Neurology of the cryopyrin-associated periodic fever syndrome

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Background and purpose: The cryopyrin-associated periodic fever syndrome (CAPS) is an autosomal dominant autoimmune disorder caused by mutations in the NLRP3 gene and is typified by recurrent episodes of systemic inflammation resulting in fever, urticarial rash and arthralgia. In addition to these systemic aspects, CAPS has multiple neurological manifestations. The largest case series to date is presented focusing on the neurological features of this disorder.

Methods: The case histories of a cohort of 38 UK patients with genetically proven CAPS who were treated with interleukin 1β (IL-1β) inhibition as part of a national treatment programme and underwent detailed neurological assessment were reviewed.

Results: Across the entire disease course neurological manifestations were present in 95% of patients; 84% had some form of headache; 66% sensorineural hearing loss; 60% myalgia; 34% papilloedema and 26% optic atrophy. Patients with the T348M mutation tended to have a more severe neurological phenotype with an earlier age of onset. Four patients had cerebrospinal fluid examination, three of whom had evidence of aseptic meningitis. There was a marked response to IL-1β inhibition, which has revolutionized management of these patients (29/32 patients with headache responding).

Conclusion: Neurological symptoms are extremely common in CAPS and these results highlight the importance of increasing awareness amongst neurologists, particularly as highly effective therapies are available.

Introduction

The cryopyrin-associated periodic fever syndrome (CAPS) is an autosomal dominant genetic autoimmune disorder typified by recurrent episodes of systemic inflammation, resulting in fever, urticarial rash and arthralgia [1]. Historically, what is now described as CAPS has been divided into three distinct clinical entities. Chronic infantile neurological, cutaneous and articular syndrome (CINCA) is the most severe phenotype and presents in the neonatal period/infancy [2]. Muckle–Wells syndrome is less severe [3], whilst familial cold autoinflammatory syndrome is the mildest phenotype [4]. It has become clear that the disease is in fact a continuum and all three of the syndromes have been associated with mutations in the NLRP3 gene on chromosome 1q44 [5,6].

The NLRP3 gene regulates interleukin 1β (IL-1β) production, and the mutations described in CAPS lead to overproduction of IL-1β and systemic inflammation [1].

Left untreated, CAPS has a profound effect on an affected patient’s quality of life [7] and carries a substantial threat of AA amyloidosis, with a risk of end stage renal failure and early death [3]. Treatments targeting IL-1 have proved to be both very effective and well tolerated and can lead to complete and sustained disease remission [8,9].

Cryopyrin-associated periodic fever syndrome has multiple neurological manifestations with chronic aseptic meningitis, cerebral atrophy, hydrocephalus, sensorineural deafness and visual loss being described in CINCA [2] and headache, myalgia, papilloedema,
sensorineural deafness and aseptic meningitis in Muckle–Wells syndrome. The baseline neurological features of CAPS have been described previously in a case series of 13 patients [10]. An analysis of the web-based Eurofever Registry found that 40% of patients with CAPS had neurological features ranging from morning headache, papilloedema and aseptic meningitis to seizures and hydrocephalus [11].

Here, a cohort of 38 adolescent and adult UK patients with confirmed NLRP3 mutations across the CAPS spectrum who have had detailed neurological, ophthalmological and audiometric assessment in a single centre, with a focus on genotype–phenotype correlation and the neurological and systemic response to treatment, are described.

Methods

Patients

The case histories of 38 patients [median age of symptom onset 1 month (range 0–44 years); median age at diagnosis 35 years (range 9 months to 62 years); 17 females, 21 males] from a cohort with genetically proven [12] CAPS who received IL-1β inhibition as part of a national treatment programme were retrospectively reviewed. Thirteen patients from this cohort formed the basis of a smaller previously published case series [10]. This study had research ethics committee approval (REC reference 06/Q0501/42) and all patients had provided written informed consent. The patients included in our case series had been examined by a neurologist and an ophthalmologist at baseline and annually during treatment. Detailed histories of each patient’s current systemic and neurological symptoms, as well as previous symptoms throughout the course of their illness, were performed as part of their clinical assessment. Mean duration of follow-up was 5.05 years following commencement of treatment.

Investigations

Magnetic resonance imaging brain scan results were available for 32 patients and were performed following commencement of treatment. Four patients had also undergone lumbar puncture as part of their work-up, three before a diagnosis of CAPS had been reached. All 38 patients had undergone audiometry and were classified on the basis of the average hearing threshold level (dB HL) over a range of sound frequencies (0.5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz). Serial C-reactive protein (CRP) and serum amyloid A (SAA) measurements were taken to assess systemic serological response to treatment at monthly intervals. Median figures for pre and during treatment CRP and SAA levels were calculated for each patient.

Treatment

All patients were monitored for treatment response at the UK National Amyloidosis Centre. Two forms of IL-1β inhibition were available: canakinumab is a fully human anti-IL-1β monoclonal antibody administered as a subcutaneous injection once every 8 weeks starting at a dose of 150 mg [8]; anakinra is a recombinant form of the IL-1 receptor antagonist delivered as a daily dose of 100 mg via subcutaneous injection [9]. Clinical response to treatment was recorded at each visit and for each symptom was defined as ‘complete’ if there was documented evidence of complete resolution of that symptom. The response was defined as ‘partial’ if there was documented evidence that the patient reported the symptom had improved but had not completely resolved.

Results

General features

Our cohort included patients with the following mutations in the NLRP3 gene: A439V (n = 11), T348M (n = 8), R260W (n = 8), V198M (n = 2), A352T (n = 1), Y859C (n = 1), T436I (n = 1), L632F (n = 1), D303N (n = 1), Y570F (n = 1), F523C (n = 1), with two patients who were somatic mosaics for an NLRP3 variant. Seventeen patients developed systemic symptoms typical of CAPS in the neonatal period, four in infancy, 13 between the ages of 1 and 12 years, two in their teenage years and two in adulthood, which persisted until treatment was instituted. All eight patients with the T348M genotype developed symptoms in the neonatal period, whilst only three out of 11 (27.3%) patients with the A439V genotype and one out of nine (12.5%) patients with the R260W genotype presented neonatally. Both patients who developed symptoms in adulthood were somatic mosaics for an NLRP3 variant. Although symptom onset was late, both these patients had severe phenotypes with significant treatment resistance.

The median age of diagnosis was 35 years (range 9 months to 62 years). The median time from symptom onset to diagnosis was 28 years.

Systemic symptoms in our cohort included urticarial rash (97%), arthralgia (87%), documented fever (52%), conjunctivitis (52%), mouth ulceration (37%) and fatigue (18%).
Twenty-two out of 38 (56%) patients had a history of genetically diagnosed CAPS in at least one first-degree relative. The majority (17 of 22) of these relatives were other patients in our cohort.

Review of each patient’s past medical history revealed a number of comorbidities, including inflammatory bowel disease \( (n = 3) \), asthma \( (n = 3) \), hypothyroidism \( (n = 3) \), hypertension \( (n = 3) \) and degenerative spinal disc disease \( (n = 3) \). One patient had also been diagnosed with Addison’s disease, one with a supraventricular tachycardia and one with glaucoma. One patient was diagnosed with hereditary neuropathy with liability to pressure palsies (HNPP) following neurological review and DNA analysis. Sixteen patients had no documented comorbid conditions.

**Neurological involvement**

Thirty-six of 38 patients had symptoms or signs that could be considered neurological (Table S1 and Fig. 1). The most prevalent symptom was headache, affecting 32 patients; 17 patients described features typical of migraine and 18 described non-migrainous headaches. Six of the patients with non-migrainous headaches had chronic daily headache, four of whom were documented to have had features of raised intracranial pressure or meningism. 23 patients reported clinically significant myalgia, with no proximal muscle weakness and no rise in creatine kinase.

Thirteen patients had evidence of papilloedema with 10 patients developing optic atrophy. 24 patients had confirmed sensorineural hearing loss on audiometry, 14 patients required peripheral hearing aids and two had cochlear implantation. Two patients had a history of previous stroke-like episode with hemiparesis, but no evidence of infarction on neuroimaging.

Figure 2 details the severity of hearing loss by mutation. All patients in the cohort with the T348M mutation \( (n = 8) \) had hearing loss (six severe or profound), compared to only 18% \( (n = 11; \) two patients only mildly affected) of those with the A439V mutation \( (P < 0.001; \) two-tailed Fisher’s exact test).

Twenty-five patients had normal magnetic resonance imaging (MRI) brain scans. Six scans demonstrated T2 hyperintensities in the subcortical white matter. One patient had high signal abnormality within the subcortical white matter of the right parietal lobe adjacent to the atrium of the right lateral ventricle and had associated mild atrophy of the adjacent cortex (Fig. 3). Another patient had a small focal abnormality at the posterior aspect of the left cerebellar hemisphere, most probably an incidental finding of arachnoid cyst or enlarged perivascular space. Incidental findings in three other patients were an acoustic neuroma, a pineal cyst and a meningioma.

Results of cerebrospinal fluid analysis were available for four patients in our cohort (Table 1).

**Treatment response**

Thirteen patients were initially treated with anakinra and subsequently changed to canakinumab once available. Eighteen patients were treated with canakinumab alone. One patient was initially treated with canakinumab but changed to anakinra during pregnancy, and then restarted canakinumab following a successful pregnancy. One patient initially received canakinumab but anakinra was added after an incomplete response. Three patients started canakinumab
but changed to anakinra after incomplete response/adverse reaction to canakinumab. One patient was initially treated with anakinra and subsequently changed to canakinumab, but changed back to anakinra due to better response. One patient was initially treated with anakinra and subsequently changed to canakinumab, but anakinra was subsequently added. Eighteen patients receiving canakinumab required up-titration of their 8-weekly dose from 150 mg to 300 mg.

The median age of treatment start was 35 years (range 8–62 years).

Of the 17 patients with migrainous headaches, six had a complete response to treatment, with nine having partial responses. Both patients whose headaches did not respond to treatment had very mild and infrequent migraines. Amongst the 18 patients with non-migrainous headaches, seven had a complete response to treatment and 10 a partial response. None of the patients with chronic daily headache had complete resolution, but treatment did lead to a partial response in five out of six patients. Each patient with chronic daily headache had presented with CAPS in the neonatal period and had a significant delay between symptom onset and treatment. Myalgia completely resolved in 19 patients with treatment whilst three patients had a partial response and one no response. In those patients with established hearing loss and optic atrophy no improvement had been noted.

Of 38 patients, 24 had complete resolution of their systemic symptoms with treatment (14 had a partial response). This was coupled with a marked improvement in inflammatory markers. The median of the median pre-treatment CRP levels for all patients was 27.5 mg/l and decreased to 3.0 mg/l ($P < 0.0001$; ANOVA) following treatment, whilst the equivalent SAA value decreased from 134.6 mg/l to 4.2 mg/l in a statistically significant manner ($P < 0.0001$; ANOVA).

**Discussion**

Neurological manifestations are common in CAPS [10]. Levy and colleagues [11] reported neurological involvement in 40% of patients. Here, neurological features were found in 95% of our patients. This discrepancy may reflect a more restrictive neurological assessment in the Eurofever Registry, as acknowledged by its authors, and highlights the importance of directly asking patients with CAPS about the presence of headaches as this may not be volunteered.
A broader range of headache syndromes was included in our study, as opposed to the narrower criteria of morning headache or proven aseptic meningitis in the Eurofever Registry analysis. The headache phenotype in our patients varied widely, with differing frequency and severity, as well as different headache phenomenology (17/32 patients described migrainous features). Although primary headaches such as migraine are frequent in the general population, the broadening of the range of headaches considered related to genetically proven CAPS is justified by the excellent response to targeted anti-IL-1 treatment in these patients, including headache resolution. However, overlap with common primary headache syndromes may be an explanatory factor in some patients, particularly those with no response or an incomplete response to anti-IL-1 treatment.

Our results show that three out of the four patients with available cerebrospinal fluid data have evidence of aseptic meningitis. Chronic aseptic meningitis can result in chronic intracranial hypertension and papilloedema eventually leading to optic atrophy, which is also a recognized feature in our cohort. Although there is a broad differential diagnosis of chronic aseptic meningitis the characteristic systemic symptoms and confirmed pathogenic mutations significantly increase the likelihood that CAPS is the underlying cause in these cases. CAPS should be included in the differential diagnosis of chronic or recurrent aseptic meningitis and genetic testing for CAPS should be considered in this context. This also highlights chronic meningitis as a potential candidate mechanism for headaches in these patients. Whether milder headaches represent low level central nervous system inflammation or are related to systemic inflammation deserves further study. For patients with migrainous features, different mechanisms may apply. In a study of 25 migraine patients, circulating levels of IL-1β were significantly higher during migraine attacks than between attacks [13], which may be relevant to the pathogenesis of headache in CAPS [10].

Hearing loss is another prominent neurological feature of CAPS. Cochlear inflammation with cochlear enhancement on MRI has been described in children with CINCA [14]. None of the MRIs in our patients showed cochlear enhancement, but many of these were performed whilst the patients were receiving anti-IL-1 treatment, which is a confounding factor. The association of the T348M variant with significant hearing loss has been described previously [11] and is reflected in our results. In addition, the T348M patients are more likely to have optic atrophy (P < 0.05; two-tailed Fisher’s exact test) or papilloedema (P < 0.01; two-tailed Fisher’s exact test) than the A439V group and have an earlier age of onset with all patients presenting neonatally. Other mutations were too rare for conclusions to be drawn. The molecular basis for these genotype–phenotype associations remains to be elucidated.

Stroke-like episodes with hemiparesis with no evidence of infarction on neuroimaging were described in two patients. These were ultimately attributed to sustained untreated CAPS with central nervous system inflammation although the exact pathophysiology is unclear.

The vast majority of patients in our cohort initially developed symptoms at birth or in early childhood. However, the median age at diagnosis and start of treatment was 35 years, whilst the median time from symptom onset to diagnosis was 28 years, representing
a significant delay. This was particularly the case for the six patients with chronic daily headache, all of whom presented neonatally. The relatively modest response of these patients to anti-IL-1β therapy may reflect irreversible changes downstream from the original inflammatory process, which may have been the result of recurrent or chronic aseptic meningitis. This suggests that treatment may be more effective when instituted earlier in the course of the disease. However, data from paediatric cohorts are required to establish this. Despite such a delay to diagnosis, 56% of patients had a history of one first-degree relative with the diagnosis as well. Often diagnosis in one family member precipitated genetic screening in relatives. Given the autosomal dominant nature of the disorder, screening of family members once a mutation is confirmed is important to enable treatment at the earliest opportunity.

Although CAPS can present in many ways, the range of neurological manifestations is relatively circumscribed. The presence of atypical features should therefore lead to a search for a second pathology. One of our patients gave a history of numbness in her limbs lasting weeks, triggered by pressure, which was not easily reconciled with her diagnosis of CAPS. Examination showed sensory loss in the left hand, approximating a median nerve distribution, and numbness of the toes on the right. DNA analysis showed a partial deletion of the peripheral myelin protein-22 (PMP22) gene on chromosome 17 as well as an unlinked NLRP3 mutation on chromosome 1, consistent with a dual diagnosis of CAPS and HNPP. These conditions segregated independently in the patient’s family.

Although white matter lesions were noted in a subset of our patients, our MRI data suggest that cranial imaging provides little in the way of specific diagnostic information for CAPS. However, it is an important investigation to exclude alternative causes of the neurological manifestations of CAPS, such as headache and sensorineural hearing loss. For example, one patient was coincidentally found to have an acoustic neuroma. As previously noted, the MRIs were performed after treatment had started, thereby potentially decreasing the yield of more specific abnormal findings, such as cochlear enhancement [14], but also making it difficult to delineate any MRI findings that may be induced by anti-IL-1 treatment.

The limitations of this study include the retrospective nature of data collection and the small numbers which preclude more in-depth statistical analysis.

Our patients, who all received anti-IL-1β therapy, show an overwhelming improvement in systemic and neurological symptoms of CAPS. This highlights the importance of clinical recognition as, although rare, CAPS is eminently treatable and prompt diagnosis, including by neurologists, can reverse many symptoms and may prevent progression of hearing loss, optic damage and headache.

**Disclosure of conflicts of interest**

This study was funded by Novartis Pharma. Dr Lachmann reports personal fees from Novartis, personal fees from SOBI, outside the submitted work. Professor Ginsberg has received honoraria and travel bur-
saries for lecturing, writing and consultancy from Shire, Boehringer Ingelheim, Baxter and Grifols. All remaining authors have nothing to disclose.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Major neurological and systemic features in CAPS patients by NLRP3 mutation.

**References**


