

TITLE PAGE

Title:

Early onset urticaria – a marker of cryopyrin associated periodic fever syndrome

Authors:

Dharshini Sathishkumar,¹ Eslam Al-Abadi,² Ina Nicklaus-Wollenteit³, Celia Moss,¹ Philip N

Hawkins,⁴ Joanna E Gach¹

Departments of Dermatology¹, Rheumatology² and Pathology³ Birmingham Children's

Hospital NHS Foundation Trust, Birmingham, United Kingdom

National Amyloidosis Centre⁴, UCL, Royal Free Hospital, London, United Kingdom

Institution in which study was conducted:

Birmingham Children's Hospital, Birmingham, United Kingdom, B4 6NH

Corresponding author:

Dr. Joanna E Gach

Department of Dermatology

Birmingham Children's hospital

Birmingham

United Kingdom

E-mail: Joanna.Gach@bch.nhs.uk

Phone +44 121 333 8225

Fax: +44 121 333 8231

Keywords: CAPS, cryopyrinopathies, autoinflammatory syndromes, NLRP3 gene, urticaria

1
2
3 **Word count:** 597 words
4
5
6

7 **Figures:** 2
8
9

10
11 **Conflict of interest:** Nil
12
13

14 **Running head:** Early onset urticaria – a marker of CAPS
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

1
2
3 **EARLY ONSET URTICARIA – A MARKER OF CRYOPYRIN ASSOCIATED**
4
5 **PERIODIC FEVER SYNDROME**
6
7

8 Dharshini Sathishkumar,¹ Eslam Al-Abadi,² Ina Nicklaus-Wollenteit,³ Celia Moss,¹ Philip N
9
10 Hawkins⁴, Joanna E Gach¹
11

12
13 Departments of Dermatology¹, Rheumatology² and Pathology³ Birmingham Children's
14
15 Hospital NHS Foundation Trust, Birmingham, United Kingdom
16

17
18 National Amyloidosis Centre⁴, UCL, Royal Free Hospital, London, United Kingdom
19
20

21
22
23
24 A one-year-old boy presented with an asymptomatic fleeting erythematous rash, **recurring**
25
26 **since** 6 hours after birth, without fever and poorly responsive to high-dose antihistamines.
27
28 The **lesions, which disappeared within hours**, appeared when he was undressed or bathed,
29
30 suggesting **cold** as a trigger. He was otherwise well, growing and developing normally, with
31
32 no relevant personal or family history. Examination showed multiple small scattered
33
34 urticarial rash on his trunk and extremities (Fig. 1).
35
36
37

38
39 Investigations revealed low haemoglobin 109 g/L (117-137), raised white blood cells 19.6
40
41 $\times 10^9/L$ (5.0-16.0), platelets 512 $\times 10^9/L$ (150-400), CRP 32 mg/L (0-10) and ESR 85 mm/hr
42
43 (0-9). Other than a slightly low IgD 0.03 g/L (0.05-0.20), immunoglobulins were within
44
45 normal limits. Histology from a representative lesion showed a neutrophilic urticarial
46
47 dermatosis characterised by perivascular and interstitial neutrophilic infiltrate with
48
49 leukocytoclasia but without vasculitis or dermal oedema (Fig. 2).
50
51

52
53 These findings prompted further investigations which demonstrated a raised serum amyloid
54
55 A protein at 15.5 mg/L (<5-10mg/L) and a previously described pathogenic heterozygous
56
57 mutation in exon 3 of *NLRP3*, Asp303Asn (D303N), which was absent in his parents and
58
59
60

1
2
3 siblings, signalling a diagnosis of cryopyrin associated periodic syndrome (CAPS). Treatment
4 with anakinra led rapidly to complete resolution of the symptoms and serological
5 abnormalities, and he remains well at 2.5 years of age.
6
7

8
9
10 CAPS, sometimes termed the cryopyrinopathies, is ~~an hereditary periodic fever syndrome~~
11 caused by dominantly inherited or *de novo* gain-of-function mutations in the *NLRP3* gene
12 located on chromosome 1q44, which encodes the intracellular protein cryopyrin (formerly
13 NALP3). Activation of cryopyrin, a constituent of the multiprotein inflammasome complex,
14 results in downstream activation of caspase 1 leading to over-production of interleukin IL-1 β ,
15 a potent inflammatory cytokine that drives the characteristic fever, vasodilation and systemic
16 inflammation.¹
17
18

19
20
21 Three subtypes of CAPS are recognised but there is considerable clinical as well as genetic
22 overlap. Familial cold autoinflammatory syndrome (FCAS) is the mildest variant with cold-
23 induced episodes of fever with rash, arthralgia, headaches and occasionally conjunctivitis. In
24 Muckle-Wells syndrome (MWS) there is additionally, but variably, sensorineural hearing loss
25 and amyloidosis in adulthood (25%). Neonatal-onset multisystem inflammatory disease
26 (NOMID)/chronic infantile neurologic, cutaneous, articular syndrome (CINCA) is the most
27 severe form with about 20% mortality before adulthood. It presents in the neonate or infant
28 with **spontaneous** urticarial rash and fever; later patients develop central nervous symptoms,
29 sensorineural hearing loss, ocular changes (80%) and disabling arthropathy.² **Although the**
30 **course of CAPS is unpredictable, sporadic occurrence, early onset (<6 months), and urticaria**
31 **not provoked by cold are associated with a higher risk of severe neurological complications.**³
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52 The relatively mild presentation **and provocation by cold in our patient are** in keeping with
53 the FCAS end of the CAPS spectrum, **but the very early onset is a concern.** Furthermore, the
54 D303N mutation in *NLRP3* gene has been reported in association with MWS and CINCA but
55
56
57
58
59
60

1
2
3 not FCAS.^{2,4} It is not possible to accurately predict the risk of neurological complications and
4
5 neurosensory hearing loss in a young patient with CAPS, since the precise features ~~severity~~
6
7 ~~of the disease~~ may vary substantially within a single family, let alone among the numerous
8
9 different causative mutations. ~~Cold trigger and autosomal dominant inheritance have been~~
10
11 ~~reported as predictors of better prognosis, but~~ All these patients require close long term
12
13 monitoring including audiometry, ophthalmology and neurological review and early IL-1
14
15 blocking treatment to minimize the risk of long-term complications.³
16
17

18
19 Our case highlights the importance of considering autoinflammatory syndromes when a child
20
21 presents with very early onset, ~~asymptomatic, fleeting urticarial lesions, unresponsive to~~
22
23 ~~antihistamines,~~ even without other features of systemic inflammation. ~~A perivascular~~
24
25 ~~neutrophilic infiltrate on histology supports a diagnosis of CAPS.~~ Prompt diagnosis allows
26
27 the use of specific treatment with anti-IL-1 agents,⁵ which dramatically improves quality of
28
29 life in most cases and hold great hope for improving outcomes long-term.
30
31

32
33 **Conflict of interest:** nil
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References:

1. Giat E, Lidar M. Cryopyrin-associated periodic syndrome. *Isr Med Assoc J* 2014; **16**: 659–61.
2. Aksentijevich I, D Putnam C, Remmers EF, et al. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* 2007; **56**: 1273–85.
3. Levy R, Gérard L, Kuemmerle-Deschner J, et al. Phenotypic and genotypic characteristics of cryopyrin-associated periodic syndrome: a series of 136 patients from the Eurofever Registry. *Ann Rheum Dis* 2015; **74**: 2043–9.
4. Dodé C, Le Dû N, Cuisset L, et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet* 2002; **70**: 1498–506.
5. ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. *Ann Rheum Dis* 2015; **74**: 1636–44.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure Legends:

Figure 1: Multiple scattered urticarial rash on the lower limbs

Figure 2: Histopathology from a representative lesion showing perivascular and interstitial neutrophilic infiltrate with leukocytoclasia but without vasculitis or dermal oedema. Haematoxylin and eosin, original magnification x 400

For Peer Review

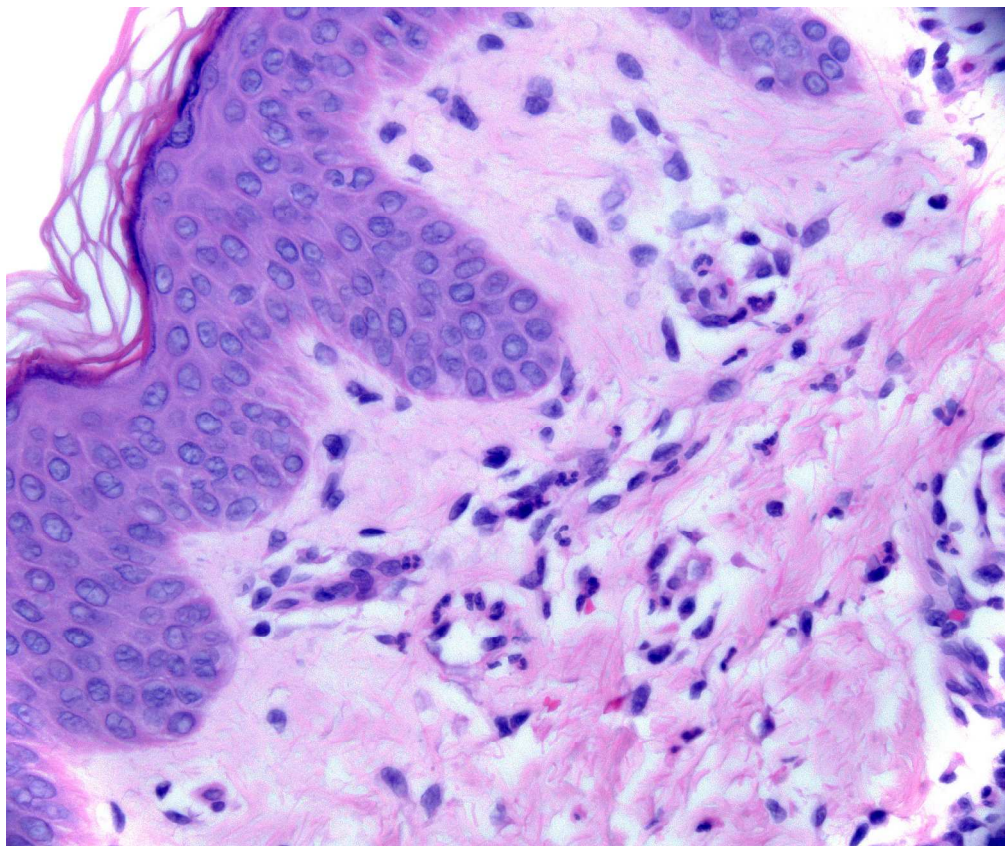
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Multiple scattered urticarial rash on the lower limbs

70x99mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Histopathology from a representative lesion showing perivascular and interstitial neutrophilic infiltrate with leukocytoclasia but without vasculitis or dermal oedema. Haematoxylin and eosin, original magnification x 400

648x543mm (96 x 96 DPI)



MCQs:**Learning objective**

To demonstrate up-to-date knowledge in the pathogenesis of cryopyrin associated period syndrome.

Question 1

1. Mutation in which of the following genes causes cryopyrin associated periodic syndrome?

- a) *MEFV*
- b) *MVK*
- c) *IL1RN*
- d) *NLRP3*
- e) *IL36RN*

Answers to question 1:

- a) Incorrect, mutation in *MEFV* gene causes familial mediterranean fever
- b) Inorrect, mutation in *MVK* gene causes Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS) or Mevalonate Aciduria (MA)
- c) Incorrect, mutation in *IL1RN* gene is implicated in Deficiency of Interleukin-1 β (IL-1 β) Receptor Antagonist (DIRA)
- d) Correct, mutation in *NLRP3* gene causes cryopyrin associated periodic
- e) Incorrect, mutation in *IL36RN* is implicated in Deficiency of Interleukin-36-Receptor Antagonist (DITRA)

Question 2:

Learning objective: To demonstrate up-to-date knowledge in the management of cryopyrin associated period syndrome.

The drugs used in the treatment of cryopyrinopathies are targeted against which of the following interleukins?

- a) IL-6
- b) IL-8
- c) IL-5
- d) IL-1

1
2
3 e) IL-17
4

5 **Answers to Question 2:**
6

7 a) Incorrect. The drugs targeted against IL-6 are used in treatment of certain rheumatic
8 disease such as Castleman's disease and rheumatoid arthritis.
9

10 b) Incorrect. The drugs used in treatment of cryopyrinopathies are not targeted against IL-8
11

12 c) Incorrect. The drugs targeted against IL-5 are tried in the treatment of eosinophilic
13 disorders.
14

15 d) Correct. The drugs such used in treatment of cryopyrinopathies are targeted against IL-1
16

17 e) Incorrect. The drugs targeted against IL-17 are used in psoriasis
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review