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ORIGINAL ARTICLE

The clinical phenotype and genotype of NLRP12-autoinflammatory disease: a Chinese case series with literature review

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Abstract

Background The nucleotide-binding oligomerization domain-like receptor protein 12 (NLRP12)-autoinflammatory disorder (NLRP12-AD) is a rare autoinflammatory disease characterized by recurrent fever, rash as well as musculoskeletal symptoms, which is rarely reported in Asian populations.

Methods Three cases of NLRP12-AD presented to our hospital were studied after parental consents were obtained. Clinical presentations were recorded on a standardized case report form. Mutations of *NLRP12* were detected by primary immunodeficiency disease panels and further examined by Sanger sequencing. PubMed literature search for relevant studies of systemic autoinflammatory disorders, especially NLRP12-AD between January, 2000 and January, 2019 was carried and the clinical data were summarized. Comparisons were made between groups in terms of onset age and of ethnicity.

Results All our patients presented with fever, rash and arthritis/arthralgia, and sensorineural as well as sensorineural deafness (1/3), uveitis (1/3), abdominal pain (1/3), and myalgia (1/3). Two novel mutation variations, p.W581X and p.L558R, are reported here. In addition, we also found that two patients inherited the mutated alleles from their healthy parents, and this may be evidence of haploinsufficiency.

Conclusions Although the genotypes are similar, the clinical manifestations between Chinese patients and Western patients vary thus highlighting the possible influence of ethnic and environmental factors. On the other hand, some genetic mutations may lead to specific phenotype, as we have found a high prevalence of sensorineural hearing loss among p.R284X patients.

Keywords Autoinflammatory disease · NLRP12-AD · Recurrent fever

Introduction

Many members of nucleotide-binding oligomerization domain-like receptor protein (NLR) family are important components of inflammasomes, including NLRP1, NLRP3, NLRC4, NLRP6, NLRP7, and NLRP12 [1]. Thus mutations in those genes may produce atypical inflammasomes and cause inflammasomopathies, an important group in systemic autoinflammatory disorders (SAIDs). The NLRP12-autoinflammatory disorder (NLRP12-AD), also called familial cold autoinflammatory syndrome 2 (FCAS 2), is such a disease caused by an autosomal dominant mutation of *NLRP12* [2]. Like other diseases of SAIDs, it was reported that patients with NLRD12-AD usually presented with recurrent fever, rash, as well as musculoskeletal symptoms [3]. While, in most cases of SAIDs, the symptoms happened in childhood, it was reported that these diseases could be found in adult populations [4]. Recently, Shen et al. reported the first case series of NLRP12-AD in the Chinese adult patients [5]. Here, we report a case series of pediatric-onset NLRP12-AD in Chinese population and compare the clinical presentations and genetic phenotype between Chinese and Western patients as well as the differences between pediatric-onset patients and late-onset patients.

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Methods

Patients

This study was undertaken at Peking Union Medical College Hospital (PUMCH). Clinical presentations were recorded on a standardized Case Report Form. All patients were children admitted to our hospital for recurrent fever as well as rash. After excluding infection and cancer as etiologies, SAIDs were suspected and DNA sequencing were carried out after written informed consent for genetic studies was obtained from parents or guardians. This research was approved by the Institutional Review Board of PUMCH and performed under the guide of the Declaration of Helsinki.

Literature review

We did a PubMed literature search for relevant studies of SAIDs, especially NLRP12-AD between January, 2000 and March, 2019, with the indexing words: "NLRP12-autoinflammatory disease", "familial cold autoinflammatory syndrome 2", "autoinflammatory disease", and "NLRP12". Eleven articles reporting cases of NLRP12-AD were found and we summarized the clinical presentations as well as their *NLRP12* mutations.

Gene trapping high-throughput sequencing

Peripheral blood DNA samples from patients and their parents were extracted. With the application of primary immunodeficiency diseases (PIDs) panel, we detected 237 PIDs related genes by gene trapping high-throughput sequencing. Suspected genes were chosen according to the following criteria: variations types are not synonymous mutations; minimum audible field < 0.02; and variations meet the Mendelian genetic model (at least one variation in AD genetic pattern genes, one homozygous or two heterozygous variations in AR genetic pattern genes). If any suspected genes or mutations were found, we would search the mutations in Human Gene Mutation Database and Online Mendelian Inheritance in Man Database and speculate the pathogenicity of the mutations by sorting intolerant from tolerant (SIFT), Polyphen, MutationTaster, and GERP++. And the mutation locus of the patient and their parents would be verified by Sanger sequencing.

Statistical analysis

Data were analyzed by Student's *t* tests with the Statistical Product and Service Solutions (SPSS) software; $P < 0.05$ would be considered as significant.

Results

Clinical cases in our institution

The first patient had suffered from recurrent fever with the macular rash, since she was 3. One year later, intermittent arthralgia was noticed. Laboratory data showed leukocytosis and increased platelets and enhanced inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). She also had a low titer (1:80) of anti-nuclear antibodies (ANA). She denied any chest pain, abdominal pain or any neural symptoms. No family history of recurrent fever was found. She carried a novel mutation of *NLRP12*, c.1742G>A, p.W581X, which was inherited from her mother, who denied any symptoms of NLRP12-AD (Table 1). It was a nonsense mutation and has not been reported in NLRP12-AD literature yet. Searching through different databases including 1000g2015aug_all, ESP6500si, ExAC_ALL, and ExAC_EAS, we found that the frequency of this allele in healthy people was quite low (0, 0, 8.24×10^{-6}, 0.0001, respectively) in healthy people. Considering that nonsense mutations always produce truncated proteins or unstable proteins and the low frequency, it is a likely pathogenic mutation.

Patient 2 presented with episodes of fever with myalgia, since she was 5 years old. The disease flares were characterized by high fever (T_{max} 40 °C), urticarial rash throughout the body, arthralgia in knees, hip joints, as well as elbow joints. She developed sensorineural hearing loss at the age of 9 and splenomegaly was also found. Laboratory data showed elevated acute phase reactants (APRs, including ESR, CRP, and ferritin). Magnetic resonance imaging (MRI) showed bilateral hip joints effusions. No autoantibodies including ANA and anti-neutrophil cytoplasmic antibodies (ANCA) were found. Her parents denied any family history of periodic fever syndrome. Genetic studies discovered a pathogenic mutated allele of *NLRP12*, c.2072+2dupT, which was reported in the first case of NLRP12-AD [3]. Notably, her father also carried the same mutation, but did not show any related symptoms such as fever or rash (Table 1).

Patient 3, a 7-year-old girl, was admitted to PUMCH in 2010. Her chief complaint was recurrent fever with rash, since she was 6 months old. She also developed hearing loss and uveitis when she was about 1 years old. Her symptoms usually lasted for 2–8 days, with an interval of 1–4 months. She occasionally suffered from abdominal pain. Musculoskeletal symptoms occurred when she was 3 years and 6 months, especially in her knees. Increased ESR, CRP, and platelets were observed during the febrile period, while the autoantibodies were all negative. There was no family history of recurrent fever. Gene trapping high-throughput sequencing revealed a de novo mutation of *NLRP12*, c.

Table 1 Clinical and genetic features of our NLRP12-AD series

Variables	Patient 1	Patient 2	Patient 3
Age of onset (y)	3	5	0.5
Family history	−	−	−
Gender	Female	Female	Female
Fever	+	+	+
Cold trigger	−	−	−
Rash	+	+	+
Headache	−	−	−
Eye involvement	−	−	+
Sensorineural deafness	−	+	−
Oral ulcer	−	−	−
Thoracic pain	−	−	−
Dyspnea	−	−	−
Diarrhoea/abdominal pain	−	−	+
Arthritis/arthralgia	+	+	+
Myalgia	−	+	−
Lymphadenopathy	−	−	−
Splenomegaly	−	+	−
Increased APRs	+	+	+
NLRP12 mutation	c.1742G>A, p.W581X	c.2072+2dupT	c.1673T>G, p.L558R
Inherited derivation	Mother	Father	De novo

NLRP12-AD nucleotide-binding oligomerization domain-like receptor protein 12-autoinflammatory disorder, *APRs* acute phase reactants, + positive, − negative

1673T>G, and p.L558R, which has not been reported in previous cases (Table 1). We speculated the pathogenicity of the mutation by SIFT, PolyPhen, MutationTaster, and GERP++, and the results were: tolerable, probably damaging, disease causing, and nonconserved, respectively.

Data from literature review

Eleven English-language published papers reporting a total of 52 cases of NLRP12-AD were identified by searching in PubMed [3, 5–14]. The clinical presentations and genetic mutations of *NLRP12* are summarized in Table 2 and Supplementary Table 1.

Most patients (45/55, 82%) were Caucasian from Western countries. Approximately half (18/40, 15 unknown) of them had the family history of recurrent episodes of fever. It seemed that gender did not contribute to occurence of the disease, since the male:female ratio was 21:23. Among those patients, most of them developed the disease in childhood (early onset), while only nine adult patients were reported, referred to as late onset hereafter.

Next, we compared the clinical differences between Chinese patients and western patients. Up to now, there are ten cases of Chinese NLRP12-AD including those three patients

Table 2 Major clinical manifestations of NLRP12-AD patients ($n=55$)

Variables	*n*	%
Late onset	9	16
Gender ratio (male:female)	21:23	
Family history	18	45 ($n=40$)
Fever	51	95
Cold trigger	26	47
Rash	31	56
Headache	14	25
Eye involvement	3	5.5
Sensorineural deafness	6	11
Oral ulcer	5	9.1
Thoracic pain	3	5.5
Dyspnea	1	1.8
Diarrhoea/abdominal pain	18	36
Arthritis/arthralgia	27	47
Myalgia	21	38
Lymphadenopathy	7	13
Hepatosplenomegaly	6	11
Increased APRs	19	71 ($n=28$)

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in our center. The age of onset and gender ratio were similar in these two groups. It seemed that the frequency of rash in Chinese patients was much higher than that in western patients (100% vs 47%, $P < 0.001$), and arthritis occurred more frequently in Chinese patients (80% vs 42%, $P = 0.026$). On the other hand, western patients were more likely to suffer from oral ulcer (11% vs 0%, $P = 0.024$). On the other hand, increased APRs might be more indicative in diagnosis of NLRP12-AD in Chinese population, for all patients in China had increased APRs, while the percentage in western countries was about 42% ($P = 0.002$) (Table 3).

Table 3 Comparison of major clinical features in Chinese patients with those of Western patients

Variables	Chinese ($n = 10$)	Western ($n = 45$)	P
Early onset	70 (7/10)	87 (39/45)	0.323
Gender ratio (male:female)	4:6	17:17	0.588
Fever	100 (10/10)	93 (42/45)	0.410
Cold trigger	50 (5/10)	47 (21/45)	0.852
Rash	100 (10/10)	47 (21/45)	< 0.001
Headache	20 (2/10)	27 (12/45)	0.669
Eye involvement	10 (1/10)	4.4 (2/45)	0.493
Sensorineural deafness	10 (1/10)	11 (5/45)	0.921
Oral ulcer	0 (0/10)	11 (5/45)	0.024
Thoracic pain	10 (1/10)	4.4 (2/45)	0.493
Dyspnea	0 (0/10)	2.2 (1/45)	0.642
Diarrhoea/abdominal pain	20 (2/10)	40 (18/45)	0.209
Arthritis/arthralgia	80 (8/10)	42 (19/45)	0.026
Myalgia	30 (3/10)	40 (18/45)	0.565
Lymphadenopathy	30 (3/10)	8.9 (4/45)	0.212
Hepatosplenomegaly	30 (3/10)	6.7 (3/45)	0.168
Increased APRs	100 (10/10)	56 (10/18, $n = 18$)	0.002

Data are presented as % (*n*/*n*). *APRs* acute phase reactants

We also analyzed the clinical presentations in those patients who had disease onset in adult and compared them with those who suffered NLRP12-AD since childhood. Although fever and rash were still the most common symptoms in both groups, many clinical manifestations were different. Sensorineural deafness and eye involvement like uveitis and vision loss were only found in the children group, with frequencies of the clinical features at 13% and 6.5% respectively ($P = 0.013$ and 0.440). However, compared to early-onset group, late-onset NLRP12-AD patients had more severe musculoskeletal symptoms. The frequencies of arthritis/arthralgia and myalgia in this group were 78% and 67% vs 43% and 33% in early-onset group ($P = 0.058$, and 0.056) (Table 4).

In terms of the genetic phenotype, literature has previously reported 18 mutations of *NLRP12* causing NLRP12-AD. We now reported two additional novel mutations from our case series. Most mutations located in exon 3, in which F402L was the most common mutated allele in both early-onset and late-onset groups. This indicates that the age of onset was not related to the mutation itself. Furthermore, mutations in Chinese patients did not differ from those in Western patients.

Table 4 Comparison of major clinical features in early-onset patients with late-onset patients

Variables	Early-onset ($n = 46$)	Late-onset ($n = 9$)	P
Gender ratio (male:female)	16:19	4:5	0.830
Fever	96 (44/46)	89 (8/9)	0.423
Cold trigger	43 (20/46)	67 (6/9)	0.210
Rash	52 (24/46)	78 (7/9)	0.145
Headache	20 (9/46)	56 (5/9)	0.081
Eye involvement	6.5 (3/46)	0 (0/9)	0.440
Sensorineural deafness	13 (6/46)	0 (0/9)	0.013
Oral ulcer	8.7 (4/46)	11 (1/9)	0.843
Thoracic pain	4.3 (2/46)	11 (1/9)	0.423
Dyspnea	2.2 (1/46)	0 (0/9)	0.662
Diarrhoea/abdominal pain	39 (18/46)	22 (2/9)	0.322
Arthritis/arthralgia	43 (20/46)	78 (7/9)	0.058
Myalgia	33 (15/46)	67 (6/9)	0.056
Lymphadenopathy	6.5 (3/46)	44 (4/9)	0.065
Hepatosplenomegaly	8.7 (4/46)	22 (2/9)	0.398
Increased APRs	71 (15/21)	71 (5/7, $n = 7$)	1.000

Data are presented as % (*n*/*n*). *APRs* acute phase reactants

Discussion

NLR family consists of several important immune regulatory proteins and can be divided into four subfamilies based on their N-terminal effector domains. NLRP12 comes from one of the subfamilies, characterized by containing a pyrin domain [15].

Among the NLRP subfamily, NLRP3 is one of the well-known proteins associated with cryopyrin-associated periodic syndrome (CAPS) characterized by chronic inflammation with skin, musculoskeletal system, eyes and central nervous system involvement, as well as sensorineural hearing loss [16].

In 2008, Jeru et al. reported five cases of CAPS-like hereditary periodic fever syndrome with *NLRP12* mutations rather than mutations of *NLRP3*, and they named this autoinflammatory disease as NLRP12-AD. This was the first time that disease-causing mutations in NLRP12 were associated with an autoinflammatory disease [3]. Since then, the function of NLRP12 had been analyzed and recent studies showed that NLRP12 might act as a negative regulator of noncanonical NF-κB activation. Furthermore, it may also act as an inflammasome component to cleave procaspase-1, leading to the processing and secretion of interleukin-1β (IL-1β). The NLRP12-IL-19-IFN-γ axis is protective during *Yersinia pestis* infection [17–20]. The precise role of NLRP12 in different conditions still remains unclear.

To date, only several reports of NLRP12-AD were published and most cases came from European countries. We reported three cases of Chinese patients of NLRP12-AD. It has been considered that NLRP12-AD behaved like FCAS [3], whose presentations include fever, urticarial rash, conjunctival infection, and arthralgia. However, our study and several prior publications [5, 9] demonstrated that the manifestations of NLRP12-AD can be more severe than FCAS; deafness as well as vision loss are not rare in NLRP12-AD patients. In addition, we found that frequencies of several clinical manifestations were different between Chinese and Western patients, suggesting that genetic and environmental factors may contribute to the clinical manifestations. We also found that the clinical phenotypes between early-onset patients and late-onset patients were different in certain clinical findings; for example hearing loss occurred solely in early-onset patients.

Summarizing all the reported mutated alleles and the associated clinical manifestations, several interesting findings emerge. First, there was no obvious difference in terms of genetic mutations between different onset-age groups, or different ethnicities. Second, similar to *NLRP3*, where the same mutation can cause different clinical phenotypes of CAPS [21, 22], we found that the same *NLRP12* mutation, such as F402L, may have varied clinical manifestations [8]. On the other hand, several mutations might have corresponding phenotypes. There were four patients carrying the p.R284X mutation, and all of them developed sensorineural hearing loss, indicating that p.R284X might be causally related to sensorineural hearing loss. In addition, a recent paper reported that a patient with a novel mutation, p.S578G, has C3 glomerulopathy, a phenotype that was not seen in other NLRP12-AD cases. This suggests that p.S578G may be specific for C3 glomerulopathy. Although more cases are needed to fully correlate between clinical phenotypes with genetic mutations, we believe that our findings here might be useful for clinicians to carry out careful follow-up of the patients with those mutations.

Another important finding in this report is that two of our patients inherited the mutated alleles from one of their parents. However, none of their parents manifested with recurrent episodes of fever or rash. A reasonable explanation is that those mutations have low penetrance, just like the Q703K mutation in *NLRP3*, the pathogenic gene causing CAPS [23], as well as the R92Q in the TNFRSF1A, which causes tumor necrosis factor receptor-associated periodic syndrome [24]. For *NLRP12* gene mutations, the low-penetrance phenomenon had also been noted. In 2013, Vitale et al. first described the existence of asymptomatic carriers of the F402L mutated allele in *NLRP12* as well as G448A [10]. A possible cause for low penetrance might be haploinsufficiency. Previous studies demonstrated that mutations in *NLRP12* could reduce the inhibitory functions of NLRP12 on NF-κB pathway, while the function of normal isoform NLRP12 protein would not be influenced by mutated protein [3]. Thus, for a heterozygous *NLRP12* mutation, it is possible to maintain NLRP12 function normally. On the other hand, the onset age of NLRP12-AD can be as late as 47 years old [5], and so, it is possible that those patients' parents are still on the way to develop the canonical manifestations of NLRP12-AD, and be diagnosed later in their lives.

In conclusion, we reported three new cases of Chinese NLRP12-AD patients and discovered two novel *NLRP12* mutated alleles that might be pathogenic for NLRP12-AD. Our review of the literature summarized the clinical features of all NLRP12-AD patients and compared the manifestations between Chinese and Western patients as well as between early-onset and late-onset patients. Our report also pointed out that several mutated alleles might be related to some specific phenotypes, which may increase our recognition of NLRP12-AD.

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Author contributions WW performed all gene detection as well as bioinformatics analysis, and wrote the manuscript. YZ collected and analyzed the clinical data, and wrote the manuscript. WW and YZ contributed equally to this work. LQZ, ZL, SJ, and XYT participated

in clinical care and recorded clinical data. HMS diagnosed the patients, designed and supervised the project, and wrote and revised the manuscript. All authors approved the final version of the manuscript.

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Compliance with ethical standards

Ethical approval This research was approved by the Institutional Review Board of Peking Union Medical College Hospital.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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