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Original article

Spectrum of the neurologic manifestations in childhood-onset cryopyrin-associated periodic syndrome

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ABSTRACT

Objective: Neurologic complications of chronic infantile neurologic, cutaneous and articular syndrome (CINCA) are well-known, whereas there are scarce data regarding neurologic features of milder cryopyrin-associated periodic syndrome (CAPS) phenotypes. We aimed to review the neurologic features in detail and summarize the other CAPS-related manifestations in 12 children.

Methods: All children with CAPS that have been followed-up from pediatric rheumatology outpatient clinic, were enrolled to the study. In addition to the neurologic examination, magnetic resonance imaging (MRI) of brain, electroencephalography, eye examination, hearing test and intellectual assessment were done. Demographic, clinical features, genetic analysis and laboratory tests were noted from patient records and hospital database.

Results: The median age of the subjects was 7 years (range 2–19 years), with a female-to-male ratio 2/1. The phenotype was consistent with familial cold autoinflammatory syndrome in 7 patients, Muckle–Wells syndrome in 3 patients and chronic infantile neurologic, cutaneous and articular syndrome in 2 patients. Most frequently noted neurologic clinical manifestation during the entire disease course was headache (n = 4/12) followed by seizures (n = 3/12), papilledema (n = 3/12), intellectual disability (n = 2/12), aseptic meningitis (n = 2/12), hearing loss (n = 2/12) and optic atrophy (n = 1/12). MRI of the brain revealed abnormal lesions in two patients. Uveitis or conjunctivitis were seen in two children. Overall, neurological involvement was detected in 6/12 of our cohort, of which half (n = 3) was in severe form.

Conclusion: Half of the children with CAPS exhibited neurologic manifestations with varying degrees of severity. Increased understanding and awareness of this rare but treatable

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syndrome among neurologists is essential. If remains untreated and unrecognized, this autoinflammatory syndrome could lead to significant morbidity and mortality. Besides complete resolution of systemic symptoms, anti-interleukin-1 treatment may also prevent progression of neurologic findings when initiated in the early stage of the disease.

1. Introduction

The cryopyrin-associated periodic syndrome (CAPS) is a rare and treatable autoinflammatory disease characterized by recurrent episodes of systemic inflammation, resulting in fever, urticarial rash and arthralgia.[1–4]

The syndrome includes three different clinical entities, which represent varying degrees of disease severity along a continuum spectrum from the mildest familial cold autoinflammatory syndrome (FCAS) to the most severe neonatal-onset multisystem inflammatory disease (NOMID). The latter was also referred as chronic infantile neurologic, cutaneous and articular syndrome (CINCA). Patients with Muckle–Wells syndrome (MWS) have an intermediate form of disease severity.[4,5]

The autosomal dominant gain of function mutations within the *NLRP3* gene results with an increased activity of the product, called cryopyrin. Oligomerization of cryopyrin activates the caspase-1 enzyme which in turn catalyzes the production of the potent interleukin-1 β (IL-1β) from the inactive prointerleukin-1β. Uncontrolled and excessive levels of IL-1β than activates endothelial cells and macrophages and increases the production/activation of other inflammatory cytokines. This exaggerated innate immune activation leads to excessive multisystem inflammation responsible from the manifestations of CAPS.[2,4,6,7]

Delay in diagnosis is not rare due to nonspecific presenting manifestations such as fever, urticaria-like skin rashes, eye redness, myalgia, arthralgia/arthritis. If it remains untreated, the patients are prone to develop secondary amyloidosis, deafness and neurocognitive delay.[8–10]

After the demonstration of overproduction of IL-1 and substantial improvement in clinical and laboratory manifestations by anti-IL agents (anakinra or canakinumab), CAPS were incorporated into the group of *IL-1β activation disorders* among the six categories of autoinflammatory diseases.[3,5,11–13] These categories were defined based on molecular pathophysiology of the disorders.[4,5] Anti-interleukin-1 (anti-IL-1) treatment has been shown to be effective both in prevention of flares and complications.[3,4,11,14]

CAPS is associated with both reversible and irreversible neurological manifestations. Cerebral atrophy, hydrocephalus, sensorineural deafness and visual loss are the irreversible neurologic damages as a result of long-term uncontrolled inflammation. In a CAPS patient, early recognition of reversible neurologic features such as headache, papilledema and aseptic meningitis, is critical to prevent these aforementioned long-term irreversible sequelae. Early diagnosis of CAPS and prompt initiation of IL-1 blockers have significant beneficial effect on the neurologic prognosis of CAPS.[3,4,15]

Herein, we describe a cohort of 12 childhood-onset Turkish patients with CAPS who have had detailed neurological assessment in a single center.

2. Methods

All children who were on canakinumab treatment due to a clinical diagnosis of CAPS in a tertiary referral pediatric rheumatology center were enrolled to the study. All of the subjects met the diagnostic criteria for CAPS.[16] Demographic data, clinical features, genetic analysis, laboratory tests were noted from patient records and hospital database. Written informed consent was obtained from the legal guardians and the study protocol was approved by the institutional review board of the Cerrahpasa Medical School (12/09/2017-333207).

Irrespective of any neurologic symptom/sign, visual and auditory complaints, all CAPS patients underwent neurologic and ophthalmologic evaluation by a pediatric neurologist and an ophthalmologist at least once at baseline or follow up. Past clinical and neurologic history of the patients were further assessed by a pediatric rheumatologist and neurologist as a part of clinical examination.

Neurologic manifestations were defined as: headaches, papilledema, aseptic meningitis, hydrocephalus, seizures, intellectual disability, optic nerve involvement (based on fundoscopic examination), sensorineural deafness (confirmed by audiograms). Among the aforementioned manifestations mental retardation, hydrocephalus and seizures were considered as severe neurological involvement.

Audiogram was used to document presence of any sensorineural deafness. Developmental screening was determined by Denver II screening test in children aged under 6 years.[17] Wechsler Intelligence Scale for Children-Revised (WISC-R) tests were given to indicate mental status in children aged above 6 years.

Neurologic assessment was reinforced by a cranial magnetic resonance imaging (MRI) scan and electroencephalogram (EEG), which were performed in all patients even in the absence of any neurologic symptom or sign. MRI of brain (T1, T2, T2 FLAIR, before and after injection of gadolinium, T2 weighted sequences, if available) scan results were assessed by the same experienced neuroradiologist both at diagnosis (when available) or at last patient visit (all subjects). All patients underwent at least one prolonged awake and sleep electroencephalographic recordings. The duration of sleep

EEG recordings were at least 1 h including Stage I and II of non-REM sleep. An international 10–20 electrode placement system was used. All EEGs were evaluated by one of two authors (SS and HK).

Continuous variables were presented as median, range (minimum–maximum) and interquartile range (IQR). Categorical variables were given as frequencies and percentages (%) where appropriate.

3. Results

A total of twelve patients with CAPS were enrolled (8 female, 4 male), with a median age at disease onset of 9 months (IQR: 0.9–4.7 years, range: postnatal 1st day to 9 years), median age at diagnosis of 6 years (IQR: 1.4–9.5 years, range: 7 months to 14 years) and a median lag time from disease onset to diagnosis of 2.8 years (IQR: 0.5–5 years, range 15 days–12.9 years).

All patients met the clinical CAPS criteria[16] and in 9 of them diagnosis was genetically confirmed. The median age of the patients at study time was 7 years (IQR: 4.0–12.7 years, range 2–19 years). The median disease duration was 6.3 years (IQR: 3.0–9.5 years, range 1–13.9 years). The patients' demographic features, disease subtypes, and work-up findings are shown in Table 1. There were no CAPS in any relative of our patients except patient #11 and #12, which were siblings.

The predominant CAPS subtype was familial cold autoinflammatory syndrome (n = 7/12), followed by Muckle–Wells syndrome (n = 3/12) and chronic infantile neurologic, cutaneous and articular syndrome (n = 2/12). The most frequently noted systemic manifestations in our case series were fever (12/12) and urticarial rash (12/12), followed by arthralgia/arthritis (11/12), myalgia (8/12) and fatigue (8/12). Development of these manifestations typical for CAPS were in the neonatal period for 3 patients, in infancy period for 8 and between the ages of 2 and 12 years for 4 subjects. At disease onset, neurologic manifestations accompanying the classical CAPS symptoms (fever, rash, etc.) were seen in 2 (Patient #3 and #5) out of 12 patients. These neurologic manifestations were in the form of chronic aseptic meningitis and seizures in both of the subjects in the neonatal period.

Overall, neurological involvement, which was frequently in the form of headache (4/12), epilepsy (3/12) and papilledema (3/12), was detected in half (6/12) of our CAPS patients in this retrospective observational study. Furthermore, severe neurological disease (epilepsy, hydrocephalus and intellectual disability) was observed in 3/12 subjects. Papilledema was noted in 2 of the subjects (Patient #1 and #9) with non-migrainous headaches (4/9). All of the subjects with papilledema were found to have headache except Patient #3. He was unable to describe the presence or absence of headache due to severe developmental delay.

The response to treatment was evaluated longitudinally. Papilledema and headache were present in Patient #1 before the initiation of canakinumab treatment, whereas in Patient #9 they appeared during the treatment period. Consent for lumbar puncture (LP) could not be obtained from Patient #1, so the LP has not performed. However the aforementioned neurologic manifestations improved after anti-IL1 and acetazolamide treatment. After detection of increased opening

Table 1 – Demographic, clinical, electroencephalography and neuroimaging features of CAPS patients.

Patient	Age	Gender	NLRP3 mutation	Hearing loss	Uveitis or conjunctivitis	Papilledema	Optic atrophy	Headache	Seizure	Intellectual Disability	Hydrocephalus	Aseptic meningitis	Phenotype	EEG	Cranial MRI
1	10	Female	Q703K	No	No	Yes	No	Yes	No	No	No	No	MWS	Normal	Normal
2	2	Male	Negative	No	No	No	No	No	No	No	No	No	FCAS	Normal	Normal
3	6	Male	G569R	Yes[a]	No	No	No	No	Yes	Yes	Yes	Yes	CINCA	Abnormal	Abnormal
4	4	Female	Q703K	No	No	No	No	No	No	No	No	No	FCAS	Normal	Normal
5	3	Female	Negative	No	No	Yes	Yes	No	Yes	Yes	No	Yes	CINCA	Abnormal	Abnormal
6	13	Male	T433I	No	No	No	No	Yes	No	No	No	No	FCAS	Normal	Normal
7	6	Male	Negative	No	No	No	No	No	No	No	No	No	FCAS	Normal	Normal
8	12	Female	T436A	No	Yes	No	No	No	No	No	No	No	FCAS	Normal	Normal
9	14	Female	A242A	No	Yes	Yes	No	Yes	Yes	No	No	No	MWS	Abnormal	Normal
10	19	Female	I313V	No	No	No	No	No	No	No	No	No	FCAS	Normal	Normal
11	8	Female	V198M	Yes[b]	No	No	No	Yes	No	No	No	No	MWS	Normal	Normal
12	4	Female	Q703K	No	No	No	No	No	No	No	No	No	FCAS	Normal	Normal

FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells syndrome; CINCA: chronic infantile neurologic, cutaneous, and articular syndrome.

[a] Bilateral sensorineural hearing loss.

[b] Left-sided hearing loss.

cerebrospinal fluid pressure in LP, headache subsided after 1-week and papilledema regressed after 6-months duration of acetazolamide and topiramate therapy in Patient #9 (Fig. 2). The onset of headache without accompanying papilledema was before the usage of canakinumab in Patient #11 and during the treatment period in Patient #6. No additional therapy was required because the mild intensity of pain. No improvement had been noted with canakinumab therapy in patients with established hearing loss (Patient #3 and #11) and optic atrophy (Patient #5).

There were two patients (Patient #3 and #5) in our cohort, at the most severe end of the disease spectrum (CINCA), that had recurrent/chronic aseptic meningitis in infancy period, which did not recur after canakinumab treatment. The diagnosis of aseptic meningitis was secured by positive clinical (our patients had fever and seizure) and laboratory evidence of meningeal inflammation with negative bacterial cultures. Though the onset of the manifestations was in neonatal period, the diagnosis of CAPS could be established as late as at 7 months of age in both of the patients. Although no aseptic meningitis has been seen in subjects after the initiation of anti-IL1 treatment, no improvement was noted in the sequel lesions on MRI. Unfortunately, severe developmental delay developed in both subjects.

Cranial MRI of all the subjects were normal except for patient #3 and #5. Cranial MRI of the patient #3 revealed diffuse parenchymal atrophy and hydrocephalus. The MRI findings of the patient #5 were illustrated in Fig. 1. It should be noted that Patient #5 has experienced recurrent aseptic meningitis until 7-month-old when the diagnosis was secured. Subsequently, the flares subsided after the initiation of anti-IL-1 treatment.

All of the subjects with a history of seizure (patients #3, #5 and #9) had abnormal EEG findings. EEG findings were as follows; focal epileptic activity in patient #3, generalized epileptic activity in patient #5 and #9. Control of the seizures was achieved by two antiepileptic regimens in the first two subjects, whereas seizure did not recur in the latter subject after a single antiepileptic drug.

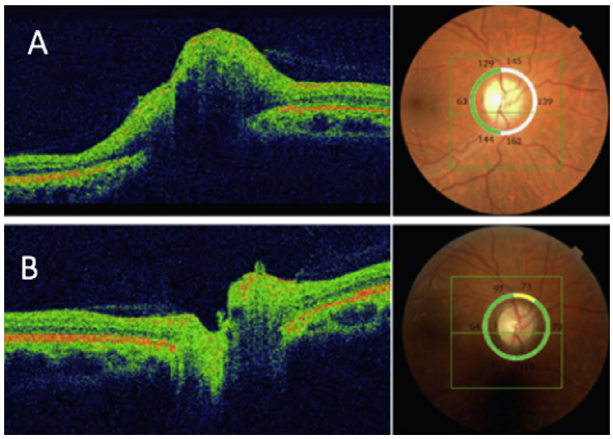

Fig. 2 – Optical coherence tomography (OCT) images of patient 9. Upper image (A) showing significant papilledema in right eye, whereas lower image (B) represents normal findings in left eye.

Results of the *NLRP3* gene analysis are given in Table 1. Four of the subjects in our cohort (Patients #3, #6, #8 and #10) were carrying mutations which have been considered as pathogenic or likely pathogenic. The Q703K and V198M variants, which are accepted as low-penetrance variants, were detected in 3 patients (Patients #1, #4 and #12) and in 1 patient (Patient #11), respectively. Patient #9 was positive for A242A genotype, which has been reported as a benign variant. No genetic mutation could be identified in the NLRP3 gene of the 3 subjects (Patient #2, #5 and #7).

4. Discussion

Our study demonstrated a higher frequency of neurologic involvement in patients with CAPS compared to the Eurofever Registry. Pediatric neurologists should be aware of this rare and treatable autoinflammatory disease and should be

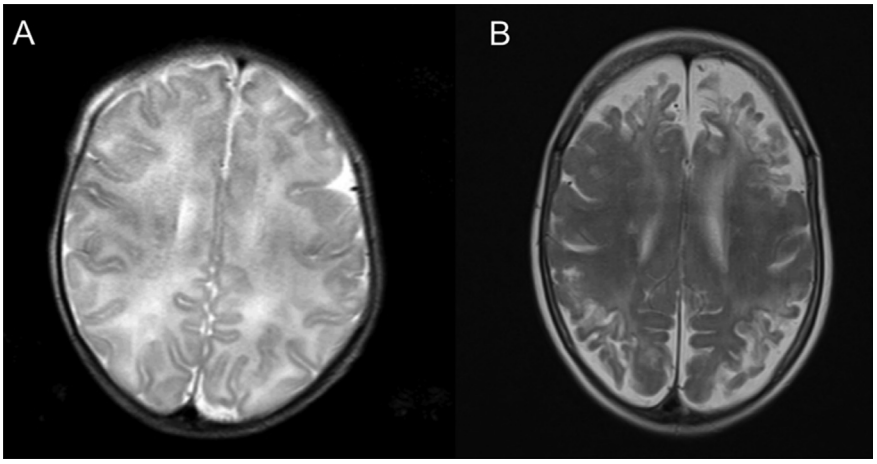

Fig. 1 – Axial T2-weighted magnetic resonance images of the patient 5, obtained when she was 1-month-old (A) and 18-months old (B). The first MRI scan (A), which was performed after the first flare with fever, rash and seizure, showing normal findings for a 1-month-old child. Significant global cortical atrophy (B) already developed, despite the patient was on anti-IL-1 therapy since 7 months-old.

involved in the management of the disease. The emergence of anti-IL1 agents and their successful usage in treatment of CAPS represent a major milestone in disease management and in the prevention of complications.[3,11–13] A historical study in pre-biologic agent era demonstrated the association of recurrent/chronic aseptic meningitis with seizures, spasticity in lower extremities, cerebral atrophy and low IQ.[18]

Neurologic involvement was detected in half of our cohort (n = 6/12), 3 of which was in severe form. Neurologic and severe neurologic manifestations were noted in 40% and 12% of a series of 136 CAPS patients, respectively, from the Eurofever Registry. This study included the largest CAPS cohort uptodate. Neurological involvement was mostly in the form of headaches (70%), followed by papilledema (52%), meningitis (26%), hydrocephalus (18%), mental retardation (16%) and seizures (4%).[19] Neurological manifestations were documented in 95% of 38 UK patients. However, it should be noted that 84% of the subjects reported headache, which was the most prevalent manifestation.[20] This large discrepancy in the frequency of neurological involvement between this study and our cohort seem to be a result of difference in the median age of the enrolled subjects (median age at diagnosis: 35 years *vs* 6 years). Headache again was the most frequent neurological manifestation which was reported by 92% (n = 12/13) of another CAPS cohort.[21] All subjects in this case series were adults with milder phenotypes without any severe neurological disease. Beside the increased frequency of primary headaches in adults, easier expression and definition of headaches in adults compared to the children may have a role in this large diversity.[20] The lower frequency of headache and neurological manifestations in our case series could be attributed to inclusion of younger patients in our study. It is obvious that, the younger the children are, the lower expression of the headache. Six of the 8 subjects without headache were equal or less than 6 years of age, of whom two had also neurodevelopmental delay.

Seizure is not a rare entity in the course of CAPS disease. However, its association with epilepsy has not been clarified in previous studies. In a study, among 57 CAPS patients, 15.8% (n = 9/57) had seizure, whereas there were only 2 subjects with seizure in the Eurofever registry (n = 136).[19,22] All of these patients with epilepsy were categorized in the NOMID group. On the contrary, neither seizure nor epilepsy had been documented in another CAPS cohorts, which predominantly included adult CAPS patients.[20,21,23] None of the studies reported any EEG finding and/or presence of any association of these seizures with epilepsy. Three out of the 12 subjects in our cohort reported seizure. Since these 3 subjects experienced at least two seizures and showed epileptiform discharges in EEG, all of them were accepted as epilepsy. Moreover, two of them were considered as symptomatic epilepsy due to the presence of brain lesions (cortical atrophy and hydrocephalus) on cranial MRI. In the other case who had generalized epilepsy, cranial MRI findings were normal. Assessment with EEG and cranial MRI is warranted in CAPS patients with history of seizure, in order to reveal the underlying etiology. Causality will be probably better elucidated by extrapolation of the data regarding the etiology of seizures in CAPS patients in future studies.

Although rare, the physicians involved in the management of the CAPS patients should be alert for the most devastating involvement, namely the neurological disease. If remains untreated, this chronic inflammation in leptomeninges leads to arachnoid adhesions. Brain atrophy and ventriculomegaly after this uncontrolled long-standing increased intracranial pressure should be considered as damage of CAPS, rather than an involvement pattern.[6,11,15,21,24–26] In accordance with this mechanism, the recurrent aseptic meningitis attacks may be responsible for the cortical atrophy and hydrocephalus in patients #3 and #5.

Due to the unestablished genotype–phenotype associations yet and high risk of devastating complications (neurodevelopmental delay and amyloidosis), the management of the CAPS mandates continued vigilance, whatever the NLRP3 variant is. Among the subjects with pathogenic or likely pathogenic mutations (n = 4/12), clinical phenotypes and namely the CAPS subtypes of 2 patients were not concordant with the subjects described previously.[27–30] The effect of Q703K and V198M mutations on phenotype is still a matter of controversy.[19,31–36] CAPS subjects with Q703K and V198M alleles tend to show milder manifestations such as malaise, fatigue, fever and cutaneous rashes without evident neurological features.[19,33,35] CAPS patient carrying low-penetrance variants (Q703K, V198M and R488K) showed a different clinical phenotype with more frequent fever and gastrointestinal manifestations; yet less frequent visual and hearing manifestations, compared to those with a known pathogenic *NLRP3* mutation.[31] Moreover, all of the subjects treated with anti-IL1 exhibited a response (with 50% complete and 50% partial). In contrast to this multicenter study, the effect of Q703K both on function and phenotype of carriers was proposed as weak by an Italian study.[32] Patient #9 was positive for A242A genotype, which has been reported as a benign variant. However, our patient exhibited typical CAPS manifestations such as fever, cutaneous rashes, uveitis, papilledema and seizures compatible with MWS/CINCA crossover features. Also, she showed complete response to anti-IL1 therapy. It is noteworthy that a *NLRP3* mutation could not be detected in a substantial number of the patients with typical CAPS (especially in CINCA group) because of somatic mosaicisms.[2,10,37] Likewise, no genetic mutation could be identified in the *NLRP3* gene of the 3 subjects (Patient #2, #5 and #7).

Its retrospective nature and small-sample size are the major limitations of our study. Despite the small number of patients, this study describes the early CAPS phenotype in an ethnically homogenous pediatric sample; it will not only enrich the relevant literature, but could also assist pediatric neurologists in meticulous assessment of this rare disease and provide significant insight regarding its long term-outcome. In conclusion, the neurologic manifestations such as aseptic meningitis and seizures may even be the presenting manifestation in CAPS patients. In clinical practice, CAPS should be kept in mind of a neurologist when there is no clear cause of these neurologic manifestations associated with chronic or recurrent elevated acute phase reactants and cutaneous manifestations. Increased awareness of this rare but treatable autoinflammatory syndrome among clinicians would probably decrease the morbidity and mortality.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.03.006.

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