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DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en D.E.S DE PEDIATRIE

Eosinophilic Meningitis: A Novel and Underrecognized Manifestation of Cryopyrin-Associated Periodic Syndromes

Les Méningites à Éosinophiles : Une Manifestation Nouvelle et Méconnue des Syndromes Périodiques Associés à la Cryopyrine

MOSCOVICI Cécilia

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Sous la direction de M. LEGENDRE Paul

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Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré (e) et méprisé(e) si j'y manque ».

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ABBREVIATIONS:

AEC	Absolute eosinophil counts
CAPS	Cryopyrin-associated periodic syndromes
CINCA	Chronic infantile neurological, cutaneous and articular syndrome
CNIL	National Commission of data processing and liberties
CRP	C-reactive protein
CSF	Cerebrospinal fluid
FCAS	Familial cold autoinflammatory syndrome
JIR	Juvenile Inflammatory Rheumatism
MWS	Muckle-Wells syndrome
NGS	Next generation sequencing
NLRP3	*NOD-like receptor family, pyrin domain containing 3*
NOMID	Neonatal-onset multisystem inflammatory disorder
NSAIDS	Non-steroidal anti-Inflammatory Drugs
VUS	Variant of Uncertain Significance
WES	Whole exome sequencing

OUTLINE :

Eosinophilic Meningitis: A Novel and Underrecognized Manifestation of Cryopyrin-Associated Periodic Syndromes

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ABSTRACT

Background: Cryopyrin-associated periodic syndromes (CAPS) are hereditary autoinflammatory diseases caused by gain-of-function mutations in the *NLRP3* gene, leading to systemic, cutaneous, musculoskeletal, and central nervous system inflammation. Eosinophilic meningitis is a rare condition and has never been reported to date in the setting of CAPS.

Methods: We conducted a multicenter, retrospective study of patients with CAPS associated with eosinophilic meningitis included in the JIR (Juvenile Inflammatory Rheumatism) cohort.

Results: We report four cases of patients with aseptic eosinophilic meningitis associated with *NLRP3* mutations. Besides aseptic eosinophilic meningitis, all 4 patients presented with blood hypereosinophilia, and neurological symptoms such as headaches or early-onset hearing loss. Three of the four patients did not exhibit CAPS-defining features such as fever, arthralgia, or urticarial rash, which led to a delay in diagnosis. When compared with other CAPS patients included in the JIR cohort, the prevalence of urticarial rash significantly differed between patients with eosinophilic meningitis and others (25% versus 83%, $p = 0.021$). All patients responded to interleukin-1 blockade therapy.

Conclusion: In order not to delay the diagnosis and onset of interleukin-1 blockade therapy, physicians must be aware that both eosinophilic meningitis and blood hypereosinophilia may be a feature of CAPS, even in the absence of urticarial rash.

Keywords: CAPS, aseptic eosinophilic meningitis, *NLRP3* gene, hypereosinophilia, hearing loss, absence of urticarial rash

INTRODUCTION

Cryopyrin-associated periodic syndromes (CAPS) are rare, inherited autoinflammatory disorders caused by gain-of-function mutations of the *NOD-like receptor family, pyrin domain containing 3* (*NLRP3)* gene encoding cryopyrin, a regulatory protein involved in interleukin-1 (IL-1) secretion. Such mutations lead to a constitutive increase of IL-1 secretion and subsequent systemic inflammation. (1) Initially, three distinct phenotypes were described including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological, cutaneous and articular syndrome (CINCA) also called Neonatal-onset multisystem inflammatory disorder (NOMID). CAPS clinical characteristics include most frequently fever, urticaria and arthralgia. Ophthalmological manifestations such as conjunctivitis and uveitis have also been described, as well as neurosensory hearing loss. Neurological involvement includes headache, papilledema and chronic meningitis aseptic. (2)
Although all three of the latter phenotypes result from heterogeneous mutations of *NLRP3*, the symptoms, affecting the skin, musculoskeletal system, eyes and central nervous system, vary between diseases, ranging from mild to severe. (3)
Regardless of the specific condition, the first-line therapy recommended for CAPS is interleukin-1 blockade, using agents such as anakinra or canakinumab. (4)

Although CAPS presents with a wide range of symptoms, a few observations in the literature have associated *NLRP3* mutations with hypereosinophilia. Interestingly, an unusual presentation of severe CAPS was described in Montreal, Canada. The patient presented prominent peripheral eosinophilia with organ infiltration, but without the classic urticaria-like rash. (5) Evidence suggests that the *NLRP3* inflammasome induces production of pro-eosinophilic cytokines (6).

Eosinophilic meningitis is a rare condition, mostly drug-induced or related to parasitic infections *e.g., Angiostrongylus cantonensis*, or *Gnathostomiasis spinigerum (7)*. Although not exhaustive, other causes of eosinophilic meningitis include solid or hematological malignancies, certain drugs, hypereosinophilic syndrome and inflammatory diseases such as sarcoidosis, or Behçet's disease. (8).

To date, no case of eosinophilic meningitis associated with CAPS has been reported. Following the management of a 14-year-old boy with intracranial hypertension secondary to aseptic eosinophilic meningitis, which ultimately led to the diagnosis of CAPS, we considered whether an association between CAPS and eosinophilic meningitis could exist.

The aim of this study was to report on the clinical and genetic features of patients with both CAPS and eosinophilic meningitis.

METHOD

We conducted a multicenter, retrospective, case series of patients with CAPS associated with eosinophilic meningitis. Patients were identified from the JIR Cohort database, an international data repository established in 2013 to collect data on patients with juvenile-onset inflammatory or rheumatological diseases (https://www.jircohorte.org - NTC02377245). The JIR cohort operates through a web-secured platform organized into different modules, one of which is dedicated to auto-inflammatory diseases. We included patients diagnosed with CAPS with at least one visit recorded in the database, and identified those with meningitis. We then restricted our analysis to those with eosinophilic meningitis (defined as the presence of eosinophils in the cerebrospinal fluid).

Data collection

Baseline was defined as the date of inclusion in the database. Disease duration was calculated from the time of onset of the first symptoms of auto-inflammatory disease. Complete medical history, physical examinations, laboratory tests including antibody status, and radiology exams were collected for each patient at the time of the event.

Ethical approval

All patients included in the JIR Cohort (or their legal guardian) signed informed consent to participate in the study. Besides, both the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS) as well as the Commission Nationale de l'Informatique et des Libertés (CNIL) approved the JIR cohort (respectively on April 21, 2015, approval number 14.302; and on March 27, 2015 ; approval number DR-2015-218).

Statistical analyses

Data were reported as numbers (n) and percentages (%) for categorial variables. Quantitative variables were expressed as median and interquartile range [IQR]. CAPS patients with

eosinophilic meningitis were compared to those without eosinophilic meningitis. Discrete outcomes were compared with chi-squared or Fisher's exact test accordingly. Statistical analysis was performed with EasyMedStat (version 3.43, editor EasyMed Stat, France).

RESULTS

From the JIR cohort database, 0.7% of patients were identified as having CAPS, and among them, 3.6% presented with eosinophilic meningitis. Four patients with both **aseptic eosinophilic meningitis and *NLRP3* mutations were reported**. The study design and patient selection process are illustrated in **Figure 1.**

Cases presentation:

Case 1:

A 15-year-old teenager was treated for papilledema in 2022. His medical history included growth delay, episodes of headache and iron-deficiency anemia.

While investigating this papilledema, blood tests revealed an inflammatory syndrome (CRP 20 mg/l), microcytic anemia, and hypereosinophilia (1,2 x10^9/L). A lumbar puncture confirmed intracranial hypertension (intracranial pressure = 50 cmH2O) associated with aseptic meningitis. Eosinophils were found in the cerebrospinal fluid (35% of eosinophils among 108 cells/mm³). Extensive complementary investigations for the workup of hypereosinophilia and eosinophilic meningitis (including multiple parasite serologies, autoimmune and hematological workups) were negative. Subsequently, the patient was diagnosed with anterior uveitis and sensorineural hearing loss.

In July 2023, whole-exome sequencing was performed, revealing a heterozygous gain-of-function variant (NM_004895.5: c.1253T>C p. Val418AIa) in exon 4 of the *NLRP3* gene, highly evocative of a diagnosis of CAPS after functional analysis. Treatment with Anakinra (an interleukin-1 receptor antagonist) was initiated at a dose of 100 mg per day, administered subcutaneously, and led to the rapid improvement of the patient's condition with resolution of

the biological inflammatory syndrome, normalization of peripheral eosinophil counts, and improvements in both headaches and papilledema within six months.

Case 2:

A 28-year-old woman had been treated since childhood for familial hearing loss and growth delay, for which she received growth hormone therapy. Regarding the hearing loss, there was a strong (yet unconfirmed) suspicion of a genetic origin of mitochondrial inheritance, as both her mother and maternal aunts were also affected.

At the age of eleven, a blood test revealed an inflammatory syndrome (CRP between 50 and 80 mg/l) as well as hypereosinophilia (1,5 x10^9/L). Investigations for the cause of hypereosinophilia were negative.

Between the ages of 15 and 17, she underwent multiple lumbar punctures due to chronic headaches, which all revealed aseptic eosinophilic meningitis (cerebrospinal fluid showing between 30 and 87 cells/mm³, including 50% of eosinophils). Although no formal diagnosis was made, she was empirically treated with systemic corticosteroids, resulting in a reduction of blood inflammatory markers and normalization of absolute eosinophil counts (AEC).

Medical follow-up was resumed at the age of 25 due to persistent inflammatory syndrome (CRP 105 mg/l) , hypereosinophilia (1,4 x10^9/L), and newly identified iron-deficiency anemia. Owing to chronic inflammation and a familial history of hearing loss, the hypothesis of an atypical autoinflammatory disease was raised, ultimately leading to the identification of a heterozygous missense variant, Y861C (NM_01243133.2 : c.2582A>G p.(Tyr861Cys)) in exon 6 of the *NLRP3* gene using next generation sequencing (NGS). Again, treatment with anakinra at a dose of 100 mg per day, administered subcutaneously, achieved sustained clinical and biological efficacy. Five years later, at the age of 30, the patient remains clinically and biologically stable.

Case 3:

A 36-year-old adult from Senegal, previously followed in multiple pediatric departments since the age of 11 for bilateral sensorineural hearing loss, growth delay, chronic headaches related to borderline intracranial hypertension, was also noted to have progressive macrocephaly with ventriculomegaly and persistent hypereosinophilia (700 x10^9/L). Starting at the age of 16, multiple lumbar punctures revealed sterile cerebrospinal fluid containing approximately 100 cells/mm³, with 2 to 5% eosinophils. Extensive infectious, autoimmune and hematological workups were negative.

At the age of 30, he had been treated with praziquantel due to a suspected *Schistosoma mansoni* meningitis, based on a positive serology. The subsequent follow-up was marked by persistent severe headaches despite high-dose analgesic therapy.

Six years later, he was found unconscious in his apartment. A CT scan revealed a subarachnoid hemorrhage along with intraventricular bleeding and signs of intracranial hypertension. He was admitted to the intensive care unit. An auto-inflammatory disease was suspected on the basis of his past medical history and childhood onset of symptoms. Nevertheless, while awaiting genetics results, treatment with cyclophosphamide was initiated due to the suspicion of central nervous system vasculitis, especially given the presence of an aneurysm. Ultimately a heterozygous missense variant (NM_001243133.2, c.2576A>G p.(Tyr859Cys)) in exon 7 of the *NLRP3* gene was identified and treatment with anakinra, at a dose of 100 mg per day, was administered subcutaneously.

Although stroke led to severe sequelae (including right hemiplegia and aphasia), the patient headaches have disappeared and inflammatory markers have returned to normal once treatment with anakinra was initiated.

Case 4:

A premature newborn, born at 35 weeks of gestation, with good adaptation to extra-uterine life, presented with a single risk factor for early-onset neonatal bacterial infection: premature rupture of membranes lasting more than 24 hours.

On day 1, blood tests revealed an inflammatory syndrome that worsened despite triple antibiotic therapy. Lumbar puncture showed aseptic meningitis with 2% eosinophils in the cerebrospinal fluid. The infectious workup returned negative. Cerebral imaging revealed stage 4 meningeal and parenchymal hemorrhage, predominantly on the right side.
The patient showed good clinical improvement under antibiotic treatment, although the inflammatory syndrome persisted.

On day 7, a pseudo-urticarial rash appeared. Further investigations did not reveal any immune deficiency or autoimmune condition.

At the age of 6 months, CAPS was suspected due to persistent inflammatory syndrome and recurrent urticarial rash. Next-generation sequencing revealed a heterozygous variant (NM_001243133, c.926T>C, p(Phe309Ser) in exon 4 of the *NLRP3* gene. Treatment with anakinra was initiated and later switched to canakinumab for greater simplicity.

Follow-up cerebral imaging showed brain volume loss with ventricular enlargement. At the age of 2½, imaging revealed a left parietal subdural hematoma, which later regressed.

Cases characteristics:

Table I summarizes the clinical characteristics of four cases of CAPS with eosinophilic inflammation as well as those of other CAPS patients from the JIR cohort, who did not exhibit eosinophilic meningitis. Patients with eosinophilic meningitis exhibited lower rates of urticarial rash (25% vs. 83%, p = 0.021), fever (25% vs. 58%, p = 0.315) and arthralgia (25% vs. 68%, p = 0.113) compared to CAPS patients without eosinophilic meningitis. Conversely, neurological manifestations (including headache, aseptic meningitis, and intracranial hypertension) were more frequent among patients with eosinophilic meningitis (100% vs. 32%, p = 0.013; 100% vs. 7,6%, p < 0.001; 50% vs. 4,4%, p = 0.019). Although not statistically significant, there was a trend toward a higher rate of hearing loss among patients with eosinophilic meningitis.

In a subgroup analysis of 11 CAPS patients with meningitis (whatever the predominant cell), we also observed that urticarial rash tended to be less frequent in patients with eosinophils in the CSF than in those without (25% vs. 85%, p = 0.088), as well as fever (67% vs. 25%, p = 0,52) and arthralgia (71% vs. 25%, p = 0,24); however, these differences were not statistically significant.

Based on the individual case descriptions, three of the four patients presented with growth delay during childhood. They also showed elevated blood eosinophil counts and persistent markers of biological inflammation, as detailed in **Table II**.

Table II also presents the cerebrospinal fluid (CSF) findings of our four patients, revealing the presence of eosinophils in the CSF.

The specific ***NLRP3*** **mutations** identified in each patient are presented in **Table III**.

Figure 2 shows the evolution of AEC and CRP levels in patient 1. Both curves are nearly superimposable, with a sharp decline occurring shortly after initiation of treatment with anakinra.

DISCUSSION

We here report the first case series of patients with aseptic eosinophilic meningitis associated with *NLRP3* mutations and CAPS.

The detailed history of our four patients revealed an atypical presentation of CAPS. Notably, three out of four never exhibited the typical skin rash or recurrent fever or arthralgia. On another note, they all shared neurological clinical features including aseptic meningitis and headaches, and three out four presented early-onset hearing loss.

While CAPS presents with a wide range of neurological manifestations, aseptic meningitis is mostly observed in severe cases and is therefore more commonly associated with the CINCA phenotype. Previous studies have demonstrated that aseptic meningitis in CAPS results from cerebrospinal fluid (CSF) alterations induced by proinflammatory cytokines, which may exert direct cytotoxic effects on neurons (9). Chronic aseptic meningitis, as seen in severe CAPS, can lead to increased intracranial pressure, ventriculomegaly, and cerebral and optic nerve atrophy (10). In our series, in addition to eosinophilic meningitis, three of our four patients exhibited hypereosinophilia in the absence of parasitic infection, as confirmed by negative serological tests, and was not induced by medication. Given the increased permeability of the blood-brain barrier, we initially hypothesized that blood eosinophils had migrated into the CSF. However, the ratio of eosinophils to total white blood cells in the CSF was markedly higher than in the blood, suggesting a localized meningeal eosinophilic reaction.

Ducharmé-Bénard *et al.* previously described a CAPS patient presenting with eosinophilia and serositis. Notably, this patient did not exhibit the classic urticaria-like rash, similar to three of our patients. Although treatment with an anti–interleukin-1 agent led to clinical remission, as

observed in our cases, the patient was left with severe neurological disability (5). Eosinophilia is typically associated with type 2 immune responses. Emerging evidence suggests a link between autoinflammatory diseases and type 2 immunity, potentially mediated by inflammasome activation and the release of cytokines such as interleukin-1. Recent findings have suggested a pathophysiological link between *NLRP3* activation and eosinophil proliferation, mediated through IL-18 production (11). For example, in eosinophilic esophagitis, epithelial cells have been identified as a source of NLRP3 and caspase-1–regulated IL-18, which induces eosinophilic inflammation in the esophageal mucosa (12). A similar mechanism is also suspected in eosinophilic rhinosinusitis (13) and asthma (14). Other findings have also shown substantial increases in IL-5, which likely play a major role in peripheral eosinophilia (15). We could hypothesize that, in our cases, chronic IL-5 secretion due to delayed diagnosis (and consequently delayed treatment) may explain the presence of eosinophils in the CSF. Among patients with CAPS, eosinophilia may therefore be driven by inflammasome upregulation (16). This possible mechanism is also supported by the fact that eosinophilia seemed to respond favorably to interleukin-1 blockade, as illustrated by patient 1 (Figure 2), whose eosinophil count normalized following initiation of anti–interleukin-1 therapy. However, only a few patients developed eosinophilia during the course of CAPS, suggesting that these individuals may have specific underlying characteristics related to an unusual *NLRP3* mutation.

Fayand *et al.* recently reported a series of 14 patients with pathogenic variants located in the LRR domain of *NLRP3*, specifically at position Y861 in exon 6, whereas such variants are typically located in the NACHT domain of *NLRP3*. Their study showed that these patients were more prone to headaches and hearing loss, and notably lacked the characteristic urticarial rash. Some also presented with hypereosinophilia prior to treatment. This phenotypic

divergence from classical CAPS may be related to the specific localization of the disease-causing variants (17).

In line with these findings**,** patients 2 and 3 in our cohort both carry pathogenic variants located in the LRR domain. They represent clear examples of significant diagnostic delay due to atypical clinical presentations. Since early childhood, both presented with growth delay, early-onset hearing loss, recurrent headaches, and an absence of urticarial skin rash. It is only during their teenage years that they presented aseptic eosinophilic meningitis, which led to a significant delay in diagnosis, with the condition only being confirmed later in adulthood. For patient 3, this resulted in prolonged exposure to systemic inflammation and, ultimately, in severe irreversible sequelae. For both patients, diagnosis was made possible through whole-exome sequencing (WES), as both carried pathogenic variants in the LRR domain. On the contrary, in the case of patient 1, who presents the same phenotype as patients 2 and 3, the diagnosis of CAPS remains debatable, as he harbors a variant located in the NACHT domain, classified as being a variant of uncertain significance (VUS). These recent findings reinforce the growing accessibility of WES, which is likely to facilitate the identification of additional atypical presentations of *NLRP3* mutations (18).

Regarding patient 4, several points warrant discussion. He presented with eosinophilic meningitis, along with stage 4 meningeal and parenchymal hemorrhage, raising the question of whether the eosinophils found in the CSF may have originated from the hemorrhage itself. In contrast to the other three patients, his clinical presentation of CAPS is different and more consistent with the classical phenotype, including the characteristic urticarial rash. This may be explained by the fact that he is the only case without a diagnosis delay. He did not exhibit hypereosinophilia, as his peripheral eosinophil count is within normal range for his age (790 × 10^9/L). Additionally, he carries a well-established pathogenic variant located in the NACHT

domain of the *NLRP3* gene. For all these reasons, the association of eosinophilic meningitis with CAPS should be reconsidered for this patient. If this case is excluded from the series, it reinforces the observation that all remaining patients share specific characteristics: eosinophilia, non-classical pathogenic *NLRP3* mutations, absence of urticarial rash, and delayed diagnosis.

The limitations of this case series include its retrospective nature and the small number of patients, which make comparisons difficult — particularly regarding blood eosinophilia, as few variables were consistently recorded. To conduct more in-depth analyses, we need to collect additional data via the JIR cohort.

In this case series, we describe CAPS patients presenting with aseptic eosinophilic meningitis, headaches and among three of the four patients, hypereosinophilia, hearing loss and, absence of urticarial rash. This clinical entity should be recognized and should prompt investigation for *NLRP3* mutations using NGS or WES, when these features are present.

CONCLUSION

We reported the first series of four patients with an atypical presentation of CAPS characterized by aseptic eosinophilic meningitis. Notably, three of the four patients lacked the typical urticarial rash and presented with hypereosinophilia, growth delay, and neurological symptoms, including hearing loss and headaches.

Our findings indicate that this clinical entity could be a potential manifestation of CAPS, associated with a non-classical *NLRP3* mutation. Therefore, it warrants investigation for NLRP3 mutations using NGS or WES, particularly when there's a positive response to interleukin-1 blockade.

Early recognition can help avoiding diagnostic delays and minimizing the risk of severe complications.

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FIGURES

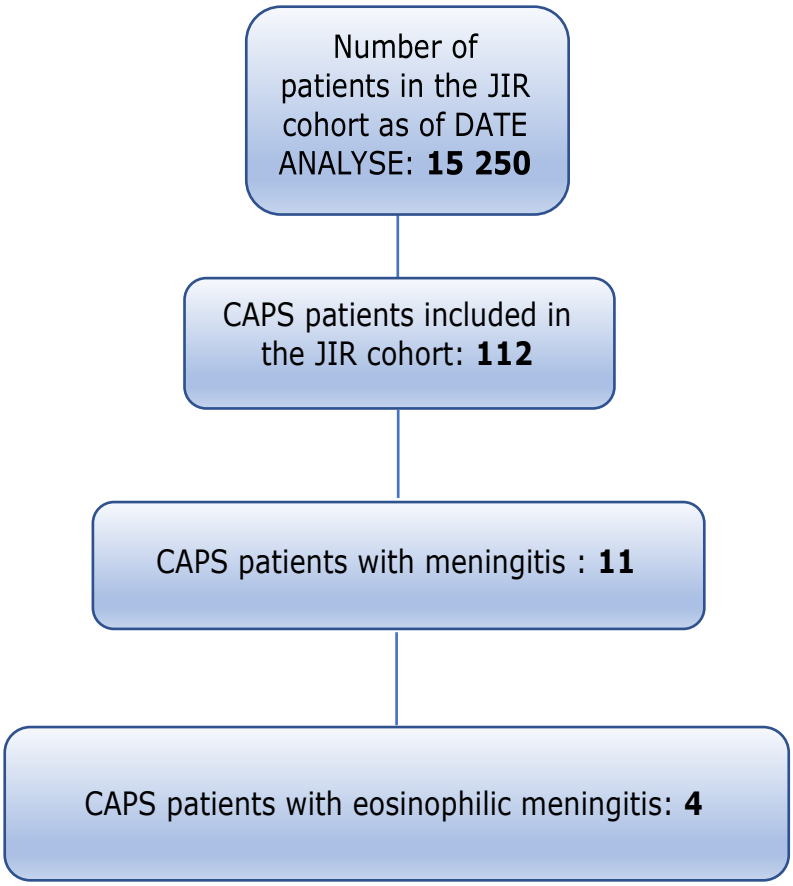

Figure 1. Flow chart
CAPS: Cryopyrin-associated periodic syndromes**, JIR:** Juvenile Inflammatory Rheumatism cohort

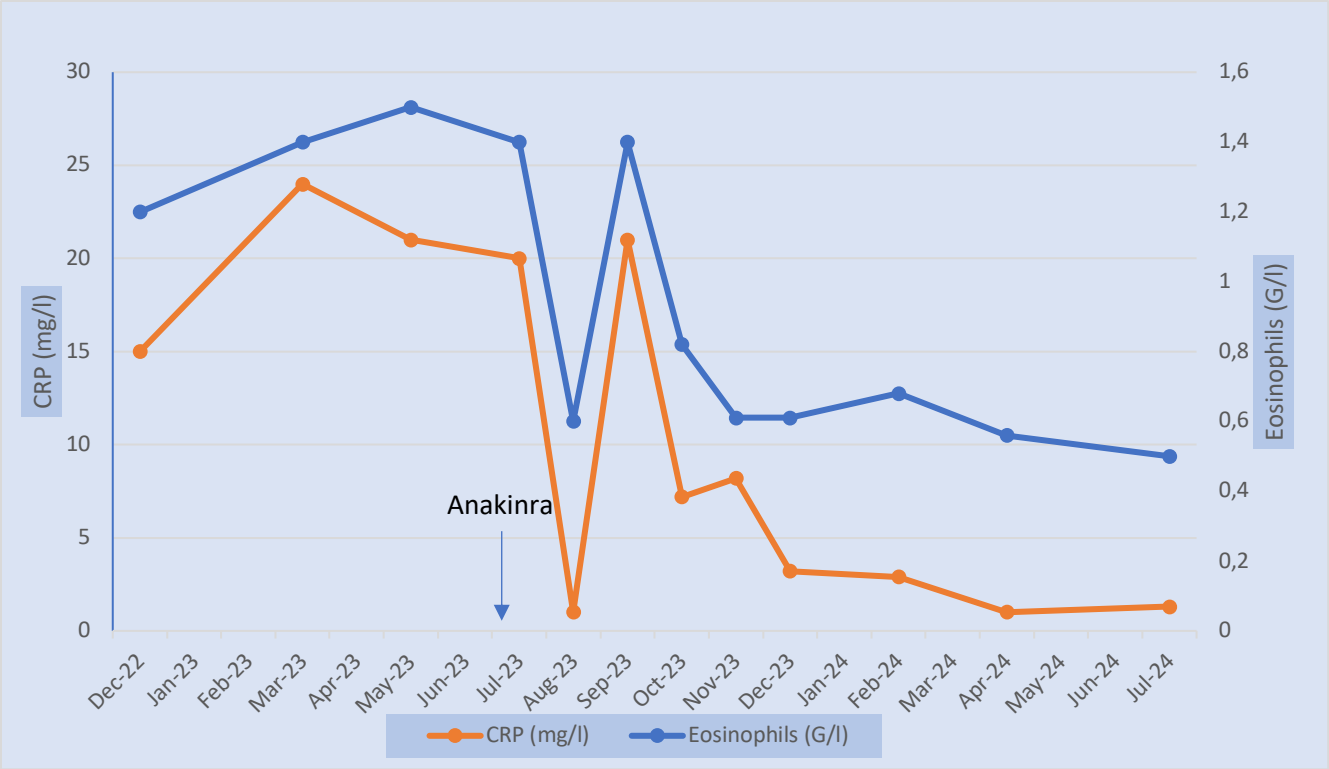

Figure 2: CRP levels (orange line) and AEC (blue line) overtime in patient 1 before and after treatment with anakinra.

TABLES

Table I. Clinical features of CAPS patients with and without eosinophilic meningitis.

	All CAPS (N= 112)	CAPS associated with eosinophilic meningitis (N = 4)	CAPS without eosinophilic meningitis (N= 108)	*P* value
General features				
Age at symptoms onset (y)	0,9 (0 – 7)	5,9 (0 – 12)	0,9 (0 – 6)	0,58
Age at diagnosis (y)	19 (5 – 37)	21,7 (11 – 30)	19 (5 – 38)	0,82
Diagnosis delay (y)	12 (1,7 – 29)	12,9 (0,9 – 25)	13 (1,9 – 25)	0,675
Male	46/112 (41)	3/4 (75)	43/108 (40)	0,304
Female	66/112 (59)	1/4 (25)	65/108 (60)	0,304
Clinical features				
Arthralgias	64/97 (66)	1/4 (25)	57/93 (68)	0,113
Recurrent fever	53/94 (56)	1/4 (25)	52/90 (58)	0,315
Urticarial rash	**81/100 (81)**	**1/4 (25)**	**80/96 (83)**	**0,021**
Hearing loss	44/97 (45)	3/4 (75)	41/93 (44)	0,326
Uveitis	11/88 (12)	1/3 (33)	10/85 (12)	0,333
Conjunctivitis	42/95 (44)	0/4	42/91 (46)	0,127
Papillary oedema	11/95 (12)	1/4 (25)	10/91 (11)	0,394
Headache	**33/95 (35)**	**4/4 (100)**	**29/91 (32)**	**0,013**
Aseptic meningitis	**11/95 (12)**	**4/4 (100)**	**7/91 (7,6)**	**< 0,001**
HTIC	**6/95 (6)**	**2/4 (50)**	**4/91 (4,4)**	**0,019**
Treatment initiated				
Use of Canakinumab	45/101 (45)	0/4	45/97 (46)	0,126
Use of Anakinra	56/101 (55)	4/4 (100)	52/97 (54)	0,126

Values are presented as median (interquartile range: Q1–Q3) or n/N (%). Abbreviations: CAPS, cryopyrin-associated periodic syndrome; Y, years; NA, not available.

Table II. Cerebrospinal fluid (CSF) characteristics and biological findings in identified cases at the time of diagnosis.

Cases	**1**	**2**	**3**	**4**
Cerebrospinal Fluid characteristics:				
White blood cells (/mm3 elements)	108	30 - 90	59	32 000
Neutrophils (%)	28	NA	54	84
Lymphocytes (%)	27	NA	33	4
Eosinophils (%)	**35**	**50**	**9**	**2**
Culture	Aseptic	Aseptic	Aseptic	Aseptic
Biological features:				
Eosinophils (/mm3)	1500	1500	700	790
CRP (Range, mg/l)	20 - 50	50 - 80	100	35 - 45

Abbreviations: NA, not available; CRP, C-reactive protein.

Table III: *NLRP3* mutation in identified cases

Cases	1	2	3	4
Exon	4	6	7	4
Variant	c.1253T>C p.(Val418AIa)	c.2582 A>G p.(Tyr861Cys)	c.2576A>G p.(Tyr859Cys)	c.926T>C p.(Phe309Ser)
Genotype	Heterozygous	Heterozygous	Heterozygous	Heterozygous

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Les Méningites à Éosinophiles : Une Manifestation Rare des Syndromes Périodiques Associés à la Cryopyrine

RÉSUMÉ

Introduction : Les syndromes périodiques associés à la cryopyrine (CAPS) sont des maladies auto-inflammatoires héréditaires causées par des mutations activatrices du gène *NLRP3*, entraînant une inflammation systémique, cutanée, musculosquelettique et du système nerveux central. La méningite à éosinophiles est une affection rare qui n'a jusqu'à présent jamais été décrite en association avec les CAPS.

Méthode : Nous avons mené une étude multicentrique rétrospective portant sur des patients atteints de CAPS associés à une méningite à éosinophiles, inclus dans la cohorte JIR (Juvenile Inflammatory Rheumatism).

Résultats : Nous rapportons quatre cas de patients présentant une méningite à éosinophiles aseptique associée à des mutations du gène *NLRP3*. En plus de la méningite aseptique à éosinophiles, les quatre patients présentaient une hyperéosinophilie sanguine ainsi que des symptômes neurologiques tels que des céphalées ou une surdité précoce. Trois des quatre patients ne présentaient pas de manifestations typiques des CAPS, comme la fièvre, les arthralgies ou l'urticaire, ce qui a retardé le diagnostic. Comparés aux autres patients atteints de CAPS inclus dans la cohorte JIR, la prévalence de l'urticaire différait significativement entre ceux atteints de méningite à éosinophiles et les autres (25 % contre 83 %, p = 0,021). Tous les patients ont répondu au traitement par inhibiteurs de l'interleukine-1.

Conclusion : Afin de prévenir tout retard dans le diagnostic et l'instauration d'un traitement par inhibiteurs de l'interleukine-1, les soignants doivent être conscients que la méningite à éosinophiles et l'hyperéosinophilie sanguine peuvent être des manifestations des CAPS, même en l'absence d'urticaire.

Mots-clés : CAPS, méningite à éosinophiles, gène NLRP3, hyperéosinophilie, surdité, absence urticaire

Eosinophilic Meningitis: An Uncommon Manifestation of Cryopyrin-Associated Periodic Syndromes

ABSTRACT

Background: Cryopyrin-associated periodic syndromes (CAPS) are hereditary autoinflammatory diseases caused by gain-of-function mutations in the *NLRP3* gene, leading to systemic, cutaneous, musculoskeletal, and central nervous system inflammation.
Eosinophilic meningitis is a rare condition and has never been reported to date in the setting of CAPS.

Methods: We conducted a multicenter, retrospective study of patients with CAPS associated with eosinophilic meningitis included in the JIR (Juvenile Inflammatory Rheumatism) cohort.

Results: We report four cases of patients with aseptic eosinophilic meningitis associated with *NLRP3* mutations. Besides aseptic eosinophilic meningitis, all 4 patients presented with blood hypereosinophilia, and neurological symptoms such as headaches or early-onset hearing loss. Three of the four patients did not exhibit CAPS-defining features such as fever, arthralgia, or urticarial rash, which led to a delay in diagnosis. When compared to other CAPS patients included in the JIR cohort, the prevalence of urticarial rash significantly differed between patients with eosinophilic meningitis and others (25% versus 83%, p = 0.021). All patients responded to interleukin-1 blockade therapy.

Conclusion: In order not to delay the diagnosis and onset of interleukin-1 blockade therapy, physicians must be aware that both eosinophilic meningitis and blood hypereosinophilia may be a feature of CAPS, even in the absence of urticarial rash.

Keywords: CAPS, aseptic eosinophilic meningitis, *NLRP3* gene, hypereosinophilia, hearing loss, absence of urticarial rash

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