Successful Management of Cryopyrin-Associated Periodic Syndrome With Canakinumab in Infancy

abstract

Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) syndrome is a rare, early-onset autoinflammatory disorder and the most severe form of cryopyrin-associated periodic syndrome, which is associated with overproduction of interleukin (IL)-1β. This is a case report of a 70-day-old boy, who was diagnosed with NOMID/CINCA syndrome and who has been treated with anti–IL-1β monoclonal antibody (canakinumab) since then, despite his early infancy. The patient presented with fever, aseptic meningitis, and rash. The clinical manifestations combined with the elevated acute-phase reactants strengthened the suspicion of the diagnosis of NOMID/CINCA syndrome. Specific immunologic workup revealed high levels of serum amyloid A and IL-6. The clinical diagnosis was confirmed by the detection of a de novo mutation of the CIAS1/NLR3 gene (p.Thr348Met), and canakinumab was started at a dose of 4 mg/kg, higher than the recommended dose for older age. White blood cell, serum amyloid A, C-reactive protein, and IL-6 levels quickly decreased and became normal within a month, and the clinical condition of the patient improved significantly. The infant remains without recurrence of disease or further complications and with satisfactory mental development with anti–IL-1β monoclonal antibody treatment for >2 years. This report indicates the importance of early diagnosis of NOMID/CINCA syndrome and medication with IL-1 blockers as soon as possible for the improvement of the prognosis of cryopyrin-associated periodic syndrome and of a better patient outcome. Pediatrics 2014;134:e1468–e1473

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KEY WORDS
aseptic meningitis, autoinflammatory disorder, cryopyrin, interleukin 1β, canakinumab, NOMID, CINCA, CAPS

ABBREVIATIONS
CAPS—cryopyrin-associated periodic syndrome
CINCA—chronic infantile neurologic cutaneous and articular
CRP—C-reactive protein
IL—interleukin
IL-1R—interleukin-1 receptor
MoAb—monoclonal antibody
NOMID—neonatal onset multisystem inflammatory disease

Dr Kanariou substantially contributed to the diagnosis, coordinated and supervised the management and follow-up of the patient, and revised and reviewed the manuscript critically; Dr Tantou wrote the initial draft of the manuscript and contributed to the follow-up of the patient and data collection; Ms Varela carried out the DNA analysis of the patient and contributed to the draft of the manuscript; Dr Raptaki contributed to the management of the patient and data collection; Dr Petropoulou contributed to the management of the patient during hospitalization and contributed to the follow-up of the patient; Dr Nikas evaluated the findings of the successive MRI examinations, participated in the writing of the manuscript, and reviewed the manuscript; Dr Valari substantially contributed to the diagnosis and follow-up of the patient and reviewed and revised the manuscript critically, and all authors approved the final manuscript as submitted.

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(Continued on last page)
Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) syndrome is a rare, early-onset autoinflammatory disease. This is the most severe form of the three clinical manifestations of cryopyrin-associated periodic syndromes (CAPS), together with Muckle-Wells syndrome and familiar cold-associated syndrome.

NOMID is characterized by a neonatal onset urticarial-like skin rash, recurrent episodes of fever, central nervous system involvement (chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, mental retardation, sensorineural hearing loss, visual abnormalities), cutaneous symptoms, chronic inflammatory arthropathy, and lymphadenopathy.

The related gene is NLRP3 (also known as CIAS1), which encodes cryopyrin. Cryopyrin is one of the proteins that form the inflammasome and activates caspase-1, resulting in the induction and secretion of interleukin (IL) 1β. The syndrome is inherited in an autosomal dominant pattern, but it is likely to be a heterogeneous disease because ~50% of affected individuals have identifiable NLRP3 mutations.

The overproduction of IL-1β, which is substantial for the organ-specific inflammatory manifestations, can be effectively managed by IL-1/IL-1 receptor (IL-1R) pathway blockers such as IL-1R antagonist (anakinra), a human dimeric fusion protein (rilonacept), and a fully human anti–IL-1β monoclonal antibody (MoAb) (canakinumab).

**PATIENT PRESENTATION**

This is a case report of a 28-month-old boy who has been diagnosed with NOMID since he was 60 days old and who commenced treatment with anti–IL-1β MoAb (canakinumab) on the 70th day, when the diagnosis was confirmed genetically.

The neonate was born at 38+2w gestational age by cesarean delivery after an in vitro fertilization, uncomplicated pregnancy from healthy unrelated parents. Twelve hours after birth, he presented with a rash on the body and limbs without fever and was referred to the NICU. Antibiotics were administered on the basis of elevated C-reactive protein (CRP) levels, the only pathologic laboratory finding. The patient was in good clinical condition, and the rash gradually subsided.

On the 17th day, he was admitted to the pediatric clinic of the local hospital because of fever (39°C) for 24 hours and dehydration caused by reduced oral intake, vomiting, and diarrhea, which he experienced for 7 days. Inflammatory markers (white blood cell count, CRP, procalcitonin) were elevated, but blood, cerebrospinal fluid, and urine cultures and polymerase chain reaction for bacteria, viruses, and fungi were negative.

He was given intravenous ampicillin and cefotaxime along with intravenous hydration. Seizures were noticed, and antiviral agents as well as anticonvulsants were added in his treatment. At 28 days, he was admitted to the NICU of our hospital. Extensive and repeated laboratory investigations revealed no specific etiology of the clinical manifestation. A ventricular drainage was placed; meningitis remained the only finding until the 60th day, when an urticarial rash appeared. The coincidence of fever, rash, and aseptic meningitis, combined with elevated acute-phase reactants, strengthened the suspicion of autoinflammatory disease and more specifically of CAPS, consequently, at that point, the clinical diagnosis of NOMID was adopted. The skin biopsy revealed a neutrophil infiltration of epidermis and capillaries with absence of vasculitis. Specific immune investigation revealed high levels of serum amyloid A and IL-6, although IL-1β and tumor necrosis factor-α values were within normal levels.

The diagnosis was confirmed by the detection of a mutation in exon 3 of the CIAS1/NLR3 gene (p.Thr348Met). This mutation is responsible for the CINCA syndrome.

Brain MRI revealed bilateral hemorrhages within the cerebral hemispheres, resulting in large cysts and reduced white matter (Fig 1). Because of further deterioration, the patient was transferred to the NICU, supported by nasal continuous positive airway pressure. Seizures were noticed, and antiviral agents as well as anticonvulsants were added in his treatment. On the 17th day, he was admitted to the pediatrics clinic of the local hospital because of fever (39°C) for 24 hours and dehydration caused by reduced oral intake, vomiting, and diarrhea, which he experienced for 7 days. Inflammatory markers (white blood cell count, CRP, procalcitonin) were elevated, but blood, cerebrospinal fluid, and urine cultures and polymerase chain reaction for bacteria, viruses, and fungi were negative.

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**FIGURE 1**

Axial (A) and sagittal (B) T1-weighted images reveal bilateral extensive hemorrhages within cerebral hemispheres with white matter edema.
mutation can be considered to be *de novo*, because it was not found in the patient’s parents (Fig 2).

With the genetic diagnosis and on the basis of the severity of clinical manifestations and poor prognosis of the disease, we started anti–IL-1β MoAb (canakinumab) at a dose of 4 mg/kg subcutaneously once every 8 weeks despite his young age and the drug indication. Before initiating the treatment, we obtained informed consent from both of his parents and the scientific committee of the hospital. White blood cell, serum amyloid A, CRP, and IL-6 levels quickly decreased to normal values (Table 1). The patient was systematically followed up for laboratory variables, weekly during the first month, monthly for a 3-month period, every 3 months for the first year under the regimen, and every 6 months thereafter. Brain MRI did not show any additional injuries after 1 year of treatment (Fig 3). The patient improved clinically, has no infections, no reactions at the sites of injections, and remains without relapses of fever or rash. Residual neurologic symptoms such as left hemiplegia and seizures have been noted; he is receiving physiotherapy and an antiepileptic regimen. Ventricular drainage and anticonvulsants are still being administered, but lumbar puncture has so far not been considered necessary.

The patient is under regular follow-up by ophthalmologists, otolaryngologists, and neurologists. Ophthalmoscopy/fundoscopy was normal, and brainstem auditory evoked response as otoacoustic emissions revealed no pathologic findings. The child began to walk with support at the age of 18 months, and at the age of 26 months he exhibited delayed language development and erratic communication skills; logotherapy and occupational/ergo-physical therapy were started. For the past 2 years, with anti–IL-1β medication, no further complications of the disease or adverse events have been noted.

**DISCUSSION**

The reported patient presented with an atypical skin rash during the first 24 hours of life, and in view of his elevated CRP was treated for presumed sepsis with antibiotics. Fever and meningitis were added, but no microorganism was identified. The brain MRI findings, in combination with the persistence of increased acute-phase proteins and cytokines and the relapse of his rash (urticaria-like at that time) led to the clinical diagnosis of NOMID/CINCA syndrome. DNA analysis confirmed the diagnosis of CAPS. Because of the high morbidity and mortality of NOMID/CINCA syndrome due to chronic meningitis, we had to administer an anti–IL-1β/IL-1R regimen to block the symptoms commencing on the 70th day of life. There was an urgent need to start treatment and we chose the anti–IL-1β MoAb because we wanted to block the inflammatory agent itself, to give an injection every 8 weeks rather than every day (at that time, canakinumab was the drug that was approved for CAPS), and because we had had satisfactory experience with canakinumab in an older patient with NOMID/CINCA syndrome.

The initial dosage was modified according to body weight, but the frequency of injections remained stable throughout the follow-up period. In 2011, there were not enough available data on the use of any IL-1/IL-1R blockers in early age. An important study by Clark et al showed brain bioavailability of anakinra in an animal model and in the human nervous system after intravenous administration in high doses but did not reveal concentrations in the local brain environment or in the other inflamed tissues. To our knowledge, our

![FIGURE 2](http://pediatrics.aappublications.org/)

Parents’ and patient’s *CIAS1* gene analysis. The patient’s mutation is shown.
TABLE 1  WBCs, Their Differential Count, and Inflammatory Markers Before and After Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Initiation of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 Days</td>
<td>1 Month</td>
</tr>
<tr>
<td>WBCs, \times 10^9/μL</td>
<td>27.37</td>
<td>15.18</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>61</td>
<td>53</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>Mononuclear cells, %</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Basal cells, %</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Rod neutrophils, %</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Atypical lymphocytes, %</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>112</td>
<td>55</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>432</td>
<td>15</td>
</tr>
<tr>
<td>SAA, mg/dL</td>
<td>2180</td>
<td>73</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>&lt;5</td>
<td>6.6</td>
</tr>
<tr>
<td>IL-1β, pg/mL</td>
<td>&lt;5</td>
<td>5.25</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>911.54</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

ESR, Erythrocyte Sedimentation Rate; ND, Not Done; SAA, serum amyloid A; TNF-α, tumor necrosis factor α; WBC, white blood cell.

It is remarkable that IL-1β levels were within normal limits, unlike the IL-6 values, which were markedly elevated before the administration of canakinumab. The same finding has been reported in another case of CINCA syndrome and in other CAPS. Additionally, Hoffman et al found that serum IL-1β was not increased in patients with familial cold-associated syndrome but was detected in high concentrations in the affected skin, suggesting that IL-1β acts peripherally and stimulates the release of IL-6. The exact mechanism of the interaction between these 2 interleukins is not clear, even though there are several studies that refer mainly to patients with rheumatoid arthritis. The massive secretion of active IL-1β observed in CAPS suggested that anti-IL-1β could represent an effective therapy. A number of studies have pointed to the efficacy and safety of anti-IL-1β-receptor MoAb (anakinra) as well as to the IL-1 blockers rilonacept and canakinumab. The prolonged half-life of canakinumab allows the 8-weekly dosing scheme and makes it well tolerated by the pediatric population.

Our decision to start anti-IL-1β MoAb, although there was no indication for the patient’s age, was based on knowledge of the IL-1β/IL-1β-receptor pathway, and on the severity and urgency of the disease. Our patient was treated with canakinumab at a dose of 4 mg/kg every 8 weeks subcutaneously, a dose higher than that recommended for older children. This dosage was based on the potent immune response of infants, which therefore needs more immunosuppression.

Our initial assessment for an IL-1β blocker regimen has been confirmed by the positive response and clinical improvement of the patient. Recent studies have shown that the dose must be individualized and determined more by the severity of phenotype than by age. Relapse of symptoms or persistence of acute reactants requires modification of the treatment, including the dosage and frequency, to prevent further complications.

The time of initiation of the therapy seems to be crucial to the outcome. In our patient, the treatment was well tolerated, with remission of the symptoms, normal values of inflammatory markers, and no noted relapse of the disease; with 2 years receiving this therapy, the infant is growing well. This report confirmed the importance of earlier indications of starting an anti-IL-1β/IL-1R regimen, canakinumab in our case, for a better outcome of neurologic and inflammatory manifestations in the NOMID/CINCA syndrome. Certainly, our patient has been vaccinated properly and, although not exhibiting any adverse reactions until now, he is under close

FIGURE 3

Axial T2-weighted (A) and sagittal T1-weighted (B) images reveal large cysts in the right hemisphere in communication with ventricles due to previous infarcts and reduced white matter. No additional injuries were seen after 14 months with therapy.
follow-up so that we can immediately recognize infections requiring proper, aggressive management. Further studies should be performed to determine the pharmacokinetics of IL-1 blockers in children, especially with regard to young infants.

The coexistence of aseptic meningitis with fever and increased inflammatory markers would appear to be the first symptoms of NOMID/CINCA syndrome and should raise the awareness of neonatologists, pediatricians, and dermatologists, so that when the syndrome is diagnosed, the therapy targeting the cause should start promptly.

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REFERENCES


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