Journal of Dermatological Science 85 (2017) 235–240

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Clinical profiles of pediatric patients with GPP alone and with different IL36RN genotypes

Yirong Wang[1], Ruhong Cheng[1], Zhiyong Lu, Yifeng Guo, Ming Yan, Jianying Liang, Peichen Huang, Ming Li*, Zhirong Yao*

Department of Dermatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form 4 November 2016
Accepted 21 November 2016

Keywords:
Children
Generalized pustular psoriasis
IL36RN gene mutation
Acitretin

ABSTRACT

Background: IL36RN mutation has been identified as one pathogenesis of generalized pustular psoriasis, but the existence of GPP patients without mutation makes this controversial.
Objective: Our study aimed at assessing the differences in clinical profiles of children with GPP, with and without IL36RN mutation.
Methods: An ambispective case series study involved review of the records of 66 childhood patients with pediatric-onset GPP and without previous psoriasis vulgaris.
Results: c.115 + 6T > C was the most common mutation in this Chinese population with GPP alone. The age at onset was nearly halved in the homozygotes/compound heterozygotes than in IL36RN-negative patients. Besides a more severe inflammatory progression, three minor signs could prioritize patients with GPP for IL36RN screening (confluent lakes of pus (P = 0.002), perianal erosion (P = 0.014), and flexural erosion (P = 0.007)). More patients with the pathogenic mutation converted to ACH than those without mutation ($\chi 2 = 4.773$, P = 0.029). Children with GPP with or without IL36RN mutation responded well to oral low-dose acitretin, but IL36RN-positive cases suffered a much higher half-year recurrence rate after withdrawl of acitretin treatment($\chi 2 = 10.370$, P = 0.001).
Conclusions: Specific clinical features can remind dermatologists of the necessity of sequencing diagnosis. The mild pustular phenotype of those without mutation may imply the possible role of the epigenetic changes of IL36RN, or other IL36-blockers in the pathogenesis. Pediatric patients with GPP alone, both with and without IL36RN mutation responded well to low-dose acitretin.

1. Introduction

Generalized pustular psoriasis (GPP) is a rare and refractory autoinflammatory skin disease, which can be lethal without proper treatment. It is clinically divided into four subtypes: acute generalized pustular psoriasis(AGPP), generalized pustular psoriasis of pregnancy, annular pustular psoriasis(APP), childhood and infantile pustular psoriasis, among which the AGPP type, and the annular type are most commonly described in pediatric patients [1].

In 2011, the IL36RN gene, which encodes interleukin 36 receptor antagonist (IL36Ra) was first identified in the genetic pathogenesis of familial and sporadic GPP [2,3]. Recently, the significant association between homozygous/compound heterozygous IL36RN mutation and GPP alone has been highlighted, which indicates GPP alone is etiologically different from GPP with psoriasis vulgaris (PV) and from PV [4–6]. However, reports of GPP without a previous history of PV in patients with the wild genotype of IL36RN have made the pathogenesis controversial [7,8].

Our group aimed to clarify the differences in clinical profiles of pediatric patients with GPP alone, with and without IL36RN mutation.

Abbreviations: GPP, generalized pustular psoriasis; APP, annual pustular psoriasis; IL36RN, interleukin 36 receptor antagonist; ACH, Acrodermatitis Continua of Hallopeau; URTI, upper respiratory tract infection; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MRSA, methicillin resistant staphylococcus aureus; DITRA, deficiency of interleukin 36-receptor antagonist.

* Corresponding authors at: Department of Dermatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China.
E-mail addresses: aypyslm@163.com (M. Li), dermatology.yao@sohu.com (Z. Yao).

[1] Yirong Wang and Ruhong Cheng contributed equally to this study.

http://dx.doi.org/10.1016/j.jdermsci.2016.11.008
0923-1811/

2. Materials and methods

2.1. Participants

This ambispective study recruited a total of 66 child inpatients with GPP alone who were admitted to our department from January 2013 to July 2014. All the recruited patients fulfilled the following inclusion criteria: a) age <18 years; b) GPP pattern as the first episode without a previous history of PV; c) histopathologic manifestations conforming to GPP. The diagnosis was made by two experienced dermatologists. All participants signed written informed consent before enrollment in the study. Our research was approved by the Ethics Committee of the Shanghai Jiaotong University School of Medicine and was conducted according to the principles of the Declaration of Helsinki.

2.2. Mutation analysis

Genomic DNA samples were isolated from peripheral blood for PCR amplification according to the instructions of TIANamp Blood DNA kits (TIANGEN Biotech, Beijing, China). Comprehensive sequencing of the IL36RN gene, including the coding regions and the exon/intron boundaries, was performed. Primers, synthesized by Sangon Biotech Co, Ltd (Shanghai, China), were designed as described previously [5]. The PCR products were directly analyzed on an Applied Biosystems 3730 DNA analyzer (ABI Corporation, Carlsbad, California, USA). DNA samples for screening were extracted from the peripheral blood of the 66 involved patients and from their parents. We have conducted the gene sequencing for the parents of 34 probands, and failed in other 10 families because of their poor compliance.

2.3. Data collected

A questionnaire was completed for all participants, recording demographic data, including age, gender, residence, and family history of psoriasis. Clinical data such as age of onset, season of onset, predisposing factors, medication history, readmissions and psoriasis-associated clinical features were also recorded. The severity averaging score of the skin lesion was assessed by both the clinicians independently, both at the peak period and at the discharge from our department. Owing to the absence of a standard scoring system for this rare disease, we adopted the scoring system approved by the Japan Ministry of Health Research Group for Rare and Intractable Dermatological Diseases [9].

Peripheral blood parameters and biochemical indicators, including blood routine test, hepatorenal function, electrolyte, IgE, ESR and CRP, were examined weekly during the hospital stay in all the patients. All the chosen parameters have been described in either the pathogenesis or evaluation of the disease [10,11]. The highest value of all the qualitative data recorded during the acute phase of the disease in each patient was selected. Abnormality was defined as beyond the normal upper limit for the biologic variable.

2.4. Treatment and follow-up

All the 66 pediatric patients with GPP received antibiotics therapy for one-week (50 mg/kg ceftriaxone sodium daily) according to their systemic inflammation, those who didn't respond well to the regimen were switched to a low-dose acitretin therapy. Considering the dose-dependent adverse effect of acitretin, the initial oral dose was 0.3–0.4 mg/kg daily.

The dosage was gradually tapered to 0.1–0.2 mg/kg daily as the maintenance dosage when the pustules didn't reappear. Topical moisturizer was prescribed as concomitant treatment. The efficacy of low-dose acitrerin was evaluated by recording the following indexes of correlation: the interval of pyretolysis; the interval of pustule fade; the phase at the first dose reduction; total treatment duration for an admission regimen; the longest remission period after discontinuing therapy with acitretin. Liver function tests were performed every month during the follow-up period to monitor the hepatotoxicity. The Tanner-Whitehouse (TW3) method was used in those who had an uninterrupted regimen of acitretin over one year, in case of the skeletal effects.

2.5. Statistical analyses

Data were analyzed with the SPSS package, version 19.0(SPSS Inc., Chicago, IL, USA). In addition to descriptive analysis, data were presented as mean (SD) or median (range) or proportions. When comparing the differences in quantitative variables between the two subgroups, GPP with and without IL36RN gene mutation, we used an independent sample *t*-test for univariate analysis according to the data distribution. For the bivariate analysis of qualitative variables, Pearson's χ^2 test or the Yate's correction of continuity was used. FDR (false discovery rate) P-value was the adjustment of P-value drawn by the multiple comparisons. The significance level was set at $P < 0.05$.

3. Results

3.1. IL36RN mutation analysis

All the proposituses inherited the mutation from their parents (including the 37 homozygotes, four compound heterozygotes and three pute heterozygotes). No de novo mutation was found. Five variations, namely c.115 + 6T > C, p.Val44Met, p.Asn47Ser, p.Pro76-Leu, and p.Arg102Trp, were identified (Table 1). The variation c.115 + 6T > C was the most common mutation in pediatric patients with GPP (63.6%), followed by the p.Pro76Leu mutation (10.6%). Two mutations, p.Asn47Ser and p.Arg102Trp, were identified in the heterozygous state in four and one patient(s), respectively. Of the four patients with heterozygous p.Asn47Ser mutation, two cases were compound heterozygotes for the c.115 + 6T > C mutation. Thus, a total of 44 patients (66.7%) carried IL36RN mutation, among whom two showed the single heterozygous state for p.Asn47Ser mutation, five, the compound heterozygous state for c.115 + 6T > C and four other mutations, and all the others were homozygotes for c.115 + 6T > C with or without the other four mutations.

A new variant named p.Val44Met has not been reported before. The proband was a compound heterozygote of c.115 + 6T > C and p. Val44Met. The allele frequency of the p.Val44Met variation in normal control was <1% (none in 96 normal control). We performed pathogenicity prediction for the variation with the SIFT software (http://sift.jcvi.org/) and the PROVEAN tool (http://provean.jcvi.org/index.php). The predictive effects were tolerated and neutral respectively, which indicated that the variation might be benign for the protein encoding.

Table 1
IL36RN mutations in GPP patients.

Common mutation	Rare mutation				
c.115 + 6T > C	Aa				AA
	p. Val44Met	p. Asn47Ser	p. Pro76Leu	p. Arg102Trp	
AA	0	2	0	0	22
Aa	1	1	1	1	1
aa	0	1	6	0	30
total	1	4	7	1	53
Frequency of allele	0.008(A)	0.030(G)	0.053(T)	0.008(T)	–