Bilateral fuchs uveitis syndrome in a patient with cryopyrin-associated periodic syndrome: A case report

Mehmet Balbaba[1], Mehmet Canleblebici[2], Hakan Yıldırım[1], Ulku Celiker[3]

ABSTRACT

In this case report, we aim to report an unusual case of in a patient with cryopyrin-associated periodic syndrome (CAPS) who had bilateral Fuchs uveitis syndrome (FUS). She had history of arthritis and sensorineural hearing loss and her ophthalmic examination revealed that both eyes had diffuse stellate keratic precipitates, diffuse stromal iris atrophy, anterior chamber cells and vitreous inflammation. The right eye intraocular pressure was high and the left one was normal. In addition, she had bilateral optic disc pallor. After genetic consultation, NRLP3 gene mutation was detected and was diagnosed CAPS and treated with anakinra. Despite maximum topical anti-glaucomatous medication, right intraocular pressure could not be controlled and then the patient had Ahmed glaucoma valve implantation. Inflammation and intraocular pressure elevation were not observed in the patient's follow-up. In patients with CAPS, FUS uveitis which is rarely seen bilaterally, may be a component of ocular findings or may be incidental finding that is unique to our case.

Keywords: Cryopyrin associated periodic syndromes, fuchs uveitis syndrome, glaucoma NLRP3 gene mutation.

INTRODUCTION

Cryopyrin-associated periodic syndrome (CAPS) is a rare systemic autoinflammatory disease spectrum with variable penetrance. The prevalence of CAPS is estimated to be about 1–3 per million.[1] CAPS is associated with mutations in the NLRP3 gene, which encodes the cryopyrin protein, a key component of the inflammasome complex that regulates the production of interleukin (IL) 1β. Therefore, dysfunction of the NLRP3 inflammasome leads to the overproduction of IL-1β, which is responsible for the characteristic features in patients with CAPS.[2]

CAPS presents with a wider variety of ophthalmic and systemic findings. Urticaria-like rashes, cold triggered episodes, sensorineural hearing loss, musculoskeletal symptoms of arthralgia/arthritis, chronic aseptic meningitis, and skeletal abnormalities are among the most common typical findings.[3] Ophthalmic manifestations can occur in all three forms of CAPS. Recurrent conjunctivitis with/without other inflammatory symptoms is the main ophthalmological symptom. We presented a case with coexisting CAPS and bilateral Fuchs uveitis syndrome (FUS), which has not been previously reported in the literature.

CASE REPORT

A 25-year-old woman presented in March 2021 for the evaluation of glaucoma and uveitis. She had a history of arthritis and sensorineural hearing loss.

On initial presentation, the best corrected visual acuity was 20/30 in the right eye and 20/40 in the left eye. Intraocular pressure was 32 mmHg in the right eye and 16 mmHg in the left eye. In the anterior segment examination, both eyes had diffuse stellate keratic precipitates, diffuse stromal iris atrophy, +0.5 anterior chamber cells and vitreous inflammation (Figure 1). The right eye was pseudophakic and the left eye had a posterior subcapsular cataract. Funduscopic examination revealed that the bilateral optic discs were pallor (Figure 2). Fundus fluorescein angiography was normal (Figure 2). The retinal nerve fiber was marked as thinned bilaterally on an optical coherence

1- Assoc. MD, Department of Ophthalmology, Fırat University, Elazıg, Türkiye

2- MD, Department of Ophthalmology, Kayseri State Hospital, Kayseri, Türkiye

3- Prof. MD, Department of Ophthalmology, Fırat University, Elazıg, Türkiye

Received: 30.12.2023
Accepted: 03.04.2024
J Ret-Vit 2024; 33: 156-159
DOI:10.37845/ret.vit.2024.33.25

Correspondence author:
Mehmet Canleblebici
Email: mehmetcl@hotmail.com

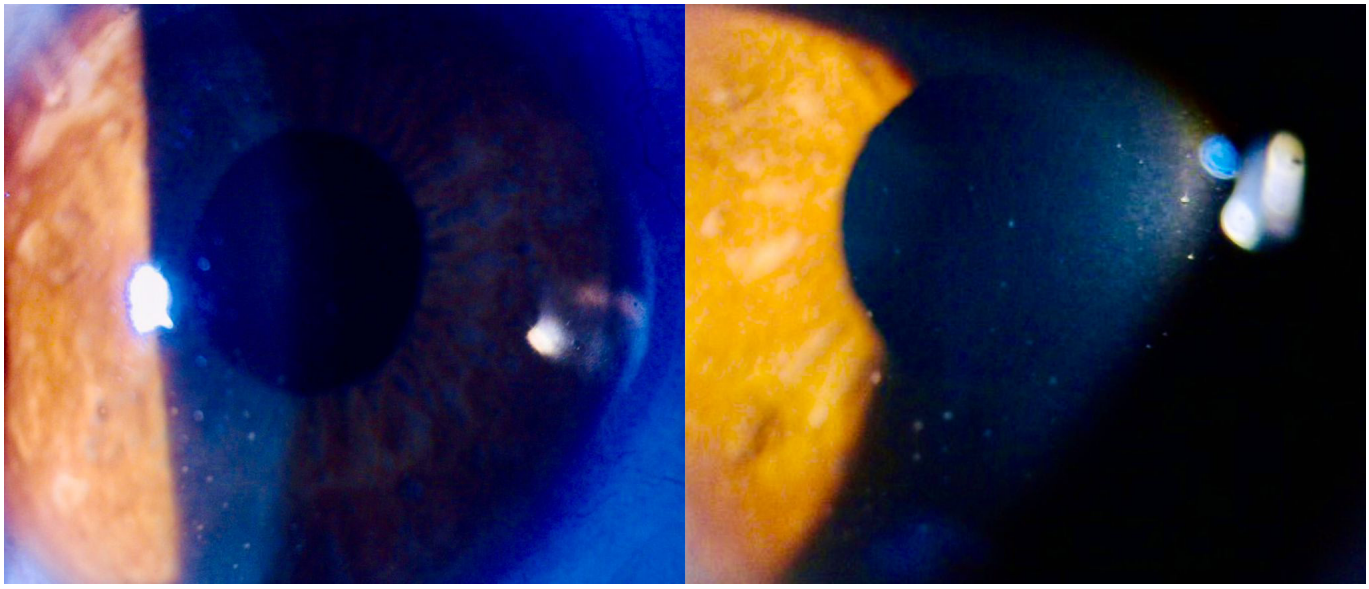

Figure 1: *In the anterior segment photographs, both eyes had diffuse stellate keratic precipitates, diffuse stromal iris atrophy, and +0.5 anterior chamber cells.*

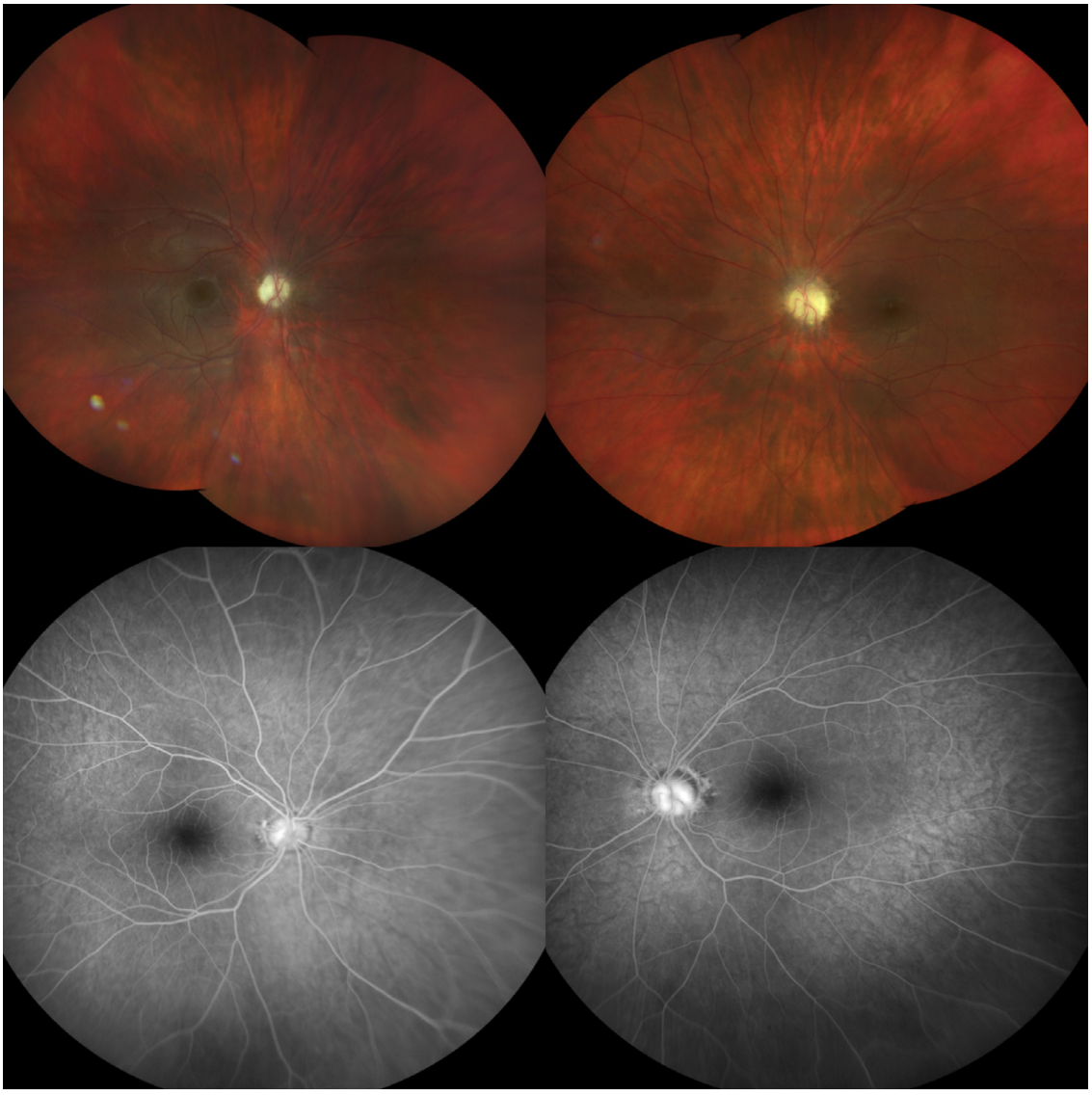

Figure 2: *Fundus photographs of the patient revealed that the bilateral optic discs were pallor and fundus fluorescein angiography was shown normal.*

tomography examination. Consultations, laboratory and radiologic tests were ordered for work up possible causes. The patient was referred to the neurology, rheumatology, and otolaryngology departments. The brain magnetic resonance imaging was negative for masses or signs of demyelinating disease. Erythrocyte sedimentation rate, C-reactive protein and serum amyloid A values were elevated. In the audiometry test, moderate hearing loss was detected.

Genetic testing for CAPS was suggested by the patient's rheumatologist, and tests revealed that there was a heterozygous for a missense mutation in the NRLP3 gene. The patient was started on anakinra therapy. Most of her symptoms, including arthritis, improved almost immediately. She has had no occult infusion reaction to anakinra. Despite the use of maximum topical anti-glaucomatous medication, right eye pressure could not be controlled, so the patient underwent Ahmed glaucoma valve implantation. After glaucoma surgery, the intraocular pressure of the right eye showed a good response to surgery, and topical medications were discontinued. The patient has been followed up every two months, and there has been no inflammation in either eye to date.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

CAPS is a rare autosomal dominant hereditary autoinflammatory syndromic disease with systemic involvement. It contains three different phenotypic spectrums, varying from the relatively mild familial cold autoinflammatory syndrome to the intermediate Muckle-Wells syndrome to the severe chronic infantile neurological cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease syndrome.[4]

CAPS has a wide range of systemic findings and can be seen with dermatologic, musculoskeletal, ocular, otologic, and neurologic disease symptoms combined with chronic systemic inflammation. The main symptoms of CAPS include episodes of fever, urticaria-like rash, red eye, and arthralgia, while neurological manifestations include headache, sensorineural hearing loss, and papilledema, optic nerve involvement.[5] The association of these findings is important in terms of considering CAPS in the differential diagnosis of diseases involving the auditory and visual systems. The patient in the present study had arthralgia and sensorineural hearing loss.

In previous studies, ocular involvement was found in 78% of patients with CAPS. Chronic conjunctivitis, papilledema, papillitis, uveitis, glaucoma, optic atrophy, corneal haze, episcleritis, and calcific band keratopathy have been previously reported in patients with CAPS.[4] Anterior chamber cells are usually observed in the CAPS and there is a good response to anakinra treatment.[6] For the patient in this study, we observed optic disk pallor, but interestingly, she had bilateral diffuse stellate keratic precipitates, diffuse stromal iris atrophy, +0.5 anterior chamber cells, and glaucoma in the right eye. FUS usually presents with mild anterior chamber cells, diffuse stromal iris atrophy, and diffuse stellate keratic precipitates unilaterally.[7] Chronic open-angle glaucoma is associated with FUS, and in the course of the disease, it can be observed up to 59% of FUS patients. FUS can present bilaterally 10–20%, and it is reported that bilateral cases seemed to have a more aggressive disease with severe glaucoma and greater requirement for cataract surgery.[8] Our patient developed glaucoma in her right eye, in which she had previously undergone cataract surgery, and despite maximum topical anti-glaucomatous treatment, glaucoma surgery was required. Ahmed glaucoma valve implantation was our choice for the surgery because of the patient's resistant high intraocular pressure. After surgery, intraocular pressure was well controlled without any topical treatment.

Altough the etiology of FUS is not fully known, many theories have been proposed to explain the pathogenes, including sympathetic, infectious, hereditary and immunological theory. La Hey et al. first described the presence of autoantibodies against corneal epithelium in almost 90% of the patients with FUS. According to previous studies on aqueous humor cytokine levels of FUS samples in comparison to noninflammatory controls, IL-1, IL-2, IL-6, IL-8, IL-12, and IL-13 were encountered at elevated. Murray et all. first reported on intraocular IL-6 levels in FUS compared with control, supporting a role for IL-6 as an inflammatory mediator in uveitis.[9] These mechanisms may explain the coexistence of CAPS, which is an autoinflammatory disease and FUS.

Anakinra is a recombinant human IL-1 receptor antagonist that competitively inhibits IL-1ß and IL-1α binding to the IL-1 receptor, thereby blocking downstream signaling. It is the first drug used in cohorts for CAPS patients and found to be effective.[10] Anakinra treatment for CAPS is safe and tolerable according to the current literature. Two daily injections of anakinra were observed to improve clinical

symptoms and laboratory results rapidly and significantly in our patient. Most adverse events occur in the first months after initiation of anakinra therapy, such as headaches and arthralgia. In our patient, we did not observe any adverse reactions to the therapy.

Because it is easily misdiagnosed due to nonspecific signs and symptoms, CAPS represents a vision-threatening association, especially if effective treatment is not provided at an early stage. As seen in our patient, papillitis symptoms was severe. If patients with CAPS gene mutations can be diagnosed earlier, they can receive earlier treatment, thus significantly reducing tissue inflammation and disease chronicity and improving organ function and quality of life.

Our report has several limitations. In previous studies, amyloid accumulation in trabecular tissue was demonstrated in patients who underwent trabeculectomy. In our case, we could not obtain a trabecular tissue sample because we performed Ahmed glaucoma valve implantation.

In conclusion, in patients with CAPS, bilateral FUS may be a component of ocular findings or an incidental finding that is unique to our case. These patients can be diagnosed by clinical symptoms, signs, inflammatory markers, and genetic testing if the diagnosis is kept in mind.

Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the conduct and writing of the article.

Funding

No specific funding has been received.

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