

Chronic urticaria in infants as the first manifestation of autoinflammatory disease

Irene Latour MD¹  | Lucero Noguera-Morel MD¹ | Isabel Colmenero MD² | Daniel Clemente MD⁴ | Angela Hernández-Martín MD¹ | Juan Carlos López-Robledillo PhD⁴ | Juan I. Arostegui PhD³ | Antonio Torrelo MD¹ 

¹Department of Dermatology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

²Department of Pathology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

³Department of Immunology, Hospital Clínic—Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain

⁴Department of Rheumatology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Correspondence

Antonio Torrelo, MD, Department of Dermatology Hospital Infantil Univ. Niño Jesús, Madrid Avda. Menéndez Pelayo 65, 28009 Madrid, Spain.
Email: atorrelo@aevd.es

Abstract

We report two unrelated infants in whom chronic urticaria was the first clinical manifestation of cryopyrin-associated periodic syndrome, which should be suspected in infants with early-onset chronic urticaria, especially if there is a neutrophil-rich infiltrate in the skin biopsy. Early diagnosis of cryopyrin-associated periodic syndrome may lead to early and successful treatment with anti-interleukin-1 medications.

KEYWORDS

autoinflammatory, chronic urticaria, infant, neutrophilic dermatosis

1 | INTRODUCTION

By definition, the presence of wheals for longer than 6 weeks is considered chronic urticaria (CU). In infants, spontaneous CU is extremely rare. It may rarely be due to food allergy or may occur as a prolongation of acute postinfectious urticaria.¹ Autoinflammatory syndromes should also be considered when CU appears in an infant younger than 2 years old.^{2,3}

Cryopyrin-associated periodic syndromes (CAPS) are rare dominantly inherited autoinflammatory diseases (estimated prevalence 1-3 cases per million).²⁻⁴ These syndromes result from heterozygous gain-of-function mutations in the *NLRP3* gene, which encodes for cryopyrin, a protein constituent of inflammasomes.⁵ The clinical phenotype of CAPS is characterized by systemic inflammation, with three allelic diseases recognized: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome (also known as neonatal-onset multisystem inflammatory disease).⁶ The main skin manifestation in all these syndromes is early-onset, long-standing urticaria that is often triggered by cold.⁷

We report two unrelated infants in whom CU was the first clinical manifestation of CAPS.

2 | CASE REPORTS

2.1 | Patient 1

A 2-month-old girl was referred for daily recurring wheals on her trunk, face, arms, and legs since birth (Figure 1A) without associated fever. Lesions persisted < 24 hours, with no trigger observed. Blood tests showed leukocytosis (19 140/μL) with neutrophilia (64.4%) and high plasma C-reactive protein (1.8 mg/dL, normal < 1 mg/dL). A biopsy of lesional skin showed a moderate perivascular, interstitial, and periadnexal predominantly neutrophilic inflammatory dermal infiltrate (Figure 1B,C). No vasculitis was noted. *NLRP3* analysis identified a heterozygous c.1705G>C transversion in exon 3, which leads to a p.(Gly569Arg) missense variant in the NACHT domain of cryopyrin. This missense variant has been previously reported in Muckle-Wells syndrome⁸ and is classified as pathogenic according to the guidelines of the American College of Medical Genetics and Genomics (Table 1). Genetic investigations in the patient's parents did not detect the missense variant, supporting the de novo nature of the mutation. At the age of 4 months, subcutaneous anakinra 10 mg/d (1.33 mg/kg per day) was initiated, leading to immediate

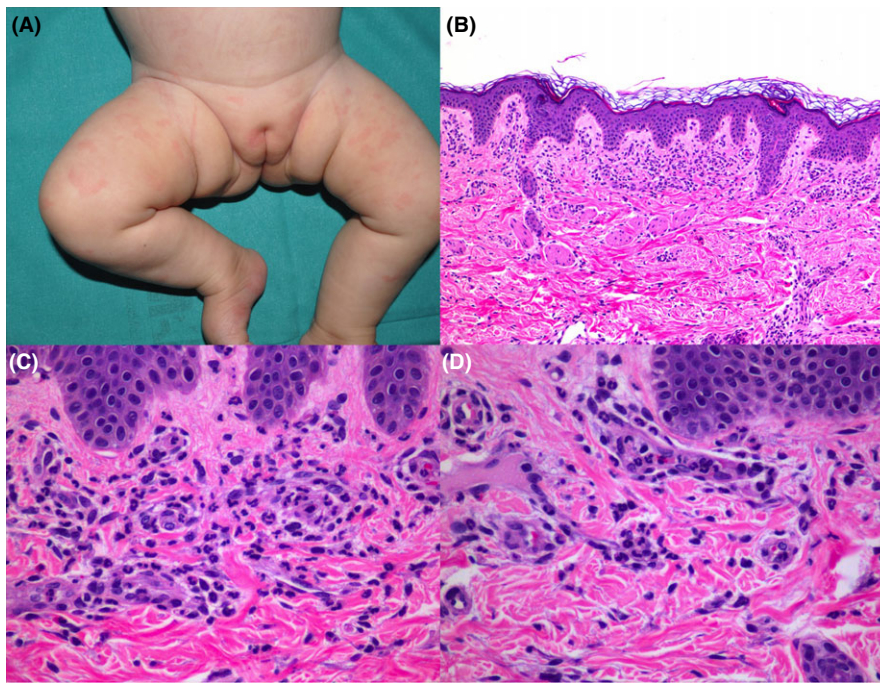


FIGURE 1 (A) Patient 1: clinical findings. Pale red urticarial wheals on the trunk and extremities. (B, hematoxylin & eosin stainx 20) Skin biopsy showing a moderate, inflammatory infiltrate in the dermis with perivascular, interstitial, and periadnexal inflammatory infiltrate mainly composed of neutrophils (C, D, hematoxylin & eosin stain, x100)

TABLE 1 Summary of genetic characteristics of detected *NLRP3* variants

Gene	Nucleotide Exchange ^a	Amino Acid Exchange	rs	Population Genetics		Bioinformatics			
				1000 Genomes Project	Genome Aggregation Database	Polyphen-2 (HumDiv score)	Sorting Intolerant from Tolerant (score)	Mutation taster (score)	Pathogenicity classification
<i>NLRP3</i>	c.777T>G	p.Cys259Trp	180177475	-	-	Probably damaging (1.000)	Damaging (0)	Disease causing (215)	Pathogenic
<i>NLRP3</i>	c.1705G>C	p.Gly569Arg	121908151	-	-	Probably damaging (0.963)	Tolerated (0.24)	Disease causing (125)	Pathogenic

^aNCBI RefSeq: *NLRP3*, NM_001243133.1.

disappearance of wheals, but because of the persistent leukocytosis, the dose was progressively increased to 25 mg/d (3 mg/kg per day). After 8 months on anakinra, blood tests showed no abnormalities, and no wheals reappeared. For more convenient dosing, treatment was shifted to subcutaneous canakinumab 35 mg/8 weeks (3.6 mg/kg), with good control of the disease.

2.2 | Patient 2

An 8-month-old girl was seen because of daily, recurring, evanescent wheals on her face and upper and lower extremities beginning at age 2 months (Figure 2A). No trigger was identified, and she was afebrile. The rest of her skin and general examination was normal. Blood tests, including hemogram, C-reactive protein, erythrocyte sedimentation rate, serum chemistry, and liver enzymes were within normal range. Lesional skin biopsy showed a sparse perivascular and interstitial, predominantly neutrophilic infiltrate (Figure 2B,C). Genetic testing revealed a heterozygous c.777T>G transversion in

exon 3 of the *NLRP3* gene, which leads to the p.(Cys259Trp) missense variant in the NACHT domain of cryopyrin. This missense variant has been previously reported in a case of mild familial cold autoinflammatory syndrome⁹ and is classified as pathogenic according to the guidelines of the American College of Medical Genetics and Genomics (Table 1). Genotyping of the patient's parents did not detect the missense variant and supported the de novo nature of the patient's mutation. Her parents declined anakinra treatment because of the mild phenotype, and she is being closely monitored.

3 | DISCUSSION

In CAPS, a mutant cryopyrin causes constitutive inflammasome hyperactivity, leading to excessive production of interleukin-1 β ,⁵ which is responsible for the clinical features. Two hundred five genetic variants of the *NLRP3* gene have been included in the INFEVERS database.¹⁰ Clinically affected patients with no germline

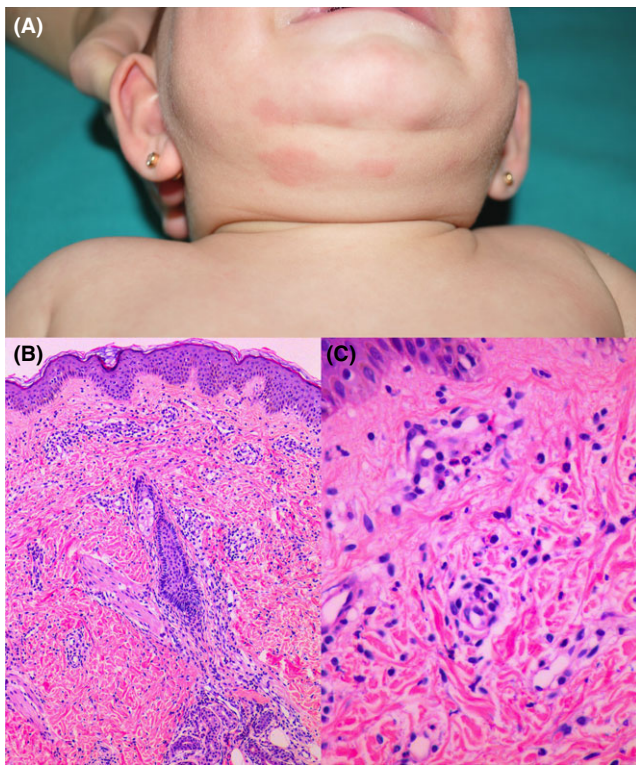


FIGURE 2 (A) Patient 2: clinical image of neck showing pale red wheals. (B, C) Skin biopsy showing perivascular and interstitial neutrophilic infiltrate in the dermis (B, hematoxylin and eosin stain x20; C, hematoxylin & eosin stain x100)

mutations may have somatic *NLPR3* mosaicism.¹¹ There is some correlation between genotype and severity of phenotype. A milder phenotype seems to be associated with the most frequent genotype (heterozygous p.Arg260Trp mutation), with an autosomal-dominant pattern of inheritance and a history of cold triggering. By contrast, rare mutations, sporadic cases, and early onset of disease (before the age of 6 months) are often associated with a severe phenotype,⁷ although identical genotypes can be associated with heterogeneous phenotypes, suggesting that environmental and additional genetic or epigenetic factors may play a significant role.

Clinically, skin rash is the most prevalent clinical manifestation of CAPS (97%).⁷ The classical urticarial rash can be found in 89% of patients, and a macular and/or papular rash can appear in 26%.⁷ Fever (84%), musculoskeletal manifestations (86%; myalgia, arthralgia, arthritis), and ocular involvement (71%; conjunctivitis, uveitis) are also prevalent features. Only 56% of patients report a trigger, usually cold exposure (85%).⁷ Sensorineural hearing loss is the most common late complication (42%–61%),^{2,7} and secondary amyloidosis is a serious late complication, with a median age at onset of 31 years.¹² Because of the hyperactivity of the innate immune system, inflammatory cells such as neutrophils are recruited to sites of tissue damage, such as the skin. Skin biopsies in patients with CAPS often show a perivascular and interstitial neutrophilic infiltrate, and neutrophils are also detectable within the epithelia of sweat glands. Neutrophilic epitheliotropism is a sensitive histologic marker (83.1%)

for immunologic disorders triggered by innate immunity,¹³ although we did not observe this phenomenon in our patients' biopsies. In our two patients, CU without triggers was observed, but the abundance of neutrophils in the biopsy led us to suspect autoinflammatory disease.

Diagnostic delay of CAPS is frequent, with a median delay of 7.2–14 years,^{2,7} and because of unchecked chronic inflammation, has been associated with risk of late complications such as secondary amyloidosis, sensorineural deafness, severe musculoskeletal involvement, and irreversible neurologic damage.^{12,14} Consequently, treatment must be initiated as early as possible. Therapies directed against IL-1 β (anakinra, canakinumab, rilonacept) dramatically improve clinical manifestations and have changed the paradigm of management of CAPS,⁶ preventing irreversible complications.

In conclusion, CAPS should be suspected in infants with early-onset CU, especially if triggered by cold. Neutrophilic infiltration in urticarial lesions in this clinical setting should raise suspicion for CAPS. Genetic testing for mutations in the *NLPR3* gene will confirm the diagnosis, allowing for prompt, early treatment to prevent late complications.

ORCID

Irene Latour  <http://orcid.org/0000-0002-5669-2283>

Antonio Torreló  <http://orcid.org/0000-0002-5940-6916>

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