Clinical features of von Zumbusch type of generalized pustular psoriasis in children: a retrospective study of 26 patients in southwestern China*

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Abstract: Background: Von Zumbusch type of generalized pustular psoriasis is a rare variant of psoriasis in children. It can occur in patients with or without psoriasis vulgaris.
Objective: The aim of the study was to discuss the precipitating factors, clinical manifestations, laboratory data and therapy of von Zumbusch type of generalized pustular psoriasis in children from southwestern China and to improve the diagnosis and treatment level.
Methods: A retrospective analysis was conducted for inpatients aged 14 years old or less with von Zumbusch type of generalized pustular psoriasis in our department from 2005 to 2014.
Results: A total of 26 patients were included, of whom four (15.38%) had previous history of psoriasis vulgaris and one (3.85%) had previous history of psoriasis arthropathica. Mean onset age was 6.90 years. Gender distribution was equivalent. Incidence of the disease in summer and autumn was higher than that in winter and spring. Nineteen (73.08%) cases were triggered by infection, two (7.69%) cases were caused by sudden discontinuation of systemic use of corticosteroid. Twenty-four (92.31%) cases had concomitant fever. The initial lesion manifested as non-follicular sterile pustules on erythema. Sixteen patients responded well to acitretin, 11 to *Tripterygium wilfordii Hook F* (TwHF), two to cyclosporine, and one to methotrexate.
Study limitations: This study is a retrospective one and the number of cases is small.
Conclusion: Von Zumbusch type of generalized pustular psoriasis is a rare disease in children, infection is the most common precipitating factor, acitretin is the first-line therapy, traditional Chinese medicine TwHF also can be used.
Keywords: Child; Diagnosis; Drug therapy; Psoriasis

INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that is not uncommon in adults and children, and 1% to 3% of the world's population is affected by it.[1] Psoriasis is divided into four categories in accordance with different clinical presentations: psoriasis vulgaris, pustular psoriasis, psoriasis arthropathica and erythrodermic psoriasis. Except for psoriasis vulgaris, the other three types are not common, especially pustular psoriasis. For children, it's even rarer. According to a separate review from Australia, there were only 0.6% cases with pustular variants in 1262 childhood psoriasis patients.[2] Von Zumbusch type of generalized pustular psoriasis (GPP) is the most severe type of psoriasis, which may be life-threatening and lead to death.[3] It is characterized by waves of widespread fiery redness with superficial sterile pustules that may coalesce to lakes of pus. Scarlatiniform desquamation appears after pustules receded. Most of patients are accompanied by signs of toxicity, fever and leukocytosis. After the original report of von Zumbusch, there had been numerous case studies, but only a few focused on children. In this study, we retrospectively investigated the clinical characteristics, laboratory examination, therapy and systemic effect of 26 pediatric GPP inpatients of Von Zumbusch type treated at dermatology unit of our hospital over the past 10 years. All these 26 cases were younger than 14 years old and from southwestern China.

METHODS

This was a retrospective survey. Twenty-six children younger than 14 years old with Von Zumbusch type of GPP were admitted to the department of dermatology in Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital in southwestern China from January 2005 to December 2014. All data used were from the inpatients medical records.

Data reviewed included sex, age of onset, onset season, family history, previous history of psoriasis vulgaris, inducing factor, body site of onset, accompanied symptoms, laboratory data, pathological examination, treatments and hospitalization days.

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RESULTS

The total 26 pediatric patients consisted of 13 boys and 13 girls, thus the gender distribution was exactly equivalent. Age of onset ranged from 2 months to 13 years old, with mean age of 6.90 years. Among them, five (19.23%) patients had the first episode of von Zumbusch type of GPP within one year old, seven (26.92%) cases within 2-7 years old, and 14 (53.85%) within 8-13 years old. The disease attack was found to be higher in summer and autumn, which consisted 65.38% cases. The duration of disease was from 12 days to 10 years. Two patients had positive family history of psoriasis (an older brother and a grandmother). Four patients (15.38%) had previous personal history of psoriasis vulgaris and one (3.85%) had previous history of psoriasis arthropathica.

Nineteen children had symptoms of upper respiratory tract infection before the onset, like cough and/or runny nose, with eight cases accompanied by tonsillitis. Two cases were triggered by sudden withdrawal of systemic use of corticosteroid. Five cases had no apparent triggers.

The skin lesion started from trunk in 15 patients, from face and neck in two patients, from limbs in one patient, and eight patients presented generalized lesions from the beginning. All patients were acute-onset with diffuse fiery redness and dense superficial pustules. The pustules might extend spirally to the surrounding and coalesced to lakes of pus. After 2-3 days, pustules dried up and gave way to crust and desquamation, but under the crust, pustules could emerge again. A few days later, new pustules appeared in bulk. Anyhow, periodical recurrence made lesions rise and fall. In addition, geographic tongue was found in 10 patients. Eleven patients had nail damage including periungual pustules, thickening nails and thimble nails. Scalp involvement was observed in 10 patients.

Twenty-four patients suffered from fever, body temperature was 38-41ºC. Twelve patients had obviously painful skin, six patients had chills and muscle soreness, one presented knee joint pain, one had convulsion, one had palpitation and four had oral ulcer.

The results of laboratory test are shown in table 1. In addition, 20 patients had pyoculture, 19 were negative except one detected for *Staphylococcus aureus*. Histopathological examination revealed acanthosis, spongiform pustule filled with neutrophils, and neutrophils, lymphocytes infiltration existed in the superficial dermis.

Sixteen patients were treated with systemic acitretin with guardian informed consent, the dose ranged from 0.5 to 1.0mg/kg/d (the maximum dose did not exceed 40 mg/d). Short-term and low-dose prednisone (0.5mg/kg) was used together with acitretin in four patients due to serious toxicity symptoms and severe skin pain. Cyclosporine (5 mg/kg/d) was given to two patients. Methotrexate was introduced to the one with psoriasis arthropathica (10 mg qw). Eleven patients were treated with *Tripterygium wilfordii* Hook F (TwHF, an anti-inflammatory Chinese herbal medicine) together with acitretin or not. All patients received supporting treatment like fluid infusion, hypothermia, maintaining water and electrolyte balance and albumin infusion, etc. The blood and urine routine, liver and renal function and blood lipid were periodically checked. After pustules faded away, corticosteroid cream and emollient were applied to promote recovery.

With the exception of four patients who left the hospital without doctor's permission, due to economic reasons, 22 patients got satisfactory clinical response. The mean time of body temperature returned to normal was 8.71±4.58 days, the mean hospitalization time was 18.78±6.88 days. No patients presented serious complication or died.

DISCUSSION

Von Zumbusch type of GPP was first described by von Zumbusch. It was also called acute generalized pustular psoriasis according to its clinical characteristics. This variant of psoriasis rarely affects children; the incidence in children still lacks specific epidemiological data. The disease started at the mean age of 6.90 years old in our data, what is in accordance with other published reports. [4,5] Some studies indicate that the incidence in male is slightly higher than in female children, while our data showed that there was no significant difference between them. [1,4] Our study also displayed that the most frequently occurring season is summer and autumn, which is different from psoriasis vulgaris, which predominates in winter.

The trigger factors are numerous, including infection, untimely withdrawal or cutting down of corticosteroid, operations, pregnancy, hypocalcemia, medications, mental stress, but some of which are not obvious. In our group, the attack was mostly induced by infection, similar to other reports in China. [6] The specific pathogenesis of GPP is still unclear, it has been considered as a subtype of psoriasis for a long time. GPP can occur in people with or without history of psoriasis vulgaris, so it has been considered to have certain internal relation with psoriasis vulgaris. Two distinct types were classified by Ohkawara *et al* – patients with a personal history of psoriasis vulgaris (pso+ GPP) and patients without a personal history of psoriasis vulgaris (pso- GPP). [7] They found that in pso+ GPP group, the disorder was frequently precipitated by corticosteroid withdrawal, whereas in the pso- GPP group, infection was the most common triggering factor. The age of onset was earlier in pso- GPP group. However, a study including 92 GPP patients in China had found the opposite results.[8] In our study, pso+ GPP cases were all induced by infections, but the number was too small (four cases), so it wasn't suitable to draw conclusions. From a genetic point of view, some cases had family aggregation whether in psoriasis vulgaris or pustular psoriasis, so gene may play a role in the pathogen-

Table 1: Results of laboratory tests in 26 patients

	Leukocytosis	Thrombocytosis	Increased ESR	Increased CRP	Hypocalcemia	Hypoproteinemia	Increased AST	Increased ALT	Increased IgE
No. of patients (%)	20(76.92)	12(46.15)	13(50.00)	17(65.38)	11(42.31)	17(65.38)	6(23.08)	5(19.23)	12(46.15)

esis of psoriasis. But HLA susceptibility loci that are significantly related with psoriasis vulgaris (HLA-A1, HLA-B37 and HLA-DRw10) were not closely related to pustular psoriasis, indicating that these may be two different diseases. In recent years, the IL-36RN gene mutations had been found in several familial and sporadic cases in Africa, Europe and Asian. [9-11] This new discovery indicates that a homozygous or compound heterozygous mutation in the gene encoding IL-36RN may cause GPP at least in some patients.

The onset of Von Zumbusch type of GPP is sudden, usually accompanied by systemic symptom of toxicity, such as fever, fatigue, leukocytosis and so on. The involvement of skin is universal, with a large number of pustules and pus lakes followed by peeling and desquamation. Complications like a secondary infection, sepsis, electrolyte disturbance, hypoproteinemia, and even liver and kidney damage may occur if treatment is not active and prompt. [12,13] The differential diagnosis that should be first considered is acute generalized exanthematous pustulosis (AGEP). It's difficult to distinguish these two diseases only according to the lesions, but different triggering factors, pathology and prognosis can help. AGEP is mainly induced by recently new applied drug, which is self-limited after the withdrawal of the specific drug. Corticosteroid is the first-line therapy and the prognosis is generally good. The presence of eosinophils, necrotic keratinocytes, a mixed interstitial and mid-dermal perivascular infiltrate and absence of tortuous or dilated blood vessels are in favor of AGEP. [14]

There is a lack of treatment guidelines and evidenced-based researches on the treatment of pediatric GPP. On the basis of a systematic review of systemic medications for pediatric pustular psoriasis, the most common therapies were acitretin, cyclosporine and methotrexate. [15] Among them, acitretin is the most common application, because of the fast response and good cost-benefit ratio. Particular concerns with acitretin are premature epiphyseal closure and lipid metabolism disorder, hence, monitoring with X-rays every 12-18 months and blood lipids testing every 1-3 months have been recommended for children receiving acitretin. [16] Sixteen children in our study who used acitretin all got good response and no serious adverse events were observed during hospitalization, but information on long-term follow-up is lacking. Cyclosporine is beneficial for induction of clearance, particularly during acute pustular flares, but potential cumulative toxicity for kidneys and hypertension should be monitored. [17] Corticosteroid should be only short-term and small-amount used for acute-stage or life-threatening patients, because of the long-term adverse events and easily to trigger recurrence. The use of biologics in recent years has gradually increased. Based on case reports, experts have recommended using etanercept as a first-line and infliximab as a second-line treatment for pediatric pustular psoriasis, but there are no relevant experiences because the expensive price limit its use. [18]

Chinese herbal medicine, as the essence of Chinese traditional medical science, also plays an important part in the treatment of psoriasis, but evidence-based studies are still lacking. The most frequently applied is a drug called "Lei Gong Teng", which is an extract of the very cheap herb TwHF. Triptolide has turned out to be the active substance of TwHF extracts and has been shown to exert potent anti-inflammatory and immunosuppressive effects, so TwHF is widely used to treat autoimmune and/or inflammatory diseases. [19-21] In Han *et al.*'s review, the use of TwHF had good effect in the treatment of plaque, pustular and erythrodermic psoriasis. [22] Complete blood count, liver and kidney function and ECG are commonly monitored every two weeks for patients receiving TwHF because of its adverse events.

CONCLUSION

We report 26 pediatric cases of von Zumbusch type of GPP in the past 10 years in our hospital. It has a good prognosis in children if patients are treated correctly and in time. Acitretin and cyclosporine are good treatment options. For patients with poor economic condition, the Chinese medicine like TwHF can be used. But, this study has some limitations. For example, it was neither multicentric nor a prospective study, as well as missing follow-up data. ❑

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