Neonatal-Onset Multisystem Inflammatory Disorder

The Emerging Role of Pyrin Genes in Autoinflammatory Diseases

Christine Kilcline, MD; Kanade Shinkai, MD, PhD; Alanna Bree, MD; Renee Modica, MD; Emily Von Scheven, MD; Ilona J. Frieden, MD

Neonatal-onset multisystem inflammatory disorder (NOMID) is a rare, congenital, systemic, inflammatory condition involving inflammation of many organ systems, including joints, skin, lymph nodes, and the central nervous system (CNS).1 The condition has also been called chronic infantile neurologic, cutaneous, and articular syndrome. Patients with NOMID have a wide spectrum of disease severity and end-organ damage. Mutations of the CIAS1 gene, a member of the pyrin gene family, have recently been found in approximately 50% of patients with NOMID.2 Mutations in this gene have also been found in 2 other diseases: Muckle-Wells syndrome (MWS) and familial cold-induced autoinflammatory syndrome (FCAS), both of which can have cutaneous manifestations.3,4 We report 3 cases that illustrate the disease spectrum and genetic basis of NOMID and highlight the emerging role of the pyrin gene family in the regulation of nuclear factor κB signaling and other pathways involved in inflammation and apoptosis.

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REPORT OF CASES

CASE 1

A 21-month-old boy was referred to the University of California, San Francisco, pediatric dermatology service for evaluation of a chronic, relapsing urticarial eruption present since birth. His skin lesions had developed in his first few days of life, and while individual lesions had worsened and improved since that time, the rash never resolved completely (Figure 1). Pruritus was occasionally present. Other systemic findings are summarized in Table 1. Findings from physical examination revealed widespread urticarial papules and plaques involving the trunk, face, and upper and lower extremities (Figure 1). The

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remainder of his examination findings were normal. Of note, he had been hospitalized at age 13 months for pericarditis with near cardiac tamponade of unclear cause.

At the time of presentation to our service, his laboratory values showed a persistently elevated immunoglobulin (Ig) G level (1180 mg/dL; normal range, 293-902 mg/dL), mildly elevated IgM level (114 mg/dL; normal range, 29-113 mg/dL), elevated erythrocyte sedimentation rate (36-80 mm/h; normal range, 0-15 mm/h), high white blood cell count (27.9 × 10^3/µL; normal range, 6 × 10^3 to 17 × 10^3/µL), and a high platelet count (404 × 10^3/µL; normal range, 140 × 10^3 to 400 × 10^3/µL). Results of investigations for infectious causes were negative. Autoimmune findings of serum analysis were negative for antineutrophil antibody and antineutrophil cytoplasmic antibody. Immune complex and T-cell subset findings were within normal limits.

Skin biopsy specimens showed sparse interstitial and perieccrine dermatitis with neutrophils. Based on clinical suspicion and laboratory findings, the patient was referred for genetic testing for NOMID and was found to have a point mutation in exon 3 of the CIAS1 gene resulting in a G326E amino acid substitution in the protein sequence, a mutation that had not been previously reported.

At age 4 years, the patient continued to experience periodic flares of urticaria every 2 to 3 weeks, a nondeforming arthropathy of the left ankle, headaches, and periodic fevers. His symptoms were partially responsive to naproxen and cetirizine, but over the previous 2 years, his growth curve dropped from the 75th percentile for height and the 25th percentile for weight to approximately the 10th and 5th percentiles, respectively. Slight “catch-up growth” was observed during periods of decreased disease activity, but growth would plateau again with recurrent flares.

Recently, the patient began clinical trials with anakinra, an interleukin (IL) 1 receptor antagonist, and experienced significant improvement in his symptoms. Currently his rash has almost completely resolved, and he has no fevers.

**CASE 2**

A 5-year-old boy presented for evaluation of a recurrent urticarial eruption that first occurred when he was a newborn. He also had recurrent fevers, lymphadenopathy, and arthralgias. Systems findings were remarkable for intermittent abdominal pain, occasional headaches, recurrent conjunctivitis, intermittent oral ulcers, and generalized muscle weakness and pain. His growth and development were normal. There was no family history of recurrent fevers.

Physical examination revealed a diffuse, polymorphous, urticarial eruption, cervical lymphadenopathy, and painful swelling of the knees bilaterally. There was no hepatosplenomegaly, and findings of the neurologic examination were normal. A summary of laboratory findings, histopathologic findings, and genetic testing and treatment strategies is included in Table 1. Genetic analysis revealed a C326E sequence mutation in exon 3 of the CIAS1 gene. The patient is currently being considered for a trial of an IL-1 receptor antagonist.

**CASE 3**

A newborn Chinese girl presented with congenital generalized urticarial rash, hepatosplenomegaly, and lymphadenopathy present since birth. Her symptoms, including early-onset arthritis, were persistent despite treatment with systemic steroids. Her arthritis progressed rapidly to an early deforming arthropathy. After extensive evaluation for congenital infections and other multisystem diseases, the patient was diagnosed with NOMID. She was treated with potent immunosuppressive therapy, as outlined in Table 1.

The patient continues to have a complicated course with persistent fevers, diffuse lymphadenopathy, urticarial rash, and severe growth retardation. Skeletal surveys have revealed bilateral epiphyseal overgrowth involving the knees and ankles with squaring of the patella. She has severe fixed-hip and knee-flexion contractures. At age 6½ years, her bone age is delayed more than 3 SDs for her chronologic age, as are her weight and her height (Table 1). Magnetic resonance imaging of the brain has shown loss of white matter and evidence of an infiltrative inflammatory process. Her laboratory findings are summarized in Table 1. Genetic findings were negative for CIAS1 mutations.

The patient is currently receiving methotrexate and prednisone treatment with the addition of aspirin and naproxen. She has recently begun therapeutic trials with anakinra, an IL-1 receptor antagonist.
A striking feature of NOMID is the generalized neutrophilic infiltration into multiple target organs.2 Perivascular neutrophil infiltration in the skin result in the classic dermatologic presentation of migratory and persistent urticaria, beginning at birth.2 Interstitial neutrophilia and neutrophilic eccrine hidradenitis in patients with NOMID have also been described.3 Progressive neurologic impairment is secondary to neutrophil infiltration leading to chronic meningitis, which can result in progressive hearing loss or visual defects.2 Dramatic neutrophil infiltration into the spleen, lymph nodes, and synovium has been observed.3 An elevated blood neutrophil count is also characteristic of NOMID, but the trigger for neutrophil recruitment is unknown, and whether these neutrophils have normal migratory and effector functions has been questioned.7

### Table 2. Clinical Manifestations of Neonatal-Onset Multisystem Inflammatory Disorder

<table>
<thead>
<tr>
<th>Affected System</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Periodic fevers, chills</td>
</tr>
<tr>
<td>Growth and developmental</td>
<td>Failure to thrive, cognitive impairment, developmental delay</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Urticarial eruption</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Chronic asectopic meningitis, seizures, transient hemiplegia, hydrocephalus, spasticity, sensorineural hearing loss</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Papillodema, anterior uveitis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Deforming and nondeforming arthralgies, epiphysial changes on radiograph, frontal bossing</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia, granulocytosis, lymphadenopathy</td>
</tr>
<tr>
<td>Immunologic and inflammatory</td>
<td>Negative antineutrophil antibody, elevated erythrocyte sedimentation rate, elevated C-reactive protein</td>
</tr>
</tbody>
</table>

### Table 1. Summary of Clinical Presentations*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Systemic Findings</th>
<th>Laboratory Findings</th>
<th>Histopathologic Findings</th>
<th>C1AS1 Defect</th>
<th>Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fevers, lymphadenopathy, nondeforming arthropathy, pericarditis, sensorineural hearing loss, elevated CSF opening pressure, mild papiledema, headaches, growth retardation, normal development</td>
<td>Leukocytosis, thrombocytosis, elevated IgG and IgM, elevated ESR</td>
<td>Sparse interstitial and periencrine dermatitis with neutrophils</td>
<td>Present at G326E of exon 3</td>
<td>Naproxen, and cetirizine, partially responsive; anakinra, an IL-1 receptor antagonist, improvement</td>
</tr>
<tr>
<td>2</td>
<td>Fevers, lymphadenopathy, deforming arthropathy of patellae, abdominal pain, headaches, irritis, myalgias, normal growth and development</td>
<td>Leukocytosis with neutrophilia, microcytic anemia, elevated ESR, elevated IgA and IgM, elevated C3</td>
<td>Superficial perivascular and interstitial neutrophilic infiltrate with nuclear dust</td>
<td>Present at G326E of exon 3</td>
<td>Prednisone, partially responsive</td>
</tr>
<tr>
<td>3</td>
<td>Fevers, lymphadenopathy, hepatosplenomegaly, early-onset deforming arthropathy of patella, pseudotumor cerebri, chronic asectopic meningitis, optic neuritis, growth delay</td>
<td>Leukocytosis, elevated ESR, elevated C-reactive protein, elevated IgG, IgM, and IgA</td>
<td>No biopsy performed</td>
<td>None detected</td>
<td>Prednisone, methotrexate, aspirin, and naproxen, unresponsive; cyclosporine regimen discontinued owing to lymphoproliferative disorder; trial of anakinra ongoing</td>
</tr>
</tbody>
</table>

Abbreviations: C3, complement 3; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IL, interleukin.

*All patients were neonates at onset with urticarial eruption as a cutaneous finding.

Neonatal-onset multisystem inflammatory disorder, also known as chronic infantile neurologic, cutaneous, and articular syndrome, is a multisystem autoinflammatory disorder characterized by urticarial rash, joint inflammation with characteristic deforming arthropathy, uveitis, systemic inflammatory signs such as fevers and neutrophilia, and CNS involvement. A hallmark of this disease is onset at birth. Although NOMID has been described as a triad of rash, arthropathy, and CNS involvement, a wide spectrum of clinical presentations has been reported, including variants without ocular inflammation or CNS involvement (Table 2).5,6 The CNS manifestations of NOMID also include a spectrum of findings ranging from sensorineural hearing loss to chronic asectopic meningitis, developmental delay, and mental retardation.

A striking feature of NOMID is the generalized neutrophilic infiltration into multiple target organs.2 Perivascular neutrophil infiltration in the skin result in the classic dermatologic presentation of migratory and persistent urticaria, beginning at birth.2 Interstitial neutrophilia and neutrophilic eccrine hidradenitis in patients with NOMID have also been described.3 Progressive neurologic impairment is secondary to neutrophil infiltration leading to chronic meningitis, which can result in progressive hearing loss or visual defects.2 Dramatic neutrophil infiltration into the spleen, lymph nodes, and synovium has been observed.3 An elevated blood neutrophil count is also characteristic of NOMID, but the trigger for neutrophil recruitment is unknown, and whether these neutrophils have normal migratory and effector functions has been questioned.7

### Autoinflammatory Disease

Neonatal-onset multisystem inflammatory disorder is one of several of the periodic fever disorders that have now been characterized as autoimmune inflammatory diseases. Other examples include Crohn disease, familial Mediterranean fever (FMF), and tumor necrosis factor (TNF) receptor–associated periodic syndrome.2 These diseases are distinguished from autoimmune diseases by their lack of high-titer autoantibodies or antigen-specific T-cell self-reactivity, but they share many clinical features of autoimmune diseases.2
Dysregulation of cytokines is a general hallmark of autoinflammatory states. Evidence for a dramatic cytokine response in NOMID, specifically, increases in levels of TNF-β, IL-1β, IL-3, and IL-6, have been described at the level of increases in both messenger RNA and protein expression. The absence of an autoantigen in the setting of elevated levels of inflammatory mediators in NOMID supports a role for dysregulated cytokine processing rather than a loss of immunologic tolerance to self-antigens as a cause of inflammation and also suggests an inability to curb inflammatory responses once they have been initiated. This notion is now supported by recent discoveries of the genetic basis of NOMID and other autoinflammatory diseases, including FMF, FCAS, and MWS. This understanding may also suggest new avenues for therapeutic strategies in affected patients. 

Despite the distinction between autoimmune and autoinflammatory diseases, NOMID shares features with many autoimmune diseases, particularly systemic juvenile rheumatoid arthritis (JRA), which is often a major consideration in the differential diagnosis. Both NOMID and JRA exhibit signs of systemic inflammation, such as high intermittent fevers, arthralgias, deformity, and rash. Patients with JRA also show a great heterogeneity of disease severity, from Still systemic-onset disease to pauciarticular or polyarticular disease. Some patients with JRA, especially those with Still disease, may lack serologic markers of autoantibody formation, which further complicates the diagnostic distinction. Despite these similarities, there are important features that differentiate the two diseases. The onset of skin disease in the newborn period, as well as a fluctuating but persistent rash, is characteristic of NOMID. In addition, joint signs and symptoms differ: NOMID shows nonspecific arthralgias and characteristic patellar bony enlargement, while true arthritis in JRA manifests as synovial hypertrophy, increased synovial fluid production, and warm, swollen, stiff joints. The common features suggest that effector pathways may be similar despite differences in pathogenesis. At the same time, their differences may also ultimately yield important information regarding the pathogenesis of both disorders.

GENETIC AND MOLECULAR INSIGHTS

Recently, gene mutations in the CIAS1 gene have been demonstrated in approximately 50% to 60% of cases of NOMID. The CIAS1 gene, located on human chromosome 1q44, encodes cryopyrin (also known as PYPAF1 or NALP3), a member of the pyrin gene family. The pyrin gene family encodes several proteins that regulate inflammation and apoptosis. Research has highlighted the role of pyrin gene family members in the pathogenesis of 4 autoimmune diseases: NOMID, FCAS, MWS, and FMF. The first pyrin protein implicated in autoinflammatory disease was MEFV, the gene underlying FMF. This pyrin protein (also known as pyrin or maeonstrin) is expressed in affected tissues, including neutrophils, activated monocytes, eosinophils, synovium, and skin. Patients with FMF are at increased risk for developing a number of other inflammatory diseases, including inflammatory bowel disease, vasculitis, and Behçet syndrome. This risk may indicate a contributing role for mutant pyrin in the pathogenesis of a broad spectrum of inflammatory diseases. 

Recently, noting a strong disease linkage of NOMID to the CIAS1 gene—containing region of chromosome 1, Feldmann and colleagues searched for and discovered a number of CIAS1 mutations in individual patients with NOMID. Although a direct causal relationship remains to be proven in experimental systems, the large number of CIAS1 mutations associated with NOMID—at least 13 reported to date—supports the idea that the underlying mutation occurs in the CIAS1 gene. In addition, the finding that CIAS1 gene expression is highly restricted to neutrophils, monocytes, and chondrocytes, tissue types specifically involved in NOMID, lends support to this hypothesis. Cases of NOMID that are CIAS1 negative might have mutations in other common pathways involved in cryopyrin interactions that result in the phenotypic expression of this disorder.

Sequence analysis of the CIAS1 gene product suggests that it bears at least 3 interesting protein domains implicated in innate immunity, inflammation, and apoptosis. Mutation analysis has identified distinct missense mutations, many of which are located in exon 3 within the NACHT domain (Figure 2). The impact of these mutations on cryopyrin protein expression, or whether the protein is expressed at all in patients with NOMID, is not known. One important role for cryopyrin may involve its ability to activate the nuclear factor of NFκB pathway. However, given the complex role of nuclear factor NFκB in inflammation, it is unclear whether cryopyrin acts to regulate NFκB as an activator of pro-inflammatory pathways or as a negative regulator curtailing inflammation. Based on structural and functional similarities to other pyrin gene family members and preliminary in vitro studies, cryopyrin may serve a critical scaffolding role, mediating homotypic and heterotypic interactions to create a multimerized complex upstream of NFκB gene activation that leads to apoptosis and/or innate immune responses.

Identification of a gene responsible for NOMID yielded the unexpected finding that NOMID, FCAS, and MWS, 3 clinically distinct autoinflammatory diseases, are all due to mutations in the CIAS1 gene. To date, at least 21 missense mutations in the CIAS1 gene have been reported in association with these 3 autoimmune syndromes. Although previously recognized as discrete diseases, the linkage of these 3 syndromes to a single gene suggests that they instead may represent stages along a spectrum of disease. While all 3 diseases share features such as urticarial rash, they can be clinically distinguished on the basis of unique findings or combinations of findings (Table 3). The CNS involvement in NOMID includes a chronic aseptic meningitis, sensorineural hearing loss, or alternatively, ocular involvement. Muckle-Wells syndrome is clinically distinguished by the development of renal amyloidosis in the absence of frank arthropathy. And, perhaps the mildest disorder of the 3, FCAS presents with cold-induced urticaria beginning in infancy, periodic fevers and chills, arthralgias with musculoskeletal stiffness, but no CNS involvement, amyloidosis, or arthropathy.
A common feature of all 3 conditions is the presence of urticarial rash composed largely of neutrophils. Although lymphocytes and eosinophils usually predominate, neutrophils are seen in up to 10% of cases of idiopathic urticaria. Recently, a small case series involving 3 patients with NOMID—1 with a new missense mutation in \( \text{CIAS1} \)—demonstrated that the surface density of CD10, an important activation antigen present on the surface of neutrophils, is significantly higher in patients with NOMID than in those with JRA and healthy controls, thus supporting the role of neutrophils as the primary inflammatory mediator in this disease. Neutrophil-mediated inflammation is also seen in FMF, which emphasizes a potential role for pyrin proteins in the induction of distinct subsets of chemotactic factors that lead to differential recruitment of innate immune cells.

The disparity between genotypes and phenotypes of \( \text{CIAS1} \) mutations in NOMID, FCAS, and MWS has not yet been explained at a molecular level. This heterogeneity may be due to the multiple biologic roles of cryopyrin. \( \text{CIAS1} \) mutations might give rise to clinically distinguishable diseases through partial loss of signaling pathways or inability to associate with other proteins, which would be consistent with its proposed role as a scaffolding component. In addition, the discovery of a single gene mutation, the R260W mutation, which has been identified in 2 families with MWS and 2 families with FCAS, suggests a role for modifier genes in the production of these clinical phenotypes. This mutation is located in the NACHT domain, a region frequently mutated in all 3 syndromes, which emphasizes the importance of this functional protein domain in the regulation of inflammatory processes.

Although the presence of \( \text{CIAS1} \) mutations in approximately 50% of patients with NOMID points to an underlying genetic cause, it is not known why the remaining 50% of cases are \( \text{CIAS1} \) negative. In the absence of known modifier genes, genetic pleiomorphism cannot be formally excluded as an alternative explanation. Furthermore, asymptomatic individuals carrying known \( \text{CIAS1} \) mutations...
gene mutations have been described, and the question of penetrance has not been fully addressed. Moreover, the significant heterogeneity in the presentations of patients with NOMID, MWS, and FCAS also suggests the potentially important role of penetrance or modifier genes in the clinical course of these diseases.

We have described the presentation of 3 young children with NOMID, 2 of whom proved to have previously unreported mutations in CIAS1, a gene that has been implicated in several autoinflammatory diseases, including NOMID, MWS, and FCAS. The growing list of pyrin mutations in connection with an expanding group of autoinflammatory diseases highlights the importance of the pyrin genes as inflammatory regulators and challenges future research to clarify and unmask additional genetic determinants of autoinflammatory disease. Given our growing appreciation of the importance of these pathways, further research is called for to understand critical aspects of this protein, including its cellular localization, binding partners, and functional properties. Defining these pathways may also reveal important mechanistic differences between the pathogenesis of autoinflammatory and autoimmune disease. Current research is focused on understanding how cryopyrin and other related genes initiate or inhibit inflammatory processes, for example, through its potential regulation of the NFκB pathway.

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