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BRIEF REPORT

NLRP12 autoinflammatory disease: a Chinese case series and literature review

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Abstract As one of the systemic autoinflammatory diseases (SAIDs), the nucleotide-binding oligomerization domain-like receptor protein (NLRP)12 autoinflammatory disease (NLRP12-AD) is an autosomal dominant disorder associated with NLRP12 mutation. SAIDs have been hardly reported in the Chinese population, and NLRP12-AD has been reported only in Caucasians. We report the first case series of NLRP12-AD in the Chinese population coupled with literature review. Three Han Chinese adult patients with clinical phenotype suggestive of NLRP12-AD carrying NLRP12 variants were treated by the authors in 2015. Their phenotype and genotype were carefully studied. A PubMed search for SAIDs was conducted between January, 1990 and January, 2016, and we focused on NLRP12-AD. All three adult patients developed periodic disease in adulthood. They presented with recurrent fever (n = 3), polyarthralgia (n = 3), myalgia (n = 3), urticaria (n = 2), lymphadenopathy (n = 2), and erythema nodosa (n = 1). All patients carry the NLRP12 mutation F402L. Based upon our analysis of a total of 26 patients with NLRP12-AD in the literature, both familial and sporadic cases were equally reported and late-onset cases accounted for 28 %. NLRP12-AD patients typically present with periodic fever, urticaria-like rash, arthralgia/arthritis, myalgia, and lymphadenopathy. Genotyping identifies the NLRP12 gene mutations, notably F402L (55 %). Relative to the literature reports, our patients had the similar phenotypic and genotypic features. Patients with NLRP12-AD usually respond to glucocorticoid therapy. Our report is the first to confirm the presence of NLRP12-AD in the Chinese population. It highlights the importance of screening NLRP12 in patients with unexplained periodic fever syndrome.

Keywords Autoinflammatory disease · Cryopyrin-associated periodic syndrome · Familial cold autoinflammatory syndrome · *NLRP12*-autoinflammatory disease · Nucleotide-binding oligomerization domain-like receptor protein · Urticaria

Introduction

Systemic autoinflammatory diseases (SAIDs) are a genetically heterogeneous group of rheumatic diseases that are driven by abnormal activation of the innate immune system [1]. In its inception of this group of diseases, SAIDs were defined to have recurrent episodes of fever and systemic inflammation without high titer of autoantibodies or high number of antigen-specific T lymphocytes [2]. Most recently, SAIDs have been defined as clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition [3]. The prototypic SAIDs are hereditary monogenic periodic fever syndromes, including familial Mediterranean fever (FMF), TNF receptor-

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associated periodic syndrome (TRAPS), hyper IgD with periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndrome (CAPS). With application of more advanced molecular techniques notably the second generation sequencing, the SAIDs spectrum is rapidly expanding. One of the examples is nucleotide-binding oligomerization domain-like receptor protein (*NLRP*)12 autoinflammatory disease (NLRP12-AD). This disease is also known as familial cold autoinflammatory syndrome 2 (FCAS 2) and is rare autosomal dominant disease that is characterized by recurrent fever and musculoskeletal symptoms associated with the mutations in the *NLRP12* gene [4, 5]. SAIDs have been primarily identified in Europe, Mediterranean region, and North America [6]. These diseases have been rarely reported in Asia except occasional publications in Japan [7] and South Korea [8]. These diseases can be seen in both pediatric and adult populations [9]. To our knowledge, we have not seen any reports of SAID cases in China other than a single report of familial Blau syndrome [10] and familial cold autoinflammatory syndrome (FCAS) [11]. Herein, we report the first case series of SAID in the Chinese patients and in conjunction with the literature review to illustrate the characteristic phenotype and genotype of NLRP12-AD.

Patients and methods

Three adult Chinese patients were selected and included in the study. These patients were referred to our tertiary medical center and treated by the lead and two co-authors, and complete medical records were established and detailed data were collected and documented. This research was approved by the Institutional Review Board of Peking Union Medical College Hospital and performed according to the Declaration of Helsinki. Informed consent was obtained from all participants. Whole genome sequencing using Sanger sequencing including periodic fever syndrome genes (*MEFV*, *TNFRSF1A*, *MVK*, *NLRP3*, *NOD2*, and *NLRP12*) for mutations was performed in the Center for Genetic Testing, Beijing, China.

In addition, a PubMed literature search for relevant information of periodic fever syndromes, particularly NLRP12-AD, was conducted between January,1990 and January, 2016, using the indexing words: "autoinflammatory disease," "periodic fever syndrome," "*NLRP12*-autoinflammatory disease," "familial cold autoinflammatory syndrome 2," and "*NLRP*". We collected and analyzed the detailed data concerning the phenotypic and genotypic characteristics and other data of NLRP12-AD patients reported in the English literature.

Results

Case descriptions

Patient 1

A 46-year-old Han Chinese man presented with recurrent fever since the age of 31. He had noted disease attacks once every several weeks to years, with each flare lasting 1–2 weeks, and the disease flares were characterized by high fever (>40 °C), headache, arthralgia in the lower extremities, and myalgia. Recurrent erythema nodosa were observed during the disease course, and a skin biopsy showed neutrophilic infiltration in the fatty tissues. He had the similar but more frequent episodes recently, with mild weight loss and splenomegaly. He denied any chest pain or abdominal pain/diarrhea. Leukocytosis and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were noted during the disease attacks, and they normalized in between the episodes. Serological markers for systemic autoimmune diseases, including antinuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor were all negative. There was no report of family history of periodic fever syndromes. Anti-tuberculous therapy was initiated but without noticeable benefits over 9 months of observation. Genetic testing for periodic fever syndromes was positive for heterozygous *NLRP12* F402L (c.1206 C>G) (Fig. 1a). The patient received prednisone (0.5 mg/kg/d) for NLRP12-AD with a complete response, and he was asymptomatic with prednisone 10 mg daily. Biologic agents were not tried due to his financial issues.

Patient 2

A 49-year-old Han Chinese man presented with episodes of fever since the age of 47. He had disease flares once every several months and each episode lasted for 3–4 weeks, with an interval of several months. These flares were associated with high fever (>40 °C), chills, itchy urticaria (Fig. 1b), upper limb arthralgia without swelling, and generalized myalgia. There was no family history of periodic fever syndromes. Radiographic examination showed superficial lymphadenopathy and mild splenomegaly, and a cervical lymph node biopsy revealed reactive hyperplasia. Leukocytosis, elevated ESR, and CRP were present during the attacks, and they normalized in between the disease episodes. Serological markers were negative for systemic autoimmune disorders. Further genetic testing identified the presence of the *NLRP12* variant, heterozygous for F402L (c.1206 C>G) (Fig. 1b). NLRP12-AD was diagnosed, and he received prednisone (0.8 mg/kg/d) initially and was asymptomatic on prednisone 5 mg daily.

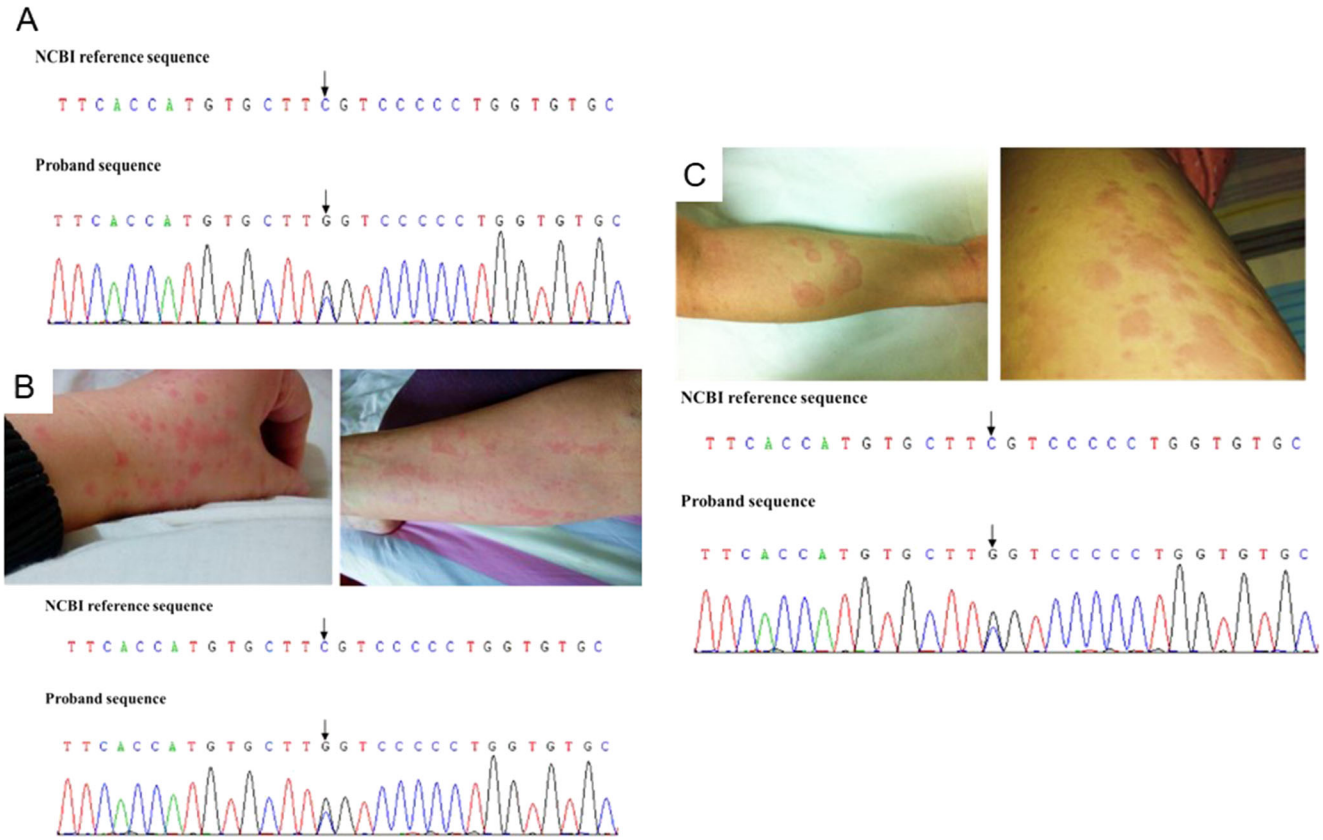

Fig. 1 **a** (*Patient 1*) *NLRP12* mutation analysis and phenotype. *Arrows* indicate the position of the mutation. **b** (*Patient 2*) Urticarial rash on the limbs. *Arrows* indicate the position of the mutation. **c** (*Patient 3*) Urticarial rash on the arms and legs. *Arrows* indicate the position of the mutation

Patient 3

A 40-year-old Han Chinese woman presented with episodes of fever for the previous year. The disease flares were frequently triggered by generalized exposure to cold and comprised high fever (38.5–40 °C), itchy urticaria (Fig. 1c), polyarthralgia, headache, sore throat, and superficial lymphadenopathy. These symptoms lasted several weeks followed by a disease-free interval of several weeks to several months. There was no report of family history for periodic fever syndromes. A cervical lymph node biopsy revealed reactive hyperplasia, and a skin biopsy showed non-specific dermatitis. ESR and CRP levels were elevated during the attacks and decreased in between the flares. Serum ANA and ANCA were negative. Genetic testing identified the compound heterozygous *NLRP12* variant F402L (c.1206 C>G) (Fig. 1c) and *MEFV* variant G304R. Due to a lack of a response to colchicine treatment (0.5 mg, three times a day), therapy was initiated for NLRP12-AD given the presence of the *NLRP12* variant. She received prednisone 30 mg daily followed by a maintenance dose of 10 mg daily and loratadine, and she noted 70 % improvement in the frequency and severity of the disease flares. The patient was initially treated with methotrexate without benefit.

Literature review

Six English-language publications detailing a total of 26 cases of NLRP12-AD patients were identified through the PubMed search [4, 12–16]. The clinical phenotype and genotype of the 26 patients and our three patients are summarized in Table 1.

The vast majority of the patients were whites; over 50 % of patients reported a positive family history, and sporadic cases accounted for 45 %. Approximately 70 % (20/29) of patients had disease onset in childhood, and the remaining (8/29) developed the disease in adulthood, with overall ratio of male to female 7:5.

The clinical features were periodic fever (27/29, 93 %), rash, primarily urticaria (18/29, 62 %), myalgia (17/29, 59 %), polyarthralgia/arthritis (17/29, 59 %), abdominal pain/diarrhea (12/29, 41 %), headache (10/29, 34 %), lymphadenopathy (8/29, 28 %), splenomegaly (3/29, 10 %), sensorineural deafness (3/29, 10 %), and thoracic pain (3/29, 10 %). Patients reported cold exposure as a trigger in 19/29 (66 %). Approximately 30 % (8/29) of patients had reported elevated acute phase reactants. Glucocorticoids and anti-histamine drugs were effective in the reported cases (11/29, 38 %). The *NLRP12* gene mutations were found in all patients, with p. F402L

Table 1 Comparison of clinical manifestations of 29 patients with *NLRP12*-autoinflammatory disease

Clinical features	Ref. 4	Ref. 12	Ref. 13	Ref. 14	Ref. 15	Our study
Cases, *n*	5	4	2	6	9	3
Country	3/5 Guadeloupe, 2/5 ND	Italian	1/2 Armenian 1/2 Italian	ND	ND	Chinese Han
Age of onset	Child*	2/4 Child, 1/4 adult**, 1/4 ND	Child	2/6 Child, 4/6 adult	Child	Adult
Family history	+ From 2 families	+ From 1 family	−	4/6 +	3/9 +	−
Gender	4M 1F	1M 3F	ND	ND	ND	2M 1F
Fever	+	+	+	5/6 +	8/9 +, 1/9ND	+
Duration of fever	2–10 days	7–15 days	Several hours to 3 days	1 day to 3 weeks	ND	1 To several weeks
Interval of fever	3 to 4 weeks	ND	1 to 4 weeks	2/6 12 days,4/6 ND	ND	Several weeks to years
Cold trigger	+	3/4 +	+	+	2/9 +	1/3 +
Rash	3/5 Urticaria	2/4 Urticaria, 1/4 itchy	1/2 Rash on cheeks	4/6 Urticaria, 1/6 maculopapular, 1/6 pseudofolliculitis,1/6 swelling of dorsum of hands and feet	4/9 Rash	2/3 Urticaria, 1/3 erythema nodosa
Headache	3/5 +	1/4 +	1/2 +	3/6 +	ND	2/3 +
Eye involvement	ND	1/4 Neuropapillitis	−	1/6 Conjunctivitis	−	−
Oral ulcer	1/5 +	1/4 -, 3/4 ND	ND	1/6 +	2/9 +	−
Sensorineural deafness	2/5 +	−	−	1/6 +	ND	−
Thoracic pain	ND	ND	−	1/6 +	1/9 +	1/3 +
Dyspnea	ND	ND	ND	1/6 +	ND	−
Diarrhea/abdominal pain	1/5 +	ND	+	2/6 +	6/9 +	1/3 +
Arthritis/arthralgia	3/5 +	3/4 +	−	5/6 +	3/9 +	+
Myalgia	2/5 +	3/4 +	+	5/6 +	3/9 +	2/3 +
Lymphadenopathy	1/5 +	ND	1/2 +	2/6 +	1/9 +	+
Splenomegaly	ND	ND	ND	ND	1/9 +	2/3 +
Increased APRs	1/5 +	ND	1/2 +	3/6 +	ND	+
Response to corticosteroids	1/5 +, 4/5 ND	2/4 +	ND	5/6 +, 1/6 ND	ND	+
Response to anti-histamines	ND	1/4 +	ND	1/6 +, 5/6 ND	ND	1/3 +, 2/3 ND
Response to colchicine	1/5 −, 4/5 ND	ND	ND	1/6 −, 5/6 ND	ND	1/3 −, 2/3 ND
Response to NSAIDS	ND	2/4 +	ND	2/6 +, 2/6 -, 2/6 ND	ND	ND
NLRP12 mutation	3/5 R284X,2/5 c.2072+ 3insT	D294E	R352C	5/6 F402L,1/6 G 448A	8/9 F402L,1/9 H304Y	F402L

ND no data, *APRs* acute phase reactants, *NSAIDS* nonsteroidal anti-inflammatory drugs

*Child age <10

**adult age >18

Table 2 Distinguishing features of FCAS, NLRP12-AD, and cold-induced urticaria

	FCAS	NLRP12-AD	Cold-induced urticaria
Inheritance pattern	Autosomal dominant	Autosomal dominant	Usually sporadic
Family history	+++	++	−
Gene mutations	*NLRP3*(missense)	*NLRP12*(nonsense and splice site)	Unknown
Early onset	++	++	−
Cold induced	++	++	+
Immediate onset after cold exposure	−	−	+++
Fever	+++	+++	−
Skin	Urticaria-like rash, maculopapular	Primarily urticaria	Pruritis, urticaria
Conjunctivitis	+	+	−
Arthralgia	+++	++	−
Myalgia	+	++	−
Chest pain	−	+	−
Abdominal pain	−	+	−
Lymphadenopathy/ splenomegaly	−	+	−
Headache	−	+	−
Sensorineural hearing loss	−	+	−
Elevated APRs	++	++	−

+++ always, ++ most, + some, − none

FCAS familial cold autoinflammatory syndrome, *NLRP12-AD* NLRP12 associated autoinflammatory disease, *APRs* acute phase reactants

(c.1206 C>G) being the most frequent (16/29, 55 %), and the other reported *NLRP12* gene variants were p. R284X (c.850 C>T), c.2072+3insT, p. D294E (c.882 C>G), p. R352C (c.1054 C>T), p. G448A (c.1343 G>C), and p. H304Y (c.910 C>T).

Discussion

Nucleotide-binding oligomerization domain-like receptors (NLRs) are divided into four subfamilies based upon the type of N-terminal domains [17]. The *NLRP*s subfamily contains *NLRP1-NLRP14* that is characterized by the presence of pyrin domain (PYD) [18]. The NLRP protein is structurally characterized by a tripartite architecture containing a central nucleotide-binding domain (NBD or NOD), a specific N-terminal PYD, and a C-terminal portion consisting of a variable series of leucine-rich repeats (LRRs) [19]. The PYD and LRR domains play an important role in the protein-protein interactions of pyrin, and NBD domain exhibits ATPase activity and regulates oligomerization.

Among the *NLRP* subfamily pathogenic genes, the *NLRP3* mutations encoding a dysfunctional protein, cryopyrin, have been associated with CAPS. Cryopyrin is a key component of the inflammasome directly involved in the interleukin (IL)-1β processing and secretion, and ultimately systemic inflammation [20, 21]. CAPS represents a continuous spectrum of one single SAID, including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic, cutaneous, articular syndrome (CINCA). These disorders share common clinical features, such as periodic fever and urticarial rash. Jeru et al. reported five patients from two separate families with the similar clinical phenotype to FCAS but with no detection of the *NRLP3* mutations in 2008 [4]. They identified two disease-associated mutations in the *NLRP12* gene among these patients and thus termed the hereditary SAID as NLRP12-AD [4]. Further studies have shown that *NLRP12* is closely related to the inflammasome scaffold, *NLRP*3. While the precise function of *NLRP12* is debatable, it forms inflammasome or regulates inflammasome function [17]. *NLRP12* is reported to regulate inflammation by activation of caspase-1 through inflammasome, leading to the processing and secretion of IL-1β [22, 23]. Meanwhile, caspase-1 induces cell apoptosis [24] and attenuates the negative regulation of NF-κB signaling induced by TNF [12]. To better understand the similarities and differences between FCAS, NLRP12-AD, and cold-induced urticaria, we summarized the phenotypic and genotypic characteristics and the functions of the gene mutations in these disorders (Table 2) [25, 26].

To date, there are only a few case series of NLRP12-AD reported in the literature, mostly in the Caucasian population

[4, 12–16]. We report the first cases of Chinese patients with NLRP12-AD in China, suggesting that NLRP12-AD can occur in multiple ethnic groups. As indicated above, NLRP12-AD is similar in the clinical phenotype to CAPS, notably FCAS. NLRP12-AD as an autosomal dominant disease can sporadically occur in both children and adults [12, 14]. Compared with the literature reports, our patients presented with the similar clinical phenotype. Several *NLRP12* gene mutations have been identified in NLRP12-AD, among which the mutation F402L is the most frequent as in our cases. In a very recent report of Chinese pedigree of FCAS [11], a novel *NLRP12* nonsense mutation Trp408X was identified without variations in *NLRP3* gene. We highly suspect this Chinese pedigree should be diagnosed as NLRP12-AD (FCAS 2) rather than FCAS.

Therapeutically, glucocorticoids and anti-histamine drugs are largely effective in the majority of patients with NLRP12-AD as in our cases. Considering the pivotal role of IL-1β in the pathogenesis of NLRP12-AD, IL-1 inhibitors may be beneficial. However, it has been reported that some patients albeit initially responsive eventually developed resistance to anakinra within a few months of treatment [16]. Unlike its definite therapeutic role in FCAS, IL-1 antagonists may be further evaluated for its potential efficacy in the treatment of NLRP12-AD.

In summary, the presence of NLRP12-AD in the Chinese population suggests NLRP12-AD may be a global disease. Our report will further increase the awareness of the SAIDs, and timely recognition and screening of the *NLRP12* gene mutations in patients with unexplained periodic fever syndrome may reduce misdiagnosis and improper treatment.

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Compliance with ethical standards This research was approved by the Institutional Review Board of Peking Union Medical College Hospital and performed according to the Declaration of Helsinki.

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Disclosures None.

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