Clinical and genetic characterization of Italian patients affected by CINCA syndrome

F. Caroli1,*, A. Pontillo2,*, A. D’Osualdo1, L. Travan2, I. Ceccherini1, S. Crovella2, M. Alessio3, A. Stabile4, M. Gattorno5, A. Tommasini2, A. Martini5 and L. Lepore2

Objective. We report the experience of the Italian Registry of patients affected by chronic infantile neurological, cutaneous, articular (CINCA) syndrome. The clinical and genetic features of 12 unrelated Italian patients with CINCA syndrome are described, focusing on the possible influence of the presence of CIAS1/cryopyrin mutations on the phenotype of the disease and on its prognosis.

Methods. The clinical features of 12 Italian CINCA patients were evaluated. Genomic DNA of the patients was sequenced using specific primers for CIAS1 and ASC genes.

Results. Our patients shared typical CINCA characteristics and, sometimes, remarkable perinatal events, peculiar of CIAS1-mutated patients. Seven patients carried CIAS1 missense mutation, localized within the nucleotide binding domain of cryopyrin. Four previously described mutations and three new heterozygous CIAS1 missense mutations were identified. ASC gene, encoding for a direct interactor of cryopyrin, was not mutated in Italian CINCA patients. Finally, we reported the efficacy and safety of anti-IL1 therapy (Anakinra) in seven patients with a particularly severe CINCA phenotype.

Conclusion. Despite some common signs—used as syndrome hallmarks—we observed a high variability in symptoms, genetic results and outcomes in Italian CINCA patients. In contrast with other authors, we cannot find out any correlation between mutations in CIAS1 and CINCA severity, but we underlined the concomitance of perinatal events and mental retardation only in CIAS1 mutated subjects. Finally, we confirmed the efficacy of Anakinra treatment, both in CIAS1-mutated and non-mutated patients.

Key words: Congenital autoinflammatory disease, ASC, CIAS1, Anakinra.

Chronic infantile neurological cutaneous and articular syndrome (CINCA; OMIM 607115), also known as neonatal onset multisystemic inflammatory disease (NOMID), is a very rare congenital inflammatory disease characterized by neonatal onset, cutaneous manifestations, recurrent fever, central nervous system (CNS) involvement, chronic arthropathy, peculiar facial and morphological features. Although some features, as urticarial-like rash—which is unresponsive to any treatment—and typical head morphology, are commonly present in CINCA patients, there is still a large spectrum of variability in clinical symptoms, time of onset, outcome and prognosis.

About 60% of the patients present missense mutations in the CIAS1/NALP3/PYPAF gene, which encodes the cryopyrin protein [1, 2]. Muckle–Wells syndrome (MWS; OMIM 191900) and familial cold-induced autoimmune syndrome (FCAS; OMIM 120100) have also been associated with CIAS1 mutations and for this reason, these three different syndromes are considered nowadays a single disorder with different degrees of gravity, with CINCA as the most severe [3–7].

Cryopyrin is a member of the cytoplasmic protein family CATERPILLER, which is involved in inflammasome molecular platform assembly, leading to inflammatory immune response and apoptosis regulation [8–11]. Cryopyrin is an inflammasome scaffold protein, which in the presence of a still unknown stimulus, oligomerizes and binds the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD). This association directly activates the interleukin (IL)-converting enzyme (ICE)/caspase-1 and—through other inflammasome components—the nuclear factor κB (NF-κB). Therefore, activated cryopyrin induces both the release of IL-1β and the transcription of pro-inflammatory and anti-apoptotic genes [12–18].

It has been hypothesized that mutant cryopyrin spontaneously oligomerizes and induces the inflammasome activation with elevated IL-1β production and the autoinflammatory phenotype observed in CINCA syndrome [19, 20]. More precisely, IL-1β is the effector molecule principally involved in local and systemic manifestation of the disease, and the specific inhibition of the IL-1β with IL-1 receptor antagonist (IL-1Ra, Anakinra) has been recently found to be extremely effective in patients with CINCA and other CIAS1-pathies (FCAS, MWS) [21–26].

Herein, we report the clinical characteristics and the CIAS1 mutation analysis results of patients collected through the Italian registry of CINCA syndrome. The aim of the present study was to focus on the differences in clinical presentation, disease course and response to anti-IL-1β (Anakinra) treatment between...
**Perinatal events**

**Disease onset**

- Prematurity and/or low birth weight and/or prolonged icterus and/or intrauterine distress or respiratory distress
- CD, celiac disease; AS, aortic stenosis; AC, atypical rash, not persistent, recurrent purpuric lesions; PA, persistent arthritis; TA, transient arthritis; mo, month;
- 'perinatal events, prematurity and/or low birth weight and/or prolonged icterus and/or intrauterine distress or respiratory distress
- CD, celiac disease; AS, aortic stenosis; AC, aspecific colitis.

**Patients and methods**

**Patients recruitment.** A properly formulated questionnaire was sent to all paediatric rheumatology departments, joining the Italian Paediatric Society, in order to identify the cases suggestive for a CINCA syndrome. According to Neven et al. [4], for the study we used for CINCA syndrome diagnosis the following three 'major' criteria: early-onset urticarial skin rash variably associated with episodic fever, CNS involvement (papilloedema, hearing loss, RMN positive headache) and inflammatory or deforming arthropathy. In younger subjects (≤4 yrs)—assuming that some signs could be revealed only during the follow-up—we take into account the typical facies for the early diagnosis, even if they present only two major criteria. Familiar history, clinical signs and symptoms, laboratory data and previous treatments were recorded, after written informed consent—according to the Declaration of Helsinki—was obtained from the patient him/herself or from his/her parents.

**Anakinra treatment.** In severe cases, Anakinra was administered—after informed consent—by subcutaneous injections at a daily dosage of 1 mg/kg in children and up to 100 mg in adults. The study was approved by the ethics committee of the IRCCS Burlo Garofolo Hospital.

**Gene mutation analysis.** All coding regions and intronic flanking sequences of the *CIAS1/PYPAF1/NALP3 and ASC* genes—as well as a portion of the *CIAS1* promoter region (1000 bp upstream 5'UTR)—were amplified by polymerase chain reaction (PCR) using specific primers designed with the Primer Express 2.0 Software (Applied Biosystems, Foster City, CA, USA). PCR products were sequenced by using the BigDye Terminator Cycle Sequencing Ready Reaction Kit 3.0 (Applied Biosystems). DNA sequencing reactions were run and detected on an automated ABI Prism 3100 Genetic Analyser (Applied Biosystems) and analysed with Seqman II Software (DNASTAR Inc.). In order to validate new mutations, we analysed 50 healthy controls.

**Results**

**Clinical details**

- Twelve unrelated Italian CINCA patients were collected by four different paediatric rheumatology departments (IRCCS Burlo Garofolo, Trieste; IRCCS Gaslini, Genoa; Federico II Hospital, Naples; Università Cattolica Sacro Cuore, Rome, Italy). The patients presented typical signs although they were heterogeneous for other clinical manifestations and for disease severity (Table 1).
- All patients showed at least two major criteria we used for diagnosis:
  1. The urticarial skin rash, which never completely disappeared, was present at birth in all but one patient (P2 showed a non-persistent atypical rash, characterized by recurrent purpuric lesions, from 6 months of age).
  2. A neurological involvement was present in 10 patients.
- Papilloedema (absent only in the two youngest

**Table 1. Clinical and genetic data described in the 12 Italian patients with CINCA syndrome. The subjects are classified on the basis of the syndrome severity**

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<td>Mutation in <em>CIAS1</em> gene</td>
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<td>E688K</td>
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CINCA severity.

- CNS-I, central nervous system involvement; OA-I, osteo-articular involvement; F, female; M, male; ●, present; □, atypical rash, not persistent, recurrent purpuric lesions; PA, persistent arthritis; TA, transient arthritis; mo, month; ●, perinatal events, prematurity and/or low birth weight and/or prolonged icterus and/or intrauterine distress or respiratory distress; CD, celiac disease; AS, aortic stenosis; AC, aspecific colitis.
subjects, P2 and P12) was the most common symptom in this area, followed by perceptive deafness (found in half of the patients), recurrent severe headache (in five patients, three of whom—P5, P6, and P7—were found to have mild cerebral atrophy at cerebral magnetic resonance imaging) and mental retardation (in P6 and P10, who also had severe articular and neurological involvement and represented our most severe CINCA cases). Only the two youngest patients (P2 and P12) did not show any CNS involvement but we could not exclude that these signs (due to CNS involvement) might appear during the follow-up.

(iii) Inflammatory or deforming arthropathy was present in all but one patient (P8). Some patients (P2, P4, P5, P6, P7, P9, P12) had a transient arthritis (TA), without persistent deformities of the involved joints and others (P1, P3, P10, P11) had a persistent severe arthritis (PA) involving knees: in P3 and P11, both knees were involved including ankles and hands. Also epiphyseal/patellar overgrowth, another disease-associated feature, was evident in most of the subjects. Moreover, at 3 yrs of age, patient P1 developed an important, painful swelling of the proximal tibial epiphysis that histologically revealed to be a ‘chondroid dysostosis’ (Fig. 1); in this individual hoarseness, which is another typical symptom, appeared very early (by 3 yrs). Considering the possibility of a malignant evolution in chondrosarcoma, as described by De Cunto et al. [27], the patient has been subjected to a strict follow-up. In this case, only low-dose steroids were able to control the pain due to lesion before Anakinra treatment was started.

(iv) the typical ‘facies’ characterized by frontal bossing and saddle back nose causing sibling-like resemblance was found in all the subjects but one (P3).

Microcytic anaemia and increased acute phase reactant (CRP, ESR, IgG, IgA) were present in all the subjects.

In about half of the patients, we observed fever and simultaneous enlargement of lymph nodes, spleen and liver (Table 1), which document the extremely severe grade of inflammation of this syndrome.

Failure to thrive was observed in six subjects; four patients (P5, P7, P9, P11) were adults (aged >18 yrs) with a final height under the genetic target.

In 10 patients, the age of onset was in the first month of life. In P2 and P7, the disease started after 6 months of age (6 and 8 months, respectively).

Seven out of 12 patients in our series presented remarkable perinatal events as following: P2: oligohydramnios, Caesarean section for abruptio placentae at 32 weeks of gestational age, neonatal birth weight 1350 g; P3: threatened abortion at 22 weeks of gestational age and neonatal prolonged icterus requiring more than 24 h of phototherapy; P6: neonatal diagnosis of severe aortic stenosis and neonatal prolonged icterus requiring more than 24 h of phototherapy; P7: Caesarean section for fetal distress at 39 weeks of gestational age, neonatal distress, small for gestational age with neonatal birth weight 2180 g and neonatal prolonged icterus requiring more than 24 h of phototherapy; P9: fetal distress, small for gestational age with neonatal birth weight 2000 g at 40 weeks and neonatal prolonged icterus requiring more than 24 h of phototherapy; P10: umbilical hernia and neonatal prolonged icterus requiring more than 48 h of phototherapy; P12: small for gestational age with neonatal birth weight 2100 g at 40 weeks and neonatal prolonged icterus requiring more than 24 h of phototherapy.

We observed two peculiar aspects not previously associated with CINCA syndrome: (i) P6 presented with a severe congenital aortic valvular stenosis that required a complex surgical correction, (ii) celiac disease (CD) was diagnosed in two patients (P3, P4) by anti-hTg antibodies analyses and was confirmed by intestinal biopsy. Both had HLA-DQ2, one of the two CD pre-disposing alleles [28].

Anakinra response

Seven patients with a particularly severe CINCA phenotype and refractory to different treatments (NSAIDs, steroids, immuno-suppressive drugs) underwent anti-IL-1β therapy with the IL-1Ra (Anakinra). In all seven patients (P1, P2, P5–P7, P10, P11), the treatment has led to a dramatic improvement of the disease. A few days after the beginning of the treatment, fever and rash completely disappeared and a general improvement of other disease-associated symptoms—for example, artralgia and papilloedema—was observed. Figure 2 shows the normalization of acute phase proteins levels (Fig. 2a: ESR; Fig. 2b: CRP) and haemoglobin (Fig. 2c) concentration during the first month of the treatment. All seven patients are still in therapy with the IL-1Ra (median follow-up 12 ± 4 months) with optimal clinic control and normal acute phase proteins levels and haemoglobin values.

Genetic results

We sequenced the nine exons including surrounding sequences from the human CIAS1/PYPAF1/NALP3 gene (GenBank accession number: NM_004895) in the 12 Italian CINCA patients in order to screen CIAS1 variants that might cause the CINCA phenotype. No consanguinity was reported among the patients’ parents, nor was the history of recurrent autoinflammatory syndrome in their respective families. Seven patients presented mutations in the CIAS1 gene (Table 1), all within exon 3. Three new heterozygous missense mutations, not previously described
in association neither with CINCA syndrome nor with other CIAS1-pathies (MWS, FCAS), were identified: c.910 G→A (E304K) in patient 3 (P3), c.1218 G→C (M406I) in P2, c.2062 G→A (E688K) in P9. None of these substitutions was found in healthy controls. In patients P6, P7, P10 and P12 we identified previously described missense mutations: c.1431 C→A (N477K), c.1043 C→T (T348M), c.1718 T→C (F573S) and c.907 G→A (D303N), respectively (Infevers Database, http://fmf.igh.cnrs.fr/infevers [29]).

Seven other nucleotide variations were detected, which are already described in CINCA patients [6] but annotated as single nucleotide polymorphisms (SNPs) present in the general population (http://www.ncbi.nlm.nih.gov). Three of these polymorphisms were identified in exon 3, c.726 G→A (A242A); c.1302 C→A (S434S); c.2107 C→A (Q703K); a G deletion in exon 5; the other SNPs were found in non-coding regions (5'UTR and introns) of the CIAS1 gene.

To verify if a transcriptional failing could represent the molecular defect underlying CINCA patients not carrying any CIAS1 coding mutations (P1, P4, P5, P8, P11), a 1000 bp region upstream of exon 1 of the CIAS1 gene—a putative promoter region according to Gen2Promoter (Genomatix Software GmbH)—was screened without finding any nucleotidic variations, except for a known SNP at position −895 C→T (rs12137901) in P1 and P4.

Then, we analysed the four exons and the exon/intron flanking regions of the ASC gene, which encodes a direct interactor of cryopyrin and it is involved in the activation of inflammasome. Only an intronic nucleotide sequence variation (c.571+31 C→A) found also in healthy controls was identified.

**Discussion**

Neven et al. [4], in a recent paper, showed that in their patients, considering all CIAS1-pathies, there exists a relative phenotype/genotype correlation, and none of the mutations identified in subjects with the most severe expression of disease (CINCA syndrome with chronic meningitis and arthropathy) was observed in patients with the mildest phenotype (FCU). Our data about CINCA syndrome were more heterogeneous from this point of view, and—in some cases, were contradictory (Table 1).

In fact, T348M—previously associated with milder forms of the CINCA syndrome and to the less severe MWS [4]—in our patient (P7) was associated with a quite severe form of CINCA (the typical CINCA signs plus hearing loss).

Instead, the F573S substitution (P10) was related to a serious grade of all manifestations, including mental retardation. This result well fits with the previous association between this CIAS1 mutation and a severe form of CIAS1-pathies [4].

The patient carrying the D303N substitution (P12)—which was previously associated with multiple CIAS1-pathies phenotypes (from MWS to severe CINCA) [4, 30]—presented few severe symptoms that could be confused with MWS, but we assume that it is a CINCA syndrome, considering the age and the presence of the typical facies.

The N477K variation was found in a patient (P6) with the most severe CINCA phenotype (all the symptoms and mental retardation). This substitution was only described in a very young Japanese female so far affected by a mild form of CINCA (with rash, facies and inflammation markers increased, but without arthropathies or CNS involvement) [29].

The new mutations can be predicted as disease-causing mutations, based on position in the protein, molecular nature and evolutionary conservation of the residue changed [31], and were associated with different degrees of CINCA manifestations (Table 1). Nevertheless, additional functional studies on the mutant alleles will be necessary to formally prove that they are indeed causative mutations for the CINCA phenotype.

Also the other patients—wild type for the CIAS1 gene—showed different severity degrees of CINCA syndrome with no substantial clinical differences with the mutated ones (Table 1). Two exceptions regard the incident of relevant perinatal events and the presence of mental retardation, both present only in CIAS1-mutated subjects.

More than a half of our patients presented with major perinatal events, as previously reported [32–33]; although the observed perinatal events are heterogeneous and not specific, their presence together with a neonatal rash without other explanations should be carefully taken into consideration from a diagnostic point of view for CINCA syndrome. The observation that only CINCA patients with CIAS1 mutations displayed major perinatal events...
of interest revealing a specific effect of CIAS1 defects and providing the ground for a still undiscovered genotype–phenotype correlation.

According to a recent Spanish study [34], mental retardation does not seem to be a peculiar feature of CINCA, as previously described in the milestone paper by Prieur [32], but could be related with mutations in the CIAS1 gene.

Interestingly, 2 CINCA subjects out of 12 also presented with celiac disease (CD) associated with the typical HLA gene (DQ2). Since CINCA is a relatively frequent condition (1:100–300), while CINCA is a very rare disease, we cannot conclude that CD is more frequent in CINCA patients; in fact, the two disorders might arise in the same patient as coincidental events. Perhaps, proinflammatory dysregulations observed in CINCA could increase the risk of CD development or, alternatively, untreated CD could worsen CINCA progression, as it occurs when untreated CD associates with other autoimmune diseases such as autoimmune urticaria [35]. Further investigations are needed to establish the relationship between CINCA and CD in these patients.

The close similarities in the pattern of disease presentation and outcome between CIAS1-mutated and non-mutated patients confirm the possibility that another gene functionally related to CIAS1 could be involved in the pathogenesis of the still orphan CINCA cases. This issue is strongly supported by the observation of a similar dramatic response to treatment with recombinant IL-1 receptor antagonist observed in all treated patients, independently from the presence of CIAS1 mutation.

For this reason, we have hypothesized the involvement of the ASC gene, coding for a downstream effector of cryopyrin known to be involved in the inflammatory response, candidate therefore as an autoinflammatory disease-causing gene. In fact, the pyrin domain of cryopyrin interacts with the ASC adaptor protein in the inflammasome complex formation, leading to the activation of NF-kB and/or caspase pathways [14–20]. Despite alterations in the ASC molecule having an effect in the deregulation of inflammation and apoptosis, similar to that observed for defective cryopyrin, we have not been able to demonstrate a role of the ASC gene in CINCA pathogenesis, since we did not find any mutation in this gene.

CINCA syndrome is nowadays a well-defined clinical condition but its early identification is often missed. Pediatricians should be aware of this rare condition in order to detect it quickly and start the appropriate treatment as soon as possible, allowing to stop the disease progression to the severe degrees (deafness, meningitis, mental retardation and perceptive deafness). Genetic testing may, of course, give a strong support to diagnosis confirmation, at present, unfortunately limited to the CIAS1 gene.

We believe that all efforts aimed at searching additional genes possibly involved in the etiology of this syndrome should be focused on molecules functionally related to the activation of inflammasome and ultimately IL-1β secretion in those cell types already involved in CIAS1-mediated inflammatory response.

Conclusions

From a clinical point of view, CINCA syndrome is a well-defined but a very heterogeneous disease. It is characterized by different degrees of three ‘major’ signs (rash, neurological and osteo-articular involvement) variably associated with the typical facies and other symptoms (recurrent fever, inflammatory marker, etc.). About half of the patients carry a missense mutation in CIAS1 gene that lead to an inflammasome pathway dysfunction responsible for the autoinflammatory phenotype observed in that syndrome. No pathogenetic hypothesis were made for the patients showed the same phenotype but without a mutation in CIAS1 gene. The IL-1Ra (Anakinra) treatment has given good results in CINCA subjects. Both clinically and genetically, Italian patients affected by CINCA syndrome were characterized. We underlined the absence of genotype-phenotype correlation between CIAS1 mutations and CINCA severity, also comparing our data with previous studies. Moreover, an ASC gene dysfunction in the pathogenesis of the syndrome in CIAS1 subjects was hypothesized. Finally, we reported the efficacy of Anakinra treatment in Italian CINCA patients—despite the presence of mutations in CIAS1 gene—that confirm previously published data.

Acknowledgements

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The authors have declared no conflicts of interest.

References

inducible inflammatory mediator with NF-κB suppressive properties.


