A pediatric CAPS patient with an unusual presentation and resistance to standard treatment

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Dear Editor,

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare, autosomal dominant autoinflammatory diseases caused by mutations in the *NLRP3* gene[1]. This gene encodes the cryopyrin protein, and gain-of-function mutations result in excessive interleukin-1β (IL-1β) production due to caspase 1-mediated cleavage of pro-IL-1β[2]. CAPS presents a wide clinical spectrum, from mild to severe phenotypes, including urticarial-like rash, fever, arthropathy, aseptic meningitis, sensorineural hearing loss, ocular involvement, and other systemic inflammatory manifestations[3,4]. Ocular involvement typically includes conjunctivitis; and in severe cases, optic nerve involvement, including optic disc edema or atrophy, may result in vision impairment or permanent vision loss[5,6]. IL-1 inhibitors, anakinra or canakinumab, are the cornerstone of treatment, controlling systemic inflammation and preventing long-term complications[7].

Here, we present a pediatric CAPS case characterized by steroid- and anakinra-resistant optic disc edema, which showed marked improvement with high-dose canakinumab. This case underscores the importance of early recognition and aggressive treatment of ocular involvement in CAPS patients to prevent irreversible visual impairment.

A 13-year-old male was referred to our pediatric rheumatology clinic with complaints of recurrent, generalized urticarial rash and arthralgia, both aggravated by cold exposure. Urticarial lesions were present since the neonatal period and migratory arthralgia for the past two years, which had not responded to non-steroidal anti-inflammatory drugs. There was no parental consanguinity.

On physical examination, failure to thrive was noted. Maculopapular rash on the face, arms and trunk, along with bilateral preorbital edema, conjunctival hyperemia was observed. No joint involvement was present, and neurological examination was unremarkable. Given the history of recurrent urticarial rash, arthralgia, and ocular findings, the patient was admitted with a preliminary diagnosis of CAPS.

Laboratory investigations revealed elevated acute phase reactants (CRP:19 mg/mL, ESR:59 mm/hour, SAA:1080 mg/L). Autoimmune profile (ANA, ANCA, anti-dsDNA) was negative. ACE, complement (C3, C4), and immunoglobulin (IgG, IgA, IgM and IgE) levels were within normal limits. Specific IgE and viral serologies were negative. Otolaryngological evaluation, including audiometry, revealed no evidence of hearing loss or other abnormalities. Skin biopsy revealed superficial perivascular dermatitis with neutrophilic and eosinophilic infiltration.

Ophthalmological evaluation revealed bilateral optic disc edema with optical coherence tomography (OCT) demonstrated grade 3 papilledema, with retinal nerve fiber layer (RNFL) thickness measuring 363 µm (right eye) and 347 µm (left eye) (Figure 1).

Cranial magnetic resonance imaging and angiography were unremarkable. Due to presence of papilledema, a lumbar puncture was performed, revealing elevated cerebrospinal fluid (CSF) opening pressure of 52 cm H_2O; CSF cytology and glucose levels were normal, and cultures were negative. Acetazolamide therapy was initiated. A hereditary periodic fever gene panel (*MEFV*, *MVK*, *NLRP3*, *NLRP12*, *NOD2*, *TNFRSF11A*, *LPIN2*, *PSTPIP1*, *IL1RN*, *IL10RA*, *IL10RB*, and *ADA2*) was performed.

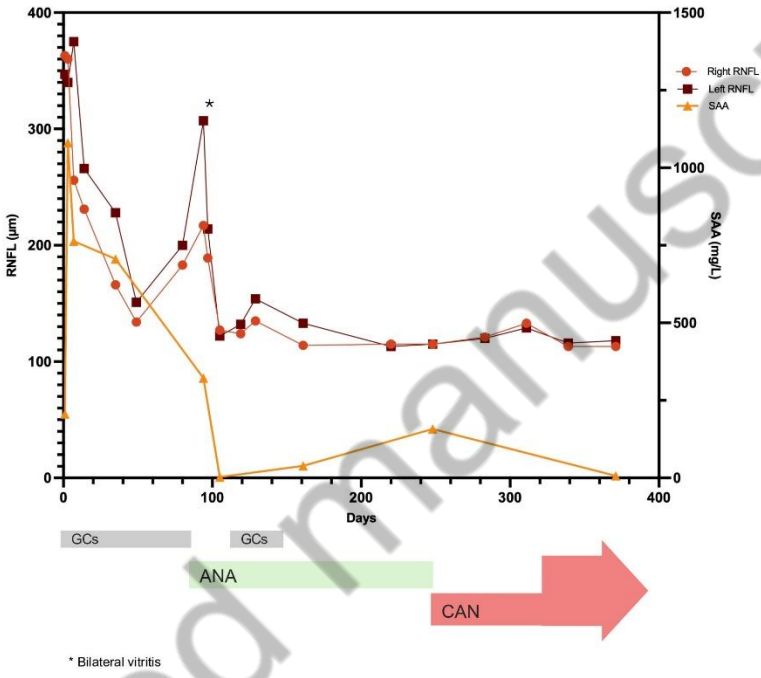
Glucocorticoid therapy (1 mg/kg/day) in combination with topical corticosteroid was initiated, leading to resolution of the rash, but optic disc edema persisted. Two months later, ophthalmologic reassessment revealed progression of optic disc edema and new-onset bilateral vitritis. Anakinra, was initiated at a dose of 3 mg/kg/day. While there was a modest improvement in optic disc findings, SAA levels remained elevated (Figure 1).

Genetic testing confirmed a heterozygous pathogenic variant in the *NLRP3* gene (c.1043C>T, p.(Thr348Met)), confirming the diagnosis of CAPS. Due to persistent optic disc edema and insufficient control of systemic inflammation, anakinra was switched to canakinumab at 5 mg/kg every two months. SAA levels remained elevated and ophthalmological findings persisted, prompting an escalation of canakinumab to 5 mg/kg monthly. After two monthly injections, a marked improvement in optic disc edema was observed, accompanied by normalization of inflammation markers, and no adverse events were observed. At 15 months of follow-up, including 12 months under IL-1 inhibition and the last four months on monthly high-dose canakinumab therapy, the patient remains in clinical remission with resolved optic disc edema and normal RNFL thicknesses.

This case highlights the importance of recognition of ocular involvement of CAPS and the effective strategy of high-dose canakinumab in cases unresponsive to corticosteroids and standard dosing of IL-1 inhibition.

Tables and Figures

Figure 1. Temporal association between RNFL thickness, serum amyloid A levels, and treatment interventions in a pediatric CAPS patient.



The graph illustrates the longitudinal changes in retinal nerve fiber layer (RNFL) thickness (µm) and serum amyloid A (SAA) levels (mg/L) over time. The green bar indicates the period of anakinra therapy (3mg/kg daily), red bars represent the initiation (5 mg/kg bimonthly and subsequent dose escalation of canakinumab (5 mg/kg monthly), and grey bars indicate systemic glucocorticoid use. RNFL measurements are shown for both eyes, and SAA levels reflect systemic inflammatory activity.

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