The First Report on Clinical Manifestation of Cryopyrin-Associated Periodic Syndrome in Korean Children

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ABSTRACT

Purpose: The aim of this study was to evaluate the clinical characteristics of children diagnosed as cryopyrin-associated periodic syndrome (CAPS) in Korea.

Methods: Diagnosis was made based on clinical features and confirmed by a mutation in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene. Especially, osteocartilaginous overgrowth in the patella or distal femur was so characteristic that its presence warranted a diagnosis of chronic infantile neurologic cutaneous and articular/NOMID.

Results: We observed the clinical features of 9 Korean CAPS patients. All the patients suffered from an urticarial rash with recurrent fever. Among the 9 patients, 6 presented with rash and 4 with fever on the 1st or 2nd days of birth. Eight patients showed myalgia, and 7 patients showed arthralgia in the joints, and 6 patients showed radiologic findings of arthropathy including cupping of the metaphysis, excessive growth of the epiphysis, osteopenia or overgrowth of the cartilage. Four patients showed brain atrophy, enlarged ventricles or leptomeningeal enhancement on magnetic resonance imaging. Intellectual disability was observed in 1 patient. Five patients had eye involvement as conjunctivitis, uveitis, chorioretinitis, avascular area or papillary edema, and 3 patients showed progressive hearing loss. All 9 patients showed increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Conclusions: After the anakinra (interleukin-1 receptor antagonist) therapy, the fever and rash immediately disappeared, and CRP and ESR were improved.

Keywords: Cryopyrin-associated periodic syndrome; Familial Cold Autoinflammatory Syndrome; Muckle-Wells Syndrome, Republic of Korea

INTRODUCTION

Cryopyrin-associated periodic syndrome (CAPS) is a monogenic auto-inflammatory disease and has a spectrum of 3 kinds of diseases characterized by their severity,1,2 which are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular (CINCA) syndrome/neonatal-onset multisystem inflammatory disease (NOMID). CAPS results from gain-of-function
mutations in the nucleotide-binding domain, leucine-rich family, pyrin domain-containing-3 (NLRP3) gene causing excessive interleukin-1 (IL-1) β release and systemic inflammation. In general, common symptoms of CAPS is recurrent fever, urticaria like rash, musculoskeletal, ocular and neurological symptoms without focus starting in the early years of age. In all 3 phenotypes, disease-causing mutations in the NLRP3/cold-induced autoinflammatory syndrome 1 (CIAS1) gene on chromosome 1q44 have been identified. NLRP3 gene controls the production of cryopyrin, a protein that regulates the production of another protein called IL-1β. NLRP3/CIAS1 is associated with apoptosis-associated spect-like protein containing CARD (ASC) and pro-caspase-1 and constitutes a massive multiprotein complex called the NLRP3 inflammasome. The ASC protein interacts with cryopyrin when cryopyrin binds to ASC, it can result in caspase-1 activation. NLRP3 inflammasome plays a direct role in CAPS development and is responsible for the secretion of cytokines such as IL-1β and IL-18. When the NLRP3 inflammasome is activated by infection or tissue damage, it converts biologically inactive pro-caspase-1 into the active caspase-1. Caspase-1 processes and secretes IL-1β and IL-18, which are mainly involved in inflammatory reactions. Mutated NLRP3 induces an excessive activation of the NLRP3 inflammasome resulting in an overproduction of IL-1β.

Most CAPS patients have heterozygous mutations in the NLRP3 coding region. So far, more than 80 disease-causing mutations have been reported. However, 40% of the clinically diagnosed CAPS patients may not show a heterozygous NLRP3 mutation in a gene analysis.

CAPS is a spectrum of 3 kinds of diseases characterized by their severity. In the past, FCAS, MWS, and NOMID/CINCA were thought to be different diseases. However, after the genetic mutation NLRP3 was found and their clinical manifestation was found to be similar among the three diseases, nowadays, they are thought to be a continuous spectrum of 1 disease distinguished by its severity. However, there are other symptoms that can help distinguish them clinically.

FCAS is known as the mildest form of CAPS and can be characterized by cold induced fever and an urticaria like rash. Exposure to cold in FCAS patients exacerbates fever and rash. MWS is a moderate form of CAPS. The patient has symptoms of recurrent fever and rash which is not provoked by the cold. They can be characterized by progressive sensorineural hearing loss and eye involvement. NOMID/CINCA is the most severe form of CAPS. These patients have central nervous system (CNS) involvement in addition to fever and rash. Progressive hearing loss and eye involvement may be present in these patients, such as MWS. Symptoms of NOMID/CINCA might overlap with those of MWS. In general, these 2 diseases are distinguished by severity and the presence of other symptoms such as CNS involvement and bone deformity. However, it may not be meaningful to classify them in clinical practice because they show clinical signs of mutuality and show the same genetic variation. In this paper, we first analyzed CAPS patients in Korea. We analyze 9 patients who were diagnosed with CAPS. The aim of this study was to determine the clinical manifestations of CAPS and the spectrum of mutations in NLRP3/CIAS1.

MATERIALS AND METHODS

We performed a retrospective cohort study of all children who were diagnosed with CAPS between 2000 and 2015 at Seoul National University Children’s Hospital. Nine Korean children diagnosed with CAPS were enrolled. Diagnosis of CAPS was initially based on
clinical manifestations and medical history and ultimately confirmed genetically. Diagnosis of all patients in this study was confirmed by genetic studies and mutations were detected in exon 3. To date, the best criteria for diagnosing CAPS has been the increase in inflammation levels, as well as at least 2 of the following: urticaria-like skin rash, sensory hearing loss, musculoskeletal involvement, chronic aseptic meningitis, and skeletal abnormality.\textsuperscript{(11)}

We examined the clinical symptoms, characteristics, laboratory findings and genetic defects of the CAPS patients. We investigated their clinical characteristics, including sex, family history, age of onset, age of diagnosis, fever pattern, skin involvement, musculoskeletal involvement, neurological involvement, ophthalmic involvement, hearing loss, C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), and genetic mutation. Musculoskeletal manifestation was defined as the presence of 1 or more of any of the clinical (including myalgia, arthralgia, and arthritis) or imaging findings (including metaphyseal cupping, epiphyseal growing, osteopenia, and patellar ossification). Neurological involvement was defined as the presence of 1 or more of any of the clinical (including papilloedema, meningitis, facial palsy, and developmental delay) or brain magnetic resonance imaging (MRI) abnormalities (including ventriculomegaly, brain atrophy, and hydrocephalus).

Ocular manifestations were defined as having at least 1 symptom during conjunctivitis, uveitis, chorioretinitis, avascular area, and optic nerve atrophy. Neurosensory hearing loss was defined as needing surgery, a hearing aid, or a cochlear implant. The initial results of CRP and ESR were analyzed, and finally, the genes of the patients were analyzed to identify any mutations. This study was approved at Seoul National University Hospital (SNUH) Clinical Research Institute with Institutional Review Board (IRB No. 1712-101-908).

RESULTS

We analyzed 9 patients with CAPS who were diagnosed at SNUH. Five patients were male (55.6%), and 4 patients were female (44.4%). Three patients (33.3%) had fever since the 1st day of birth; 1 patient (11.1%) started on the 2nd day, and 5 patients (55.6%) started after several months (<6 months). In the case of rash, 5 patients (55.6%) had a rash from the 1st day; 1 patient (11.1%) had a rash within 2 days, and 3 patients (33.3%) started to show a rash within 6 months. No patients had a family history of CAPS. The median onset age was 2.8 months (Table 1).

Recurrence fever and skin lesions were present in all patients (100%). All the skin lesions showed an urticaria-like rash (100%). Eight patients (88.9%) had musculoskeletal involvement, and all of them had myalgia. Seven patients complained of arthralgia.

Among the arthralgia patients, 6 patients complained of knee joint pain, and one of them complained of ankle joint pain. One patient complained of wrist joint and ankle joint pain. In the X-ray examination of the joints, 3 patients showed metaphyseal cupping; 3 patients had epiphyseal growing; 2 had osteopenia, and 1 had patellar ossification (Figs. 1 and 2). Neurological involvement was noted in 4 patients (44.4%) which included papilloedema (n=3), facial palsy (n=1), developmental delay (n=2), and brain MRI abnormalities (n=4). Brain MRI abnormalities were brain atrophy, enlarged ventricles, or leptomeningeal enhancement (Fig. 3). Ophthalmological involvement was observed in 5 patients which included conjunctivitis (n=2), uveitis (n=1), and avascular area (n=1). Sensory hearing loss was reported in 4 patients (44.4%) among the cases. All patients showed an increased CRP.
**Table 1. Classification criteria of CAPS**

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
<th>Patient 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age at onset (day)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Age at Dx (mon)</td>
<td>9</td>
<td>26</td>
<td>27</td>
<td>19</td>
<td>20</td>
<td>84</td>
<td>142</td>
<td>12</td>
<td>192</td>
</tr>
<tr>
<td>Skin rash</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Musculoskeletal involvement</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>CRP (mg/L)</td>
<td>8.67</td>
<td>4.48</td>
<td>2.02</td>
<td>7.94</td>
<td>5.44</td>
<td>91</td>
<td>10.93</td>
<td>16.25</td>
<td>8.15</td>
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<td>ESR (mm/hr)</td>
<td>120</td>
<td>50</td>
<td>42</td>
<td>64</td>
<td>112</td>
<td>10.73</td>
<td>113</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>Hb (mg/dL)</td>
<td>9.4</td>
<td>10.4</td>
<td>13.3</td>
<td>10</td>
<td>9.1</td>
<td>7</td>
<td>10.2</td>
<td>9</td>
<td>12.4</td>
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<tr>
<td>WBC (mm$^3$)</td>
<td>17,690</td>
<td>12,120</td>
<td>13,150</td>
<td>14,850</td>
<td>14,930</td>
<td>21,120</td>
<td>12,220</td>
<td>32,000</td>
<td>20,010</td>
</tr>
<tr>
<td>Segs (%)</td>
<td>58</td>
<td>52</td>
<td>50</td>
<td>48</td>
<td>37</td>
<td>83</td>
<td>69</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>ANC (mm$^3$)</td>
<td>10,331</td>
<td>6,290</td>
<td>6,509</td>
<td>7,098</td>
<td>5,884</td>
<td>17,614</td>
<td>8,456</td>
<td>27,648</td>
<td>17,969</td>
</tr>
<tr>
<td>Platelet (×1,000/mm$^3$)</td>
<td>853</td>
<td>463</td>
<td>437</td>
<td>468</td>
<td>421</td>
<td>460</td>
<td>366</td>
<td>805</td>
<td>353</td>
</tr>
</tbody>
</table>

Abbreviations: CAPS, cryopyrin-associated periodic syndrome; Dx, diagnosis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; WBC, white blood cell; Segs, segmented neutrophil; ANC, absolute neutrophil count.

**Fig. 1.** Knee swelling in a 10-year-old boy diagnosed with CAPS. Abbreviations: CAPS, cryopyrin-associated periodic syndrome.

**Fig. 2.** Patellar ossification in a 10-year-old boy diagnosed with CAPS. Abbreviations: CAPS, cryopyrin-associated periodic syndrome.
Diagnosis of CAPS was confirmed with a genetic study, and all the patients in this study had mutations in exon 3 of CIAS1/NALP3 on chromosome 1q44 (Table 3, Fig. 4). Two patients had the same mutation (c1217T > C). Eight different sequence variants were detected, and all were missense mutations. Six have already been reported in other countries (p.Glu304Lys, p.Asp303Gly, p.Met664Thr, p.Tyr572Cys, p.Arg262Trp, and p.Asp303His). The other 2 are novel mutations (p.Tyr570Gly and p.Met406Thr). Patients were treated with anakinra (IL-1 receptor antagonist, Kineret®; Swedish Orphan Biovitrum, Stockholm, Sweden), and thereafter, the fever and rash disappeared, and the blood test results showed improvement in the CRP and ESR.
DISCUSSION

CAPS is a rare autosomal-dominant inherited autoinflammatory disease which encompasses the 3 entities of FCAS, MWS, and NOMID/CINCA syndrome. CAPS patients are characterized by a recurrent fever and an urticaria-like skin rash. Additionally, disease progression is predominantly chronic. In most cases, CAPS is caused by mutations in the NLRP3 gene.

This study constitutes a detailed description of the clinical and genotypic characteristics of CAPS patients. In many ways, our data confirm previous clinical explanations. Generally, fever in CAPS patients occurs within 6 months of birth. Fever is repetitive and chronic. Especially in FCAS, fever and rash appear within 1 to 2 hours of exposure to cold. One of our patients had fever and rash after exposure to the cold. Although the fever pattern is important in patients with CAPS, the characteristic feature of the rash can be helpful in the diagnosis. Skin lesions of CAPS are clinically described as urticaria and similar to neutrophil urticaria when viewed under a microscope. However, these urticarial rashes are clinically and histopathologically distinct from typical urticaria. Among the spectrum of acute urticaria, the skin lesions seen on CAPS patients would best be classified as neutrophil urticaria dermatosis (NUD).

Table 3. Gene mutation of CAPS

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex (male/female)</th>
<th>Gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>c.910G&gt;A; p.Glu304Lys</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>c.908A&gt;G; p.Asp303Gly</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>c.1709A&gt;G; p.Tyr570Gly</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>c.1991T&gt;C; p.Met664Thr</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>c.1277T&gt;C; p.Met406Thr</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>c.1277T&gt;C; p.Met406Thr</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>c.1715A&gt;G; p.Tyr572Cys</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>c.784C&gt;T; p.Arg262Trp</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>c.907G&gt;C; p.Asp303His</td>
</tr>
</tbody>
</table>

Abbreviations: CAPS, cryopyrin-associated periodic syndrome.

Fig. 4. All the patients had mutations in exon 3 of CIAS1/NLRP3 on chromosome 1q44. Eight different sequence variants were detected, and all were missense mutations. Six have already been reported in other countries (p.Glu304Lys, p.Asp303Gly, p.Met664Thr, p.Tyr572Cys, p.Arg262Trp, and p.Asp303His). Abbreviations: CIAS1, cold-induced autoinflammatory syndrome 1; NLRP3, nucleotide-binding domain, leucine-rich family, pyrin domain-containing-3; UTR, untranslated region.
slightly elevated non-itching macular and speckle. There is no angioedema. The distribution usually includes the trunk and the upper limb. Histopathologically, NUD is characterized by interstitial and perivascular neutrophils with little leukocytosis without vasculitis or skin edema. Three of our patients underwent a skin biopsy which showed perivascular and interstitial neutrophilic dermatitis. Although not yet considered as complete specificity, the clinical and histopathological presentation of NUD will be of great help in diagnosing CAPS patients by distinguishing them from common urticarial rashes.

Neurological involvements were observed in 44.4% (n=4) of the patients. The occurrence of neurological symptoms is well known in children with the CINCA phenotype but has not been previously reported in MWS or FCAS. Neurological features seen in CINCA include brain atrophy, hydrocephalus, chronic aseptic meningitis, hearing loss, and visual impairment. The mechanisms of the neurological symptoms are not well known. However, there is evidence that the levels of IL-1β is elevated in migraine patients. The loss of hearing in CAPS patients is thought to be due to cochlear inflammation. More research is needed to reveal the mechanisms behind the neurological symptoms in CAPS. Severe musculoskeletal involvement has been reported less frequently than in previous series. Among the arthralgia patients, 6 patients complained of knee joint pain, and one of them complained of ankle joint pain. Based on the patients in this study, the most common site of arthralgia was the knee joint (66.7%). Joint involvement causes a wide variety of limb deformities. Approximately 60% of patients with NOMID have prominent joint disorders, most commonly in the knee joints; however, the cause is still unknown. Involvement of the joints is generally asymmetric and mainly involves the knee joint. However, some may be symmetrical, and other joints may be involved. Interestingly, there is no correlation between joint deformity and NLRP3 mutations. CAPS can be diagnosis by clinical symptoms such as recurrent fever and rash at an early age and finally confirmed by a gene mutation in NLRP3/CIAS1. The patients were ultimately diagnosis by a genetic mutation in NLRP3/CIAS1. We found a total of 9 patients with NLRP3 genetic mutations including 2 previously unreported mutations (c1709A > G and c1217T > C). The types of the NLRP3 variants documented in this study were similar to those shown in previous studies. Following the discovery of the gene responsible for CAPS and understanding the common molecular basis of the syndrome, some studies have reported some degree of a genotype/phenotype correlation. However, the assessment of genotype/phenotype correlations may be limited by the nature of the disease. Although FCAS, MWS, and NOMID/CINCA are distinguished by the severity of their symptoms, due to the overlap of the symptoms from the 3 subtypes, bias can be introduced into the analysis. For this reason, CAPS should be thought of as a continuous spectrum of 1 disease rather than strictly be divided into 3 distinct diseases. In addition, the phenotypes of the 3 subtypes can change over time; thus, a strict classification may not have much meaning. Nevertheless, our patients can be divided into 2 FCAS (patients 7 and 9), 2 MWS (patients 1 and 2), and 5 NOMID/CINCA patients (patients 3, 4, 5, 6, and 8). Our patients were often classified as NOMID/CINCA because there were many patients with an early onset of disease and neurologic involvement. None of the patients included in the study had family history. The reason for this is that 50% of patients have de novo missense mutations in NLRP3 and this is probably due to idiopathic cases.

In CAPS patients, IL-1 has an important role. It is known that blocking IL-1 is the main treatment. At SNUH, anakinra (Kineret®; Swedish Orphan Biovitrum) was used to treat the patients. Daily injections of anakinra (Kineret®; Swedish Orphan Biovitrum) block the activity of IL-1. Other kinds of IL-1 blocking agents are being studied to increase the injection period.
In the acute phase, it is known that the CRP and ESR of CAPS patients are elevated. In our study, we followed-up the CRP and ESR level and observed a decreased level of CRP and ESR after treatment with anakinra (Kineret®; Swedish Orphan Biovitrum).

However, clinical features and laboratory findings did not improve completely. Additionally, in the case of anakinra (Kineret®; Swedish Orphan Biovitrum), daily dosing is required. Patients may experience fever and rash after 24 hours of treatment. Recently, new drugs, rilonacept (Regeneron, Tarrytown, NY, USA) and canakinumab (Ilaris®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), have been developed. rilonacept (Regeneron) is a weekly medication, and canakinumab (Ilaris®; Novartis Pharmaceuticals Corporation) is a medication administered every 8 weeks. These treatments have a longer duration of action than that of anakinra (Kineret®; Swedish Orphan Biovitrum) and may help to control clinical symptoms and the CRP and ESR blood levels of future patients.

Although CAPS patients may have serious adverse effects at the time of pneumococcal vaccination, none of the children included in this study had side effects (type of pneumococcal vaccination was unknown).29) Care should be taken when administering pneumococcal vaccine in CAPS patients.

This study was first report in Korea and is useful for diagnosing CAPS patients in Korea. Our results provide new insights into CAPS that can be valuable in routine clinical practice. To avoid long term complications, it is important to diagnose CAPS prematurely in children with recurrent fever and rash from an early age. These patients must be closely monitored and treated early on.

REFERENCES


요약

목적: 국내에서 cryopyrin-associated periodic syndrome (CAPS) 환자로 진단된 소아들의 임상 양상을 확인하고자 하였다.


결과: 모든 환자는 재발하는 열 및 두드러기 발진이 있었다. 9명의 환자 중 6명은 발진이 그리고 4명은 발진이 출생 1일 또는 2일 안에 있었다. 근육통을 보인 환자는 8명이었고, 관절통이 있는 환자는 7명이었다. 이들은 방사선학적 소견상 골단의 과도한 성장, 골감소증 또는 연골의 과성장과 같은 소견을 보였다. 4명의 환자는 뇌뇌증, 뇌실 확장 또는 자기공명영상에서 연수막 증대 소견을 보였다. 지적 장애가 1명에서 관찰되었다. 5명의 환자는 결막염, 포도막염, 망막염, 후두부종으로 시력에 영향을 받았으며 3명은 진행성 난청을 보였다. 9명 모두에서 초기 C-반응성 단백질과 적혈구 침착속도가 증가되었다. 모든 환자는 CIAS1 유전자 ex 3에서 돌연변이를 보였다. Anakinra 치료 후 발열과 발진이 사라졌으며 C-반응성 단백질과 적혈구 침착 속도가 호전되었다.

결론: 이 연구는 국내에서 처음으로 CAPS 환자들의 임상 증상을 고찰한 논문으로 향후 새로운 환자들을 진단하는데 유용할 것이다. 또한 환자들의 장기적인 합병증을 예방하기 위해 이른 나이부터 발생하는 반복적인 발열과 발진이 있는 소아에서 초기에 CAPS를 진단하고 치료하는 것이 중요하다.