Socio-professional impact and quality of life of cryopyrin-associated periodic syndromes in 54 patients in adulthood

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Abstract

Objective

Cryopyrin-associated periodic syndromes (CAPS) belongs to the group of hereditary recurrent fever disorders characterised by interleukin1β-mediated systemic inflammation. Specific treatment by IL-1 targeting drugs has significantly modified the disease evolution. We aimed to evaluate the socio-professional impact of CAPS in the long term and the influence of genetic variants in the phenotype.

Methods

We made a multicentre, observational and descriptive study and collected retrospective data from childhood to adulthood, and until the last year of follow-up. We assessed the quality of life (QoL) of the patients by phone interviews. We also used the SF36 questionnaire including 8 domains: physical function, physical role, body pain, general health, vitality, social function, emotional role and mental health. A high score means a better QoL.

Results

Fifty-four patients were evaluated (14 familial cold autoinflammatory syndrome, 27 Muckle-Wells syndrome, 7 chronic infantile neurological cutaneous and articular syndrome. The study showed improvement in symptoms in adulthood and good QoL in all domains apart from school (87%) and work (61%) absenteeism. The MWS group is intermediate in terms of symptoms but seems to describe a better QoL compared to the other groups. The genetic variant alone does not determine the expression of the disease.

Conclusion

Our study shows that CAPS patients have an improvement of symptoms in adulthood and a satisfactory QoL for most of them. Anti-IL1 treatment is the main factor linked to this improvement and therefore early initiation should be encouraged.

Key words

cryopyrin-associated periodic syndromes (CAPS), familial cold urticaria (FCAS), Muckle-Wells syndrome, chronic infantile neurological, cutaneous and articular syndrome (CINCA), quality of life

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Introduction

Cryopyrin-associated periodic syndrome (CAPS) belongs to the group of interleukin1β-mediated autoinflammatory disorders and represents the hallmark of the inflammasomopathies. CAPS includes three clinical entities initially described as distinct but part of the same clinical continuum (1, 2): familial cold urticaria (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological, cutaneous and articular syndrome or neonatal onset multisystem inflammatory disease (CINCA/NOMID). The prevalence in France is currently estimated at 1/360,000 (3, 4).

CAPS is characterised by inflammatory flare-ups clinically associated with maculo popular rash, conjunctivitis, headaches, arthralgia and myalgia, as well as fever and elevated acute phase reactants, *i.e.* C-reactive protein (CRP) and serum amyloid A protein (SAA). As the symptoms are not very specific, they can lead to misdiagnosis, and significant diagnostic delay, which can reach years (5). Delayed diagnosis is very harmful for patients as it exposes them to CAPS complications, such as neurosensory deafness, vision loss and AA amyloidosis. The discovery of a common genetic cause (mutation of the NLRP3 protein) led to these 3 disorders being classified under the same entity called CAPS (6-10).

Specific treatment with anti-IL1 (2, 11, 12) has considerably changed the prognosis of these pathologies and has significantly improved the patients' quality of life (QoL), making most of them asymptomatic.

Our study aimed to assess QoL and to describe the clinical symptoms of patients in adulthood. We also wanted to evaluate the clinical phenotypes and QoL of patients according to their genetic variants. Other studies have already investigated the clinical symptoms of this disease, but our study is the only one that compares different ages and provides a long follow-up through different periods of life.

Patients and methods

Patients

The patients included in this study were followed in the Internal Medicine and Paediatric Departments of Lille University, France, the Paediatric Rheumatology and Immunology Department of the Necker Enfants Malades Hospital in Paris and the Paediatric Rheumatology Department and Internal Medicine of the Bicêtre Hospital in Le Kremlin-Bicêtre, France.

All selected patients belonged to CAPS clinical spectrum (CINCA/NOMID, Muckle-Wells or familial cold urticaria). Mutation and the determination of the variant was confirmed by genetic analysis sequencing the NLRP3 gene.

Inclusion criteria were diagnosis of FCAS, MWS or NOMID/CINCA; age <16 years at the first symptoms of the disease; age ≥16 years at inclusion; with follow-up in a reference centre.

Non-inclusion criteria were age <16 years at inclusion, and non-consent.

Study design

Our study was a multicentre, observational, descriptive study, and was approved by the Data Protection Advisory Committee and the Centre National de l'Informatique et des Libertés (CNIL) according to the French law (reference: 2021-A00585-36). Patients received an information note. A phone interview was given by the investigator doctor who could certify, using a non-opposition form, that patients did not oppose to participate in the study and to the collection of data.

The primary objective of our study was the description of the clinical characteristics of patients with CAPS in adulthood and the assessment of their QoL.

The secondary objectives were to compare their clinical status between childhood and adulthood and to assess the effect of their genetic variant on both their clinical status and QoL.

Data collection

Patient data were collected from their medical records, retrospectively. Data collection of adult patients in the Kremlin-Bicêtre and Necker hospitals was carried out using their paediatric files.

Collected data assessed the childhood period starting from the appearance of symptoms, symptoms during the last year of follow-up, and patient's lifestyle and QoL at the time of the assess-

ment. Data collection was stopped on February 20, 2022.

The patients' characteristics that we studied included: the type of genetic variant, the disease course (relapsing or chronic), the characterisation of the attacks (triggering factor(s), presence or absence of fever, duration of attacks) and the description of constitutional clinical signs (fever, abdominal pain, nausea, vomiting, diarrhoea, chest pain, sore lymph nodes, urticaria, arthritis, arthralgia, myalgia, headache, conjunctivitis, keratitis, uveitis, papilledema, amyloidosis, meningitis, sensorineural deafness, mental retardation, hypogonadism, growth retardation), characteristics during pregnancy (number of children and how many are symptomatic, treatment during pregnancy).

All the information on the growth and size, the main cytological (including CSF), histological, neurofunctional and imagery results available were collected.

In addition, we collected demographic data related to the patients' lifestyle (health, activities, professional and social relationships) and we conducted individual phone interviews lasting 15 minutes to complete the quality of life questionnaire, using the SF36 questionnaire (Supplementary Table S3) to assess eight domains, each corresponding to a different aspect of health. These dimensions were physical function (PF); physical role (RP); body pain (BP); general health (GH); vitality (VT); social function (SF); emotional role (RE); and mental health (MH) (13). A high score meant a better QoL.

Some missing data could be completed during the phone calls.

Statistical analysis

Categorical data were expressed as numbers and percentages. Quantitative data were expressed by the mean and standard deviation in the case of the Gaussian distribution or by the median and interquartile range (25^{th} and 75^{th} percentiles) in other cases. The normality of the distributions was checked graphically and using the Shapiro Wilk test. The statistical analysis was carried out using the SAS software, v. 9.4 (SAS Institute, Cary, NC, USA) by the Biostatistics Unit of the Lille University Hospital.

Results

Patients' selection

Of the 67 eligible patients, only 54 were included. 13 were excluded because of missing data or non-response to the questionnaire (Fig. 1).

Patients, demographics and baseline characteristics

The study population comprised 54 adults (>16 years) with more females (57.4%). The most common phenotype was the MWS (55.5%)

Median age at onset of symptoms was 1 year, median age at diagnosis was 18 years and median age at the last visit was 34 years. 51 patients received a specific treatment (94.4%). These patients were all treated by canakinumab. The median age at giving an anti-IL1 treatment was 24 years and 15 patients had started the treatment before the age of 16.

The major identified mutations were A439V (n=17) and R260W (n=16). A439V was found in the 3 major subtypes (12 in FCAS, 3 in MWS, 2 in CINCA) whereas the R260W mutation was only identified in the MWS group.

Clinical situation

- Clinical characteristics in adulthood

The most frequently reported symptoms in the last year for all patients were fever, urticaria, mouth ulceration, myalgia, arthralgia, arthritis, headache, conjunctivitis and hearing loss (Table I).

In the CINCA group, there were proportionally more patients with all of these symptoms, with the exception of urticaria, which was more common in the FCAS group (**S1**). MWS patients had an intermediate phenotype with the exception of myalgia which was more prevalent in the FCAS group than in the MWS group.

Regarding the variants, patients with the R260W mutation had more symptoms than A439V patients except for urticaria and myalgia (Suppl. Table S2).

- Clinical characteristics between adulthood and the last year

The most frequent symptoms during childhood were the same as in adulthood (Table I). There was a difference between childhood and adulthood for most of these symptoms (fever, nausea and vomiting, painful lymph nodes, urticaria, mouth ulcers, myalgia, arthralgia, arthritis, headache, conjunctivitis). For intellectual disability, amyloidosis, hypogonadism and hearing loss, there was a worsening of symptoms with a significant difference for hearing loss.

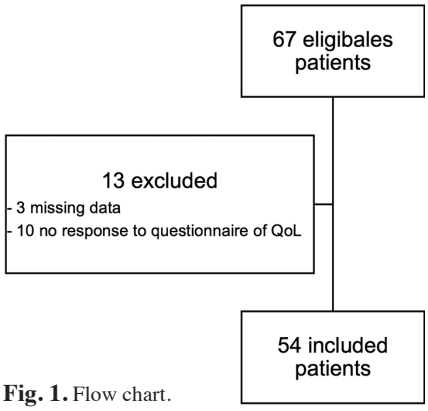

Fig. 1. Flow chart.

- Flare-up characteristics

Regarding the flare up characteristics (Suppl. Table S3), CAPS patients presented on average less than 12 attacks per year (43%), of a duration of less than 3 days (60%), without associated fever (52%) and without seasonal factors (80%), the attacks being most often triggered by cold (44%) and fatigue (33%). CINCA patients had the longest attacks, mainly without fever, the main factors being cold and temperature change. MWS patients had the most flare-ups per year.

Academic and professional situation

During childhood, they often had school absenteeism due to their illness. 86% of them had finished their studies, 32% had a BTEC Diploma as their highest qualification and 20% had no qualification, which together represents half of the patients. The majority (52%) were in employment and were not considered disabled workers, 66% of patients had to give up a job and most of them had had to take time off (61%). The majority of CINCA patients reported a greater impact on schooling (43% without higher education) and on work (74% with a disability rate >80%) (Suppl. Table S4).

Personal situation

The patients described good social relationships: 69% of them had sen-

Table I. Symptoms of 54 adult patients with CAPS.

	In childhood n (%)	At time of the phone call, evaluation over the last year n (%)
Fever	**42 (79)**	**12 (22)**
Abdominal pain	8 (15)	6 (11)
Nausea and vomiting	**9 (17)**	**1 (2)**
Diarrhoea	7 (13)	8 (15)
Chest pain	5 (9)	3 (6)
Painful lymph nodes	**13 (24)**	**4 (7)**
Urticaria	**50 (93)**	**9 (17)**
Mouth ulcers	**27 (50)**	**14 (26)**
Myalgia	**36 (67)**	**23 (43)**
Arthralgia	**49 (91)**	**27 (51)**
Arthritis	**39 (72)**	**14 (26)**
Headache	**29 (54)**	**18 (33)**
Papillary oedema	4 (7)	1 (2)
Conjunctivitis	**34 (64)**	**14 (26)**
Episcleritis	2 (4)	2 (4)
Keratitis	1 (2)	0 (0)
Uveitis	4 (7)	0 (0)
Meningitis	**7 (13)**	**2 (4)**
Intellectual deficiency	7 (13)	8 (15)
Hearing loss	**25 (46)**	**32 (59)**
Amyloidosis	3 (6)	6 (11)
Growth retardation	14 (26)	10 (18)
Hypogonadism	3 (13)	6 (26)

timental relationships and 91% had friendly relationships.

The majority of CINCA patients reported a greater impact on social life (57% lived with a parent, 71% had no sentimental relationship) (Suppl. Table S4).

Quality of life

Most of CAPS patients felt that their health and emotional well-being were satisfactory. They played sports regularly, 84% of them never smoked or had stopped smoking, and 56% were sometimes involved in cultural activities (Suppl. Table S4).

Even though CINCA patients had an impact in academic and social areas, they considered their health and emotional state as the same level as FCAS and MWS' patients.

Regarding the SF36 score (Suppl. Table S5), the scores in the 8 domains were lower in CAPS patients compared to the general French population. The highest domain was the Emotional Role (RE) and the lowest was Vitality (VT). MWS patients had the highest scores and CINCA patients the lowest of the 3 subtypes.

For the A439V variant, the PF (physical function), SF (social function) and GH (general health) domains were higher while MH (mental health) dimension was lower than for the R260W variant. This domain is possibly decreased because 2 patients with the A439V mutation are clinically labelled CINCA. Regarding the other domains, they had almost identical scores (Suppl. Table S6).

Discussion

In our study, we treated 51 of the 54 patients included and we showed an improvement of symptoms in adulthood compared to childhood, which can be explained by the introduction of anti-IL-1 treatment.

An Italian study by Lepore *et al*. (14) assessed the QoL of CAPS children treated with anakinra, the study by Goldbach-Mansky *et al*. (15) evaluating the benefit of anakinra treatment in 18 NOMID patients, and a study by Koné-Paut *et al*. (16) including 35 CAPS patients treated with canakinumab for 48 weeks, showed an improvement in clinical symptoms. These data were consistent with the symptomatic improvement described in adulthood as compared to childhood in the patients in our study.

However, in our study, some symptoms, such as hearing loss or amyloidosis, once acquired, were irreversible. The study by Neven *et al*. (12) showed that of 10 patients with NOMID delayed diagnosis and treatment could lead to residual deafness and persistent central nervous system inflammation in some patients. In our study, 3 patients had amyloidosis in childhood, which persisted into adulthood. For these patients, the ages of initiation of treatment were at 35 years (MWS), 13 years (MWS) and 4 years (CINCA), which was after the onset of this complication, except for the last patient, who had a severe form of the disease. These results indicated the need for treatment before irreversible damage occurs.

Patients assessed their emotional and health status, cultural activities, and social relationships, rather positively. However, they had significant school and work absenteeism.

In the 2018 study Mulders-Manders *et al*. (17) reported that 92% of the included patients were treated with biotherapy, half of the patients with paid employment reported absenteeism from work due to CAPS, and all patients in school (n=5) reported absence from school due to the disease. This school and work absenteeism was also found in our study. However, in the ENVOL study (18), the data were consistent with improvement in social activity, relationships, sexuality and energy measures in over 40% of participants after treatment.

Although the QoL was satisfactory in our study, it remained lower than in the French general population. In addition, QoL varied between disease subtypes and different mutations; MWS patients on average rated themselves as being in better general health than other phenotypes according to the SF36 score. These results may be explained by the fact that MWS patients show the greatest difference in symptoms between pre- and post-treatment, which explains their better QoL compared with CINCA and FCAS patients for whom the progression of symptoms is less.

However, even if interleukin 1β inhibitor treatments improved the QoL, the 2018 study by Mulders-Manders *et al*. (17) including Dutch patients showed that QoL was still lower than in the general population as in our study. They assessed QoL using the EQ-5D-5L in adults and the CHQ-PF50 in children. Higher disease activity and the presence of complications had a negative influence on QoL.

Our study also showed a possible diversity of clinical manifestations in patients with the same *NLRP3* variant. Indeed, patients carrying the A439V mutation could manifest as either FCAS, MWS or CINCA. However, for other mutations, the same subtype was mostly found.

In 2014 the study by Levy *et al*. (19) included 136 patients and made genotype and phenotype correlations. The R260W variant (the most frequent variant in the literature) was significantly (p<0.01) linked to a known family history, to the development of the disease after 6 months of life and to a cold trig-

ger for the onset of attacks. Concerning the A439V variant, the phenotype described is of moderate intensity, as for the R260W variant. In our study, the R260W mutation was the most frequent, and R260W mutated patients all belonged to the MWS group. However, the A439V mutated patients showed a more variable phenotype ranging from FCAS to CINCA. Jesus *et al*. (20) suggested that the same mutation can be associated with different clinical phenotypes, which was consistent with the data in our study. In our study, we could conclude that there was a genotype/phenotype link for some mutations (R260W), however, for others (A439V), the spectrum of symptoms was broader.

Conclusion

Our study is the only longitudinal study to evaluate the status of patients at different ages of life after several years of treatment. The evidence from our study showed that CAPS patients described an improvement in symptoms in adulthood and for most of them a good QoL. Treatment with anti-IL1 was the main factor related to this improvement and early initiation seems to be necessary to obtain a better evolution of the disease. Knowledge of the genetic variant involved in the disease does not in itself determine the course of the disease and implies systematic follow-up and rigorous individual management as well as early detection of complications.

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