------|-------|
| <5 years         | 67   | 70       | 13     | 7           | 3       | 166   |
| ≥5 years         | 22   | 48       | 19     | 22          | 1       | 112   |
| total            | 89   | 118      | 32     | 29          | 4       | 272   |

Hidradenitis suppurativa patients with disease duration of ≥5 years were significantly more severe ($\chi^2 = 28.688$, $P < 0.001$; $\chi^2$-test). PGA, Physician Global Assessment.

Figure 2. Correlation between modified Sartorius score and Hurley stage. Hurley stage correlated with the modified Sartorius score ($P < 0.001$; Kruskal–Wallis test).

Table 8 shows the relationship between the Hurley stage and the treatments. One hundred and twenty-two patients (40.6%) were administrated topical antimicrobials, among which nadifloxacin was the most frequently prescribed. On the© 2021 The Authors. The Journal of Dermatology published by John Wiley & Sons Australia, Ltd on behalf of Japanese Dermatological Association.
Japanese official diagnostic criteria are developed. Duration is not included. Considering that HS is a chronic condition, this issue should be taken into consideration when Japanese official diagnostic criteria are developed.

In the most recent European HS guidelines, the diagnostic criteria and severity classification used in this study were prepared with reference to the European criteria proposed in the second congress organized by the Hidradenitis Suppurativa Foundation. While there were no histopathological components for diagnostic items in the European criteria, histopathological criteria were introduced into our diagnostic criteria as diagnostic aids to confirm the diagnosis by excluding other skin diseases because the concept of HS is still not well-recognized in Japan. In addition, we think that histopathological examination is important to verify the presence or absence of SCC. Histopathological examinations were conducted in almost half of the 300 patients in this study. This may indicate that diagnostic histopathological evaluation is practical in Japan.

In the most recent European HS guidelines, the diagnostic criteria include a history of recurrent painful or purulent lesions more than twice/6 months. In our criteria, however, disease duration is not included. Considering that HS is a chronic condition, this issue should be taken into consideration when Japanese official diagnostic criteria are developed.

Table 5. Association between anatomical location and sex

|                | Presence of symptoms | No symptoms | Unknown | P      |
|----------------|----------------------|-------------|---------|--------|
| Axillae        | M (n = 219)          | 49 (23.3%)  | 134 (61.2%) | 37 (16.9%) | <0.001 |
|                | F (n = 81)           | 31 (38.3%)  | 32 (39.5%) | 17 (21.0%) |        |
| Groin          | M (n = 219)          | 19 (8.7%)   | 200 (91.3%) | 0       | <0.001 |
|                | F (n = 81)           | 24 (29.6%)  | 57 (70.3%) | 0       |        |
| Buttocks       | M (n = 219)          | 145 (66.2%) | 74 (33.8%) | 0       | <0.001 |
|                | F (n = 81)           | 17 (21.0%)  | 64 (79.0%) | 0       |        |

The numbers of affected anatomical sites are shown based on the presence or absence of the lesion(s) on three anatomical sites: axillae, buttocks and groin. Others include patients having lesions in the areas other than axillae, buttocks and groin.

Table 6. Number of affected anatomical locations by sex

| No. of affected sites | Total (n = 300) | Male (n = 219) | Female (n = 81) |
|----------------------|----------------|---------------|---------------|
| 1                    | 190 (63.3%)    | 138 (63.0%)   | 52 (64.2%)    |
| 2                    | 29 (9.7%)      | 20 (9.1%)     | 9 (11.1%)     |
| 3                    | 12 (4.0%)      | 11 (5.0%)     | 1 (1.2%)      |
| Others               | 69 (23.0%)     | 50 (22.8%)    | 19 (23.5%)    |

Familial HS has attracted attention in recent years. It was reported that 30–40% of HS patients in Europe have a family history. In the present study, only 12 (4%) of the 300 patients had a family history, indicating that the incidence of familial HS is low in Japan. This finding also confirms the result in another Japanese study that familial cases were only two (2%) of 100 HS cases. The very small number of patients with a family history may be caused by the fact that HS is not well understood in Japan, and therefore detailed family histories had not necessarily been obtained. Although there are few familial Japanese cases, a mutation in a gene encoding γ-secretase subunit was found. It is known that familial HS patients tend to have more severe symptoms, especially in patients with mutations in the genes encoding γ-secretase subunits. Interestingly, in our study, disease severity tended to be higher in the 12 familial HS patients, although the difference did not reach statistical significance, probably because of the small number of patients with a family history.

Hidradenitis suppurativa is predominant in women in Western countries. However, we found that Japanese HS patients showed a male predominance, which was consistent with the previous Japanese survey. A similar result was also reported from Korea. In Turkey, which is located between Europe and Asia, HS is also more common in men. Various factors including genetic background behind the differential male : female ratios need to be further studied.

The relation between sex and the distribution of the lesions is also intriguing. The study in Minnesota, USA, showed no relation between sex and buttoc symptom, while another report from Europe indicated that perianal region and buttocks were more commonly affected in male patients. Our study showed that buttock lesions were more frequently seen in males, which was in accordance with previous reports from Japan and Korea. Thus, the predominance of buttock lesions in males may be a characteristic feature in HS patients of Japanese and Korean populations, or in Asian countries generally.

Unexpectedly, symptoms on the axillary fossae, but not on the buttocks, were correlated with disease severity in our study, although the reason for this result is currently uncertain. However, 18% of our patients lacked information about the axillary symptoms, which may reflect the fact that the concept of HS is still uncommon in Japan.
4.6% and is more common in men.18 During the period of this study, SCC was observed in only one patient (0.33%). This result was not fully confirmed, probably because of the small number of HS patients. Limitations in our survey were that some information including the body mass index and Brinkman index were missing in the medical records, that we could not explore the treatment in detail, and that we were able to examine only past information due to the nature of cross-sectional study.

In conclusion, this study showed actual pictures of HS in Japan, which differ from those seen in Western countries. However, prognosis, therapeutic outcome and QoL associated with the disease remain unclear. Further research is needed to better understand the detailed epidemiology of HS in Japan.

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Hidradenitis suppurativa may be considered as an infectious disease. However, infections were able to be eliminated in this study because infection was an exclusion criterion. Nonetheless, many physicians used topical nadifloxacin, instead of topical clindamycin, the treatment recommended by the guidelines for HS.1 This implies that there is still a confusion with respect to the disease concept of HS in Japan. Correct information on the pathophysiology of HS needs to be widely recognized.

Western HS patients are at higher risk for obesity and it correlates with HS severity.4 We found tendencies for lower frequency of obesity compared with HS patients in Western countries.1 On the other hand, we found that diabetes mellitus was related to disease severity, which was not observed in Western populations.15,16 Smoking is a well-known exacerbating factor in HS,13 but it was not correlated with disease severity in Japanese patients. These results also suggest that the background factors for HS in Japan are different from those in Western countries. In our study, however, the risk of complications was not fully confirmed, probably because of the small number of HS patients.

Hidradenitis suppurativa may also develop secondary SCC.17 Prognosis is very poor in such cases.17 Even in Western countries with less male prevalence, SCC is four-times more common in males, and often observed on the perineum and buttocks. After the onset of HS, it takes an average of 25 years to develop SCC.17 Another study reported similar results that the prevalence of SCC in HS is approximately 4.6% and is more common in men.18 During the period of this study, SCC was observed in only one patient (0.33%). This patient showed very severe HS with a family history and died of metastasis 2 years after the onset of SCC. The low frequency of the development of SCC in the current study may also be due to the lower degree of recognition in Japan, and HS may not be considered as a cause of SCC in the buttocks.

To determine the severity of HS, MSS has been widely used in the world.1 MSS was reported to correlate with the Hurley staging system,4 while there is no study that demonstrated the relationship between the PGA score and MSS. In our study, the correlation between MSS and the Hurley staging system was also found, and additionally MSS was correlated with PGA score. The median scores of MSS in this study were 10.5 (5–20), 18.5 (11–35.5), 67 (40.75–113.5) and 161 (83–254) in patients classified as mild, moderate, severe and most severe by PGA, respectively, verifying the usefulness of MSS to evaluate the severity of HS patients. Thus, our study has demonstrated for the first time that there is a highly significant correlation between PGA score and MSS.

In our study, the ratios of patients categorized as Hurley stage I, II and III were 23%, 36.3% and 40.3%, respectively, while those in Western countries were 68%, 28% and 4%, respectively, suggesting that Japanese patients may be more severe than Western patients. A high rate of severe forms in Japan was also reported by Kurokawa et al.2 This discrepancy may be caused by some biases, because we surveyed only relatively large institutions, mostly university hospitals, which led to the increase in the number of cases of severe HS. In addition, by lower awareness of the concept of HS in Japan, many relatively mild types might have been underdiagnosed and not included in this study. Indeed, many respondents to our first questionnaire stated that they had no HS patients.

Table 7. Association between anatomical location and PGA score

| Symptom in axillae | Severity (PGA) | Total |
|-------------------|---------------|-------|
|                   | Mild | Moderate | Severe | Most severe | Unknown |  |
| No                | 60   | 81       | 14     | 9           | 2       | 166 |
| Yes               | 28   | 29       | 10     | 12          | 1       | 80  |
| Unknown           | 12   | 23       | 10     | 8           | 1       | 54  |
| Total             | 100  | 133      | 34     | 29          | 4       | 300 |

Patients with lesion(s) in the axilla(e) had higher Physician Global Assessment (PGA) score ($\chi^2 = 8.6378; P = 0.03452; \chi^2$-test).

Table 8. Association between disease severity and applied treatment

| Treatment             | Hurley stage |
|-----------------------|--------------|
|                       | I  | II | III |
| Topical antimicrobials| 30 | 42 | 50  |
| Oral antimicrobials   | 55 | 79 | 97  |
| i.v. antimicrobials   | 17 | 19 | 32  |
| Surgical resection    | 26 | 65 | 68  |

The relationship between severity and treatment was expressed as the number of patients. No significant correlation between disease severity and applied treatment was detected ($\chi^2 = 7.800, P = 0.081$).
CONFLICT OF INTEREST: H. K. has received honoraria for speaking and consultancy from AbbVie, Eisai and Novartis, Sanofi and Mitsubishi Tanabe. H. F. has received honoraria for speaking and consultancy from AbbVie, Eisai, Novartis, Janssen Pharmaceutical, Marho, Taiho, Eli Lilly and Tanabe-Mitsubishi. T. T. has received honoraria for speaking and consultancy from AbbVie, Eisai, Novartis, Janssen Pharmaceutical, Marho, Taiho, Eli Lilly, Bristol-Myers Squibb and Tanabe-Mitsubishi.

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