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REVIEW ARTICLE

The Prevalence and Disease Characteristics of Generalized Pustular Psoriasis

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Abstract

Generalized pustular psoriasis (GPP) is a rare disease that has only recently benefited from a consistent definition and clinical coding standard. A lack of disease awareness combined with clinical similarities to other types of psoriasis have historically complicated the diagnosis of GPP. It is now clear that GPP requires a differential diagnosis from psoriasis vulgaris (plaque psoriasis), and better understanding of the genetic characteristics underlying GPP may improve the accuracy of diagnoses in the future. GPP can present at any age but is most common in the fifth decade of life. There appears to be a female preponderance in GPP, although there is notable variability in prevalence by geographical region and between ethnicities. GPP is potentially life-threatening, associated with several serious complications, and may require emergency treatment, particularly for complications arising from systemic inflammation. As with many rare diseases, there are inherent challenges to understanding the epidemiology of GPP. In addition to small patient numbers, estimating the prevalence of rare diseases is further complicated by studies that use non-standardized methodologies and that are conducted in different populations. These complications in data gathering have led to marked variability in GPP case estimates by geographical region and between ethnicities. There is ongoing research into disease characteristics, and insights into regional measures of prevalence are essential to increasing our understanding of GPP.

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Key Points

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening disease. While it shares some signs and symptoms with other, less serious, forms of psoriasis, GPP is a separate condition and requires an accurate diagnosis, which should lead to distinct treatment and management approaches.

Estimating the number of individuals who are affected by GPP is challenging because rare diseases are often misdiagnosed and patient numbers are small. Several claims database analyses have been conducted that might increase our understanding of the prevalence of GPP.

Medical claims database analyses can provide up-to-date insights into various aspects of GPP, including disease characteristics and estimates of disease prevalence in defined cohorts.

1 Introduction

Over the past two decades, knowledge of skin pathologies, particularly psoriasis, has increased markedly [1]. Psoriasis is categorized into several distinct subtypes: plaque (or psoriasis vulgaris, which accounts for around 90% of cases), guttate, inverse, erythrodermic, and pustular psoriasis. Pustular psoriasis is subclassified into generalized pustular psoriasis (GPP) and localized pustular psoriasis (palmoplantar

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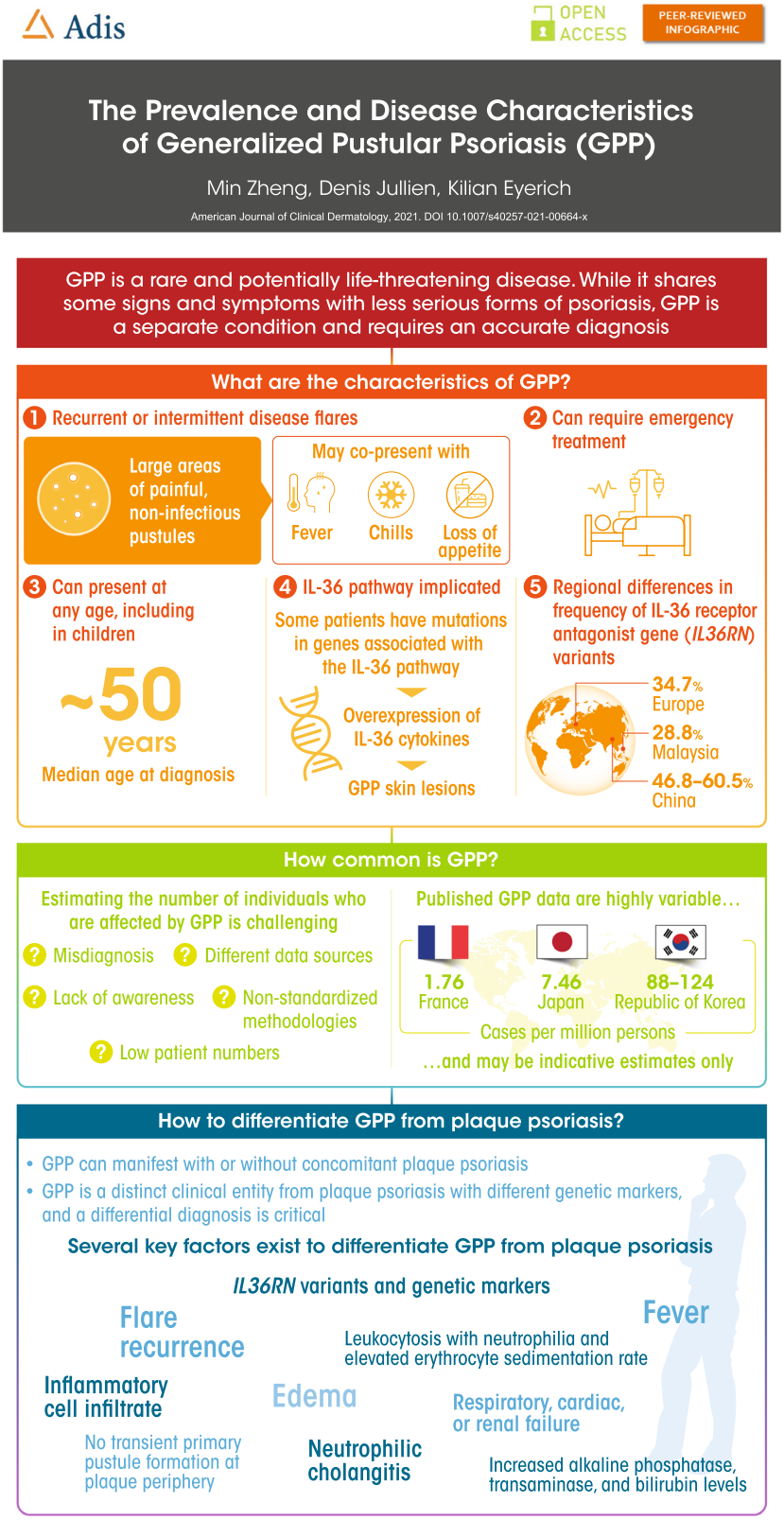
Graphical abstract



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pustulosis and acrodermatitis continua of Hallopeau). Erythrodermic psoriasis can develop alongside any other psoriasis subtype, presenting as erythematous inflamed skin that covers over 90% of the total body surface area [1].

GPP was first described by Leopold von Zumbusch in 1910. However, since its discovery, the disease characteristics have not been consistently defined and several descriptions and diagnostic criteria have been reported in the literature [2]. Following recent international consensus by the European Rare and Severe Psoriasis Expert Network (ERASPEN), GPP is defined as primary, sterile, visible pustules on non-acral skin (excluding cases in which pustulation is restricted to psoriatic plaques). GPP can occur with or without systemic inflammation and with or without psoriasis vulgaris, and can be relapsing (more than one episode) or persistent (> 3 months) [3].

Despite the heterogeneity of rare diseases, there are common barriers to achieving accurate disease prevalence estimates. A lack of widespread awareness and accurate diagnoses, combined with research approaches that use very different data sources and non-standardized methodologies, mean that gathering insights into disease prevalence at a regional, national, or global level is challenging [4]. Recognition of GPP as a rare disease is increasing globally; however, describing the epidemiology of GPP is complicated by the challenges associated with studying rare diseases.

In this first chapter of the supplement titled 'Understanding Generalized Pustular Psoriasis to Improve Patient Outcomes', the characteristics of GPP and key differentiators between GPP and plaque psoriasis are considered, alongside current epidemiology estimates.

2 Disease Characteristics of GPP

2.1 Describing GPP

The clinical course of GPP is heterogeneous; it can be considered a relapsing disease with recurrent flares, or a persistent disease with intermittent flares [3, 5]. Disease flares manifest as the sudden appearance of large areas of painful, non-infectious pustules, which may co-present with fever, chills, and loss of appetite [6, 7]. Symptom severity may vary with each flare for a given individual, and flares may occur several times per year or with long dormant periods between each episode [6, 8].

GPP has been subcategorized into four forms based on the onset of flares and the morphology of lesions [9]. GPP (also called GPP of von Zumbusch) presents with rapid onset (7 days or fewer) of a generalized pustular flare and may be experienced by up to 90% of patients with GPP [9, 10]; it is recognized as the most severe presentation of the disease [11]. Annular GPP presents with a generalized pustular flare that develops between 7 days and 3 months, and is often associated with relatively mild symptoms [2, 12]. Chronic acral GPP presents with the onset of a generalized pustular flare over more than 3 months, with lesions that begin with an acral distribution in the extremities and then gradually spread into a generalized pustular flare [9]. The 'mixed GPP' category captures patients who have features that are associated with more than one subtype, with localized pustular psoriasis that develops into a generalized pustular flare over a range of onset periods [9].

GPP can manifest with or without concomitant plaque psoriasis [7]. It is important to recognize that GPP is a distinct clinical entity from plaque psoriasis and that a differential diagnosis is critical [6, 11, 13]. A diagnosis of GPP should be considered in patients with sudden onset of erythema and pustulosis, and emergency care may be required in patients with fever or severe pain, or with signs of systemic inflammation that may lead to respiratory, cardiac, or renal failure [2, 11]. GPP should be distinguished from the transient, primary pustule formation that may occur at the periphery of plaques in patients with psoriasis vulgaris [2, 3]. See the article on Diagnosis of Generalized Pustular Psoriasis (https://doi.org/10.1007/s40257-021-00652-1).

2.2 Common Disease Characteristics

Several characteristics of GPP have become apparent from published case reports. It has been suggested that there may be a female preponderance in GPP; however, the extent of this varies by geographical region and between ethnicities. A study in 102 patients from Malaysia reported a 2:1 ratio of GPP in females versus males; a study of 74 patients in the US reported a 1.03:1 ratio; and in a study of over 700 patients in Japan, 51.5% were female [9, 10, 14]. Findings from a recent inpatient database of 1516 people with GPP in Japan reported that 56% were male, and a registry in Western Japan observed that 52% of 102 GPP cases were male [15, 16]. GPP can present at any age, including as juvenile GPP [8]; however, the majority of cases present in the fifth decade and the mean age at diagnosis has been reported as 45.6–50.0 years [5, 9, 10]. It has been suggested that females may be diagnosed earlier (mean age 39.4 years) than males [17]. The prognosis of GPP in older patients may be poorer than in younger patients due to the systemic complications of the disease, including cardiorespiratory failure and risk of infection and sepsis [2, 6].

2.3 Genetic Markers in GPP

The etiology of GPP is not fully understood; however, the interleukin (IL)-36 pathway appears to be pivotal in the pathogenesis of the disease. The potential role of IL-36 has been supported by the identification of loss-of-function

mutations in the IL-36 receptor antagonist gene (*IL36RN*) and the overexpression of IL-36 cytokines in GPP skin lesions [18]. The *IL36RN* gene is responsible for suppressing proinflammatory responses triggered by IL-36α, IL-36β, and IL-36γ via the encoding of a functional IL-36Ra protein [6]. In addition, variants of *CARD14*, which encodes a keratinocyte adaptor protein, and *AP1S3*, which encodes a subunit of the adaptor protein 1 complex, have also been implicated in GPP [2, 19]. *CARD14* variants are relatively rare, with some regional variability. A recent review of published evidence on the genetic basis of GPP noted that *CARD14* variations rarely present in patients with GPP alone and are more commonly found in cases of GPP with concomitant psoriasis vulgaris; however, *CARD14* variations specific to either GPP or psoriasis vulgaris have not yet been characterized [20]. In a recent variant-screening study conducted in 863 patients with pustular psoriasis, no *CARD14* substitutions were observed among European patients with GPP, but were present in Chinese patients [19]. A *CARD14* variant was identified in Japanese patients with both GPP and psoriasis vulgaris, but was not associated with psoriasis vulgaris alone, and was not reported in patients with GPP alone, in this population [21].

AP1S3 variants have been reported consistently across pustular psoriasis subtypes. Over 95% of patients with variations in this gene were female, indicating that sex-specific factors may alter the penetrance of *AP1S3* variants [19].

Recently, loss-of-function variants of myeloperoxidase gene (*MPO*) that are associated with increased neutrophil accumulation and activity have been reported in some patients with GPP [22]. A rare loss-of-function variant in *SERPINA3*, which encodes serine protease inhibitor A3 (serpin A3), has also been identified in patients with GPP [23].

Loss-of-function variants of *IL36RN* have been identified in 23–37% of familial and sporadic GPP cases [18, 24]. The frequency of *IL36RN* variants shows regional differences, from 28.8% in Malaysian patients to 34.7% in European patients with GPP, and 46.8–60.5% in Han Chinese patients; one study noted that *IL36RN* may be the major gene associated with the pathogenesis of GPP in the Han population in China [5, 25]. Further analysis in the Chinese population suggested that the mechanisms of IL-36 overexpression differ between patients with GPP and those with psoriasis vulgaris, which may explain previous observations of a lack of association between *IL36RN* variation and the development of psoriasis vulgaris [13]. In patients with homozygous *IL36RN* variants, the age of onset of GPP can be earlier than usual, and *IL36RN* disease alleles have a dose-dependent effect on age of onset in all pustular psoriasis subtypes [19].

While *IL36RN* and *CARD14* variations are implicated in the pathogenesis of GPP, clinical experience of patients presenting with both mutations simultaneously is limited. In 2019, the first published case described a patient with heterozygous *IL36RN* variation (compared with typical homozygous or combined heterozygous variation in GPP), with the authors suggesting that coexisting mutations in *IL36RN* and *CARD14* may also predispose individuals to GPP [26].

Screening of *IL36RN*, *CARD14*, and *AP1S3* is not routinely indicated; however, *IL36RN* status is becoming increasingly recognized as a useful tool in the diagnosis of GPP [2].

2.4 GPP in Pregnancy

Impetigo herpetiformis, or GPP during pregnancy, has a typical onset in the last trimester, and while the etiology is unclear, associations with hypocalcemia and hypoparathyroidism have been suggested in some cases [27]. Pregnancy has been identified as a precipitating factor for flares in patients with GPP [10], and GPP in pregnancy is associated with severe outcomes, including placental insufficiency leading to an increased risk of stillbirth, neonatal death, and fetal abnormalities [28].

3 GPP and Plaque Psoriasis: Contrasting Conditions with Key Differentiators

GPP is clinically, phenotypically, and genetically different from plaque psoriasis and requires a differential diagnosis [5–7]. This is important because GPP flares are potentially life-threatening and may require immediate treatment [2]. In practice, distinguishing the two diseases is challenging because of the relatively low familiarity with GPP among physicians and the apparent similarities between GPP and plaque psoriasis, especially when pustules develop at plaque sites. Since GPP presents in over two-thirds of individuals with history of or existing plaque psoriasis, it is often incorrectly categorized as a form of plaque psoriasis [6]. Previous studies have suggested that around 1% of people with psoriasis have GPP; however, these estimates were based on unclear definitions of GPP.

While there may be morphological similarities at presentation, several key factors exist to differentiate GPP from plaque psoriasis. As a first principle, it might be considered that GPP is an autoinflammatory disease [6] and that plaque psoriasis is an autoimmune disease [29]. Genetic studies suggest that GPP and plaque psoriasis have immunologic pathways that both overlap and are independent from one another [30]. A key difference is that *IL36RN* variants that drive proinflammatory responses are not as common in plaque psoriasis (36.8–37.8%) as they are in GPP (70.6–79.2%) [13, 25]. This important distinction could play a key role in GPP differential diagnosis and screening.

Edema is notably greater in GPP than in plaque psoriasis, in which it is relatively rare, and inflammatory cell infiltrate is also more prominent in GPP [2, 8]. Plaque psoriasis characteristically presents as acanthosis, parakeratosis, and dermal inflammatory infiltrates. In contrast, in GPP, acanthotic changes are accompanied by epidermal neutrophilic infiltrates and neutrophil accumulation beneath the stratum corneum, which cause pustule formation [6, 8]. Such Kogoj's spongiform pustules may not be present in plaque psoriasis lesions, although they may be observed histologically [8].

GPP does not feature the transient primary pustule formation at the periphery of plaques as often seen during exacerbation or irritation of plaque psoriasis [2]. In addition, flare recurrence is a hallmark of GPP, which may not be seen as consistently in plaque psoriasis [2, 7]. There are also several common laboratory anomalies that may differentiate GPP from plaque psoriasis, including leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate, as well as increased alkaline phosphatase, transaminase, and bilirubin levels [2, 7, 8]. The Japanese guidelines for the management and treatment of GPP note that fever, C-reactive protein level, hypoalbuminemia, and white blood cell count are important in the diagnosis, and the grading of severity, of GPP [7]. Concurrent increased alkaline phosphatase, transaminase, and bilirubin levels are linked to neutrophilic cholangitis associated with the flare's skin eruption [31]; neutrophilic cholangitis is not a common feature of plaque psoriasis, and thus may support a diagnosis of GPP.

The female preponderance in GPP is not apparent in plaque psoriasis, in which equal numbers of males and females are affected.

4 Challenges in Determining the Epidemiology of GPP

Since GPP is a rare disease, clinical awareness is limited and inaccurate diagnosis presents challenges to estimating disease prevalence. Considering the available evidence, GPP is understood to affect all populations, but prevalence varies by geographical region and between ethnicities.

There is a large degree of global and regional variability in the prevalence of GPP in the published literature. Interpreting the available data is challenging because of the different methodologies, populations, and definitions of GPP used across studies, as well as the inclusion, or lack of differentiation from, palmoplantar pustulosis. In many cases, data from hospital audits or claims database analyses have not been extrapolated to reflect national population-level prevalence estimates. This means caution must be used in drawing wide-ranging or comparative conclusions of prevalence estimates from the available studies. Over the past two decades, several initiatives that provide national population-level insights into the epidemiology of GPP have been published (Table 1) [32–34].

In France, a study conducted in 2004 using a questionnaire-based assessment in 121 hospital dermatology wards showed 99 cases of GPP across 46 wards, leading to an estimated disease occurrence of 1.76 cases per 1,000,000 persons [32]. The authors noted this estimate was similar to earlier findings in 1998 and 2001 from the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS) French health insurance database [32].

Prevalence data in another study were obtained using questionnaires sent to 575 community center hospitals throughout Japan that captured details of visiting patients with GPP from 1983–1989. The study included 541 patients with GPP and reported a GPP case estimate of 7.46 patients per million, with 2.87 patients per million presenting with acute GPP [33]. A recent analysis of the Japanese national database of health insurance claims suggests this figure could be higher. The database covers approximately 90% of Japanese residents and recorded 4636 codings of pustular psoriasis, which would indicate over 30 cases per million people [35].

A review of a national insurance claims database in the Republic of Korea conducted between 2011 and 2015 estimated a prevalence of 1.2 cases per 10,000 persons. In patients with psoriasis (range 219,429–233,909 across study years), 2.0–2.7% were categorized as having GPP. The authors equated prevalence in the database to national prevalence because of compulsory enrollment in the insurance database for all residents of the Republic of Korea [34].

A US insurance claims review was conducted between 2016 and 2019 using the IQVIA PharMetrics® Plus database. Patients were required to be continuously enrolled in the medical and pharmacy benefits for 6 months before and at least 2 months after the index date (date of diagnosis). This database analysis identified 990 patients with GPP over the study period [36].

It should be noted that the large variations reported across the published studies do not necessarily transcribe an epidemiological reality, and that available data should perhaps be considered as indicative of prevalence only. The variability is likely driven by challenges related to the study of a rare and relatively unknown disease, as well as differences in the distribution of genetic variants and cofactors in separate populations, and reported estimates represent a range that must be interpreted while considering methodological differences.

Table 1 Examples of published GPP estimated cases

Country	Estimated GPP cases	Data source
France	1.76 per 1,000,000 persons	Survey of 121 dermatology clinics in France, 2004 [32]
Japan	7.46 per 1,000,000 persons	Survey of 575 community center hospitals in Japan, 1983–1989 [33]
Republic of Korea	88–124 per 1,000,000 persons	Korean Health Insurance Review and Assessment Service database, 2011–2015 [34]

GPP case estimates have been calculated per million people in this table. Please note, no direct comparisons can be drawn between these studies

GPP generalized pustular psoriasis

5 Adding Evidence to the Understanding of GPP Disease Characteristics and Prevalence

To date, GPP has been described by a range of clinical definitions, which may have hindered accurate collection of prevalence data. These include the classification of GPP as a variant of plaque psoriasis, given the frequent comorbidity of this type of psoriasis in patients with GPP [6]. The introduction of a specific GPP diagnostic code (code L40.1) into the International Classification of Diseases, 10th Revision (ICD-10) in 2015 may aid accurate recording of cases and allow more precise estimates of disease prevalence. It is hoped that the increased awareness of GPP and better differential diagnosis, coupled with the availability of specific pustular psoriasis subtype codes, will drive more accurate prevalence estimates in the future.

As described, the considerable interstudy variation in methodologies and populations means that physicians have an incomplete view of the epidemiology of GPP. It is likely that determining national population-level prevalence estimates will remain challenging for some time. However, database assessments can provide specific insights into certain aspects of GPP, including regional variations, and there is value to the pustular psoriasis community in continuing to generate insights into aspects of GPP epidemiology. While database studies cannot act as proxies for accurate estimates of disease prevalence in the wider population, they can contribute to disease understanding.

In Japan, data were collected for 718 patients with GPP and 27,773 patients with plaque psoriasis between January 2015 and December 2019 using the Japanese Medical Data Vision database. There was a slight female preponderance in patients with GPP (51.5%) compared with those with plaque psoriasis, in which a minority of patients were female (38.7%). Patients with GPP were more likely to have comorbidities than patients with plaque psoriasis; these comorbidities included hypertension, peptic ulcer disease, osteoporosis, type 2 diabetes, gout, psoriatic arthritis, chronic obstructive pulmonary disease, obesity, asthma, insomnia, interstitial pneumonia, thyroid disorders, and other forms of psoriasis [14]. These findings suggested that patients with GPP in Japan had a higher disease burden than those with psoriasis vulgaris [37]. However, it is important to consider that some comorbidities may be related to lifestyle in any given country and will not necessarily be specific to GPP or be generalizable to other geographical regions or ethnicities [10].

6 Conclusions

Since GPP is a rare disease with limited clinical awareness, it is associated with several challenges, including consistent descriptions of the disease characteristics and accurate prevalence estimates. The characteristics of GPP, previously considered to be idiopathic, are gradually being elucidated, and this is aided by increased understanding of genetic variants that contribute to the development of pustular psoriasis, particularly GPP. Although GPP can present with plaque psoriasis, the two diseases are clinically and genetically distinct and require a differential diagnosis and distinct management approaches. Key morphological, disposition, and histological differences between GPP and plaque psoriasis are emerging, as well as genetic markers that could aid disease screening in the future.

As with many rare diseases, forming a clear picture of the clinical characteristics and disease prevalence is challenging. Key barriers include limited disease awareness and the different approaches to assessing prevalence, which are often performed using database studies or small hospital audits. In addition, the data gained from these initiatives are not commonly extrapolated to a national population-level prevalence. Despite the inherent limitations of medical database analyses, these studies can contribute up-to-date insights into various aspects of GPP, including disease characteristics and prevalence in defined cohorts.

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