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RESEARCH ARTICLE

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# Optic disc changes in Chinese patients with *NLRP3*-associated autoinflammatory disease

Yuezhu Lu[a,b*], Min Shen[c,d*], Zhikun Yang[a,b], Xiao Zhang[a,b], Donghui Li[a,b], Zhangwanyu Wei[a,b], Bing Li[a,b], Xufeng Zhao[a,b], Na Wu[c,d], Bingxuan Wu[c,d], Weihong Yu[a,b] and Yong Zhong[a,b]

[a]Department of Ophthalmology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [b]Key Laboratory of Ocular Fundus Diseases, State Key Laboratory of Complex Severe and Rare Diseases, Chinese Academy of Medical Sciences, Beijing, China; [c]Department of Rare Diseases, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; [d]Department of Rheumatology and Clinical Immunology, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, PUMCH, Beijing, China

**ABSTRACT**

**Objective:** To investigate the optic disc changes (ODC) in Chinese patients with *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID).

**Methods:** Patients who were diagnosed with *NLRP3*-AID at the Department of Rheumatology, Peking Union Medical College Hospital between April 2015 and December 2022 were retrospectively reviewed and analyzed.

**Results:** A total of 20 patients were enrolled in this retrospective study. All 20 patients had a moderate MWS *NLRP3*-AID phenotype. Thirteen patients (65%) had ocular involvements. The interval between symptoms onset and diagnosis was significantly longer in patients with ocular involvement than in patients without ($p=0.044$). The incidence of hearing loss was significantly higher in patients with ocular involvement ($p=0.017$), while the incidence of abdominal pain was significantly lower when compared to patients without ocular involvement ($p=0.007$). Optic disc swelling (ODS) (50%) was the most common ODC. All of the four T348M mutation carriers within our cohort exhibited ODS with visual-field defects. There was a significant difference between patients with/without ODS regarding the number of patients carrying T348M mutation ($p=0.014$). The occurrence of hearing loss and CNS involvement was significantly higher in the group with ODS compared to the group without ($p=0.0014$, $p=0.0198$). Of the eight patients who underwent lumbar puncture, five presented with intracranial hypertension (IH). ODS was observed in all patients with IH. The serum inflammatory markers were significantly higher in patients with ODS than in those without. Two patients receiving regular subcutaneous IL-1 inhibitor treatment showed improvements in ODC.

**Conclusions:** ODC is common among Chinese patients with NLRP3-AID, with ODS being the most common manifestation. Hearing loss and CNS involvement often accompany the occurrence of ODS. The serum inflammatory markers are associated with ODS. The T348M mutation is more likely to lead to ODC with visual-field defects.

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*NLRP3*; autoinflammatory disease; *NLRP3*-AID; optic disc changes; optic disc swelling

## Introduction

*NLRP3*-associated autoinflammatory disease (*NLRP3*-AID) is a rare heterogeneous autoinflammatory disease caused by *NLRP3* gene mutations on chromosome 1q44, which results in interleukin (IL)-1β overproduction [1,2]. The prevalence is ~1–3 per million adults and children, and no sex or ethnic differences have been found yet [3]. It is characterized by recurrent cold-induced fever, urticaria-like rashes, chronic aseptic meningitis, and hearing loss. These symptoms present as three overlapping clinical phenotypes of increasing severity: familial cold-associated autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and

**CONTACT** Weihong Yu yuweihongpumch@163.com Chinese Academy of Medical Sciences, Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing, 100730, China; Yong Zhong zhongy@pumch.cn Chinese Academy of Medical Sciences, Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing, 100730, China
*These authors contributed equally to this work.

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articular syndrome (CINCA). Delayed diagnosis owing to diverse clinical manifestations cause irreversible organ damage, such as sensorineural hearing loss, amyloidosis, sight impairment, joint deformities, and mental retardation.

Several cases of ocular involvement in *NLRP3*-AID have been reported [4–6]. Conjunctivitis is the most common manifestation of MWS [4]. The optic nerve is the most frequently affected structure in patients with NOMID/CINCA [6]. Neurological manifestations of *NLRP3*-AID have been reported [7–9]. Since the optic nerve acts as an extension of the central nervous system (CNS), manifestations, such as optic disc swelling (ODS) and optic atrophy have been reported [6,10], and optic disc lesion is the primary factor leading to poor vision in *NLRP3*-AID patients. However, the data are limited, and the analyses are insufficiently detailed. To date, there have been no comprehensive reports specifically addressing the optic disc changes in cohorts of Chinese patients with *NLRP3*-AID.

Our tertiary medical center is the only adult systemic autoinflammatory diseases center in China. We previously reported a series of studies on Chinese patients with *NLRP3*-AID [8,11–15]. In the present study, we aimed to describe *NLRP3*-AID-associated optic disc changes (ODC) in a cohort of Chinese patients.

## Materials and methods

This single-center, retrospective, and observational cohort study was approved by the institutional review board of Peking Union Medical College Hospital (study code ZS-3272) and performed in accordance with the Declaration of Helsinki. Written consent to publish the patient details was obtained from all participants (or their legal guardians).

### *Subjects*

All patients diagnosed with *NLRP3*-AID at the Department of Rheumatology, Peking Union Medical College Hospital, between April 2015 and December 2022 were reviewed. Diagnosis was based on the clinical criteria proposed by Kuemmerle-Deschner et al. [1], which involve elevation of inflammatory markers (C-reactive protein [CRP] or serum amyloid A), and at least two of the following six typical signs/symptoms: urticarial rash, cold-triggered flares, chronic aseptic meningitis, neurosensory hearing loss, musculoskeletal symptoms, and skeletal abnormalities. Five healthy volunteers were matched with five patients with ODS in terms of sex and age for the analysis of retinal nerve fiber layer (RNFL) thickness.

### *Data collection*

All patients underwent evaluations by an ophthalmologist and an otolaryngologist. Demographic data, clinical characteristics, serum inflammatory marker levels, lumbar puncture examination results, and treatment details were collected and reviewed for all patients. Whole-exome sequencing by next generation sequencing (Joy Orient Translational Medicine Research Center Co., Ltd., Beijing, China) was performed for each patient to investigate *NLRP3*-AID-related mutations. Based on the systemic conditions, a senior rheumatologist developed the final treatment plan for all patients.

We collected the highest values of serum inflammatory markers during the disease course, including the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and CRP level from all patients. Available data on intracranial pressure (ICP), cerebrospinal fluid (CSF) protein levels, and leukocyte counts were collected from the patients with ocular involvement (not all ocular involvements patients were included, as some did not undergo these tests). A complete ophthalmic examination, including best-corrected visual acuity and intraocular pressure (IOP) examination, slit-lamp examination of the anterior segment, and ophthalmoscopic examination of the vitreous and retina, was performed at the patients' first visit to our clinic. Fundus photography (CX-1, Topcon, Topcon Corporation, Tokyo, Japan), swept source-optic coherence tomography (OCT) (VG200, SVision Imaging, Ltd., Luoyang, China), fluorescein angiography (FA) (Heidelberg Engineering, Inc., Germany; Optos Daytona P200T, Dunfermline, UK), and visual-field examination (Octopus 900, Haag-Streit, Koeniz, Switzerland) were performed at the first visit or during the follow-up. Past ocular medical records and diagnoses were carefully reviewed to determine whether the patients had prior consultations at other eye clinics.

### *Statistical analysis*

Continuous variables are presented as the mean ± standard deviation (*SD*), medians, or ranges. Counts and percentages were used to categorize variables. Continuous variables were analyzed using an independent *t*-test. The Fisher's exact test was used to analyze categorical variables. Data was analyzed by GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA) software. A value of $p < 0.05$ was considered statistically significant.

## Results

### Demographic and general data

A total of 20 patients were enrolled (Table 1) and they all belonged to the Chinese Han nationality and had a moderate MWS *NLRP3*-AID phenotype. Eleven were men and nine were women, with the average age of disease onset being 13.25 years (median, 6 years; range: 0–49 years), and the average interval between symptom onset and confirmed diagnosis being 16.5 years (median, 18.5 years; range: 0–37 years). Seven patients had a family history of *NLRP3*-AID. There were 15 *NLRP3* mutation types and 1 negative.

### Clinical characteristics of NLRP3-AID patients with and without ocular involvement

Among the 20 patients with MWS, a total of 13 patients (65%) had ocular involvement. The patients were divided into two groups based on the presence or absence of ocular involvement (Table 2). The results showed no significant difference in gender, age of disease onset, and family history between the two groups. However, the interval between symptoms onset and diagnosis was significantly longer in patients with ocular involvement than patients without ($p = 0.044$). Among all mutation types, only the T348M mutation was recurring, so we only analyzed the T348M mutation in the two groups. The four patients with the same T348M mutation all had ocular involvement and none of the patients without ocular involvement had T348M mutation, although the difference was not statistically significant. Furthermore, the majority of patients with ocular involvement (9 out of 13) did not have the T348M mutation.

In terms of systemic manifestations, the incidence of hearing loss was significantly higher in patients with ocular involvement ($p = 0.017$), while the incidence of abdominal pain was significantly lower when compared to patients without ocular involvement ($p = 0.007$).

### Ocular involvements and examinations of NLRP3-AID patients

As shown in Table 3, Conjunctivitis (50%) and ODC (50%) are the most common ocular involvement within the 20 patients. Regarding ODC, 8 (40%) had ODS and 4 (20%) had optic atrophy (2 had both ODS and optic atrophy). Although patients 9 and 10 had elevated IOP, we considered the cause to be secondary glaucoma due to steroid eye drops used to treat uveitis rather than *NLRP3*-AID. Of the 13 patients with ocular involvement, the 3 patients with poorer visual acuity (#3, #4, and #9) all exhibited ODC. Visual-field examinations were performed on 12 patients, 8 of whom had visual-field defects. Among the eight patients with ODS, five had visual-field defects (4 of whom had the T348 mutation). All patients with optic atrophy had visual-field defects. Of the 8 patients with ODS, we obtained FA images from 5 patients, all of whom showed dye leakage at the optic disc (Figure 1). Additionally, we collected RNFL thickness data from 5 patients with ODS and their age- and sex-matched healthy controls. We found that the RNFL thickness in the ODS patient group was significantly higher than that in the healthy control group ($p < 0.001$) (Supplement Table 1).

### Clinical characteristics of NLRP3-AID patients with and without optic disc swelling

To conduct further analysis, we categorized the patients into two groups depending on whether they had ODS (Table 4). For the same reason as mentioned in the previous section, we continued to put emphasis on T348M mutation. All of the 4 T348M mutation carriers within our cohort exhibited ODS, while none of the patients in the group without ODS had T348M mutation. There was a significant difference between the two groups regarding the number of patients carrying T348M mutation ($p = 0.014$). In terms of systemic manifestations, the occurrence of hearing loss and CNS involvement was significantly higher in the group with ODS compared to the group without ($p = 0.001$, $p = 0.020$), especially with a 100% incidence of hearing loss among the ODS patients in our cohort.

### Lumber puncture examination and serum inflammation markers

Among the 13 patients with ocular involvement, we obtained lumbar puncture results from 8 patients (Table 5), of whom 7 had ODC (#6, #3, and #2 with ODS, optic disc pallor, and both manifestations, respectively), and 1 had no ODC. Among these eight patients, five presented with intracranial hypertension (IH), all of whom had ODS. Although patient 8 had ODS, her ICP was normal. Patient 6 underwent lumbar puncture more than once and had normal ICP despite having ODS. Of the 8 patients, 4 had elevated CSF protein levels and five had elevated CSF leukocyte levels, all of whom had ODS. The serum inflammatory markers WBC, ESR, and CRP were significantly higher in patients

**Table 1.** Baseline demographics and clinical characteristics of 20 *NLRP3*-AID patients.

| Patients | 1* | 2* | 3* | 4* | 5* | 6* | 7* | 8* | 9* | 10 | 11* | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender | M | F | M | M | F | M | M | F | F | F | M | M | F | M | F | M | F | F | M | M |
| Age at onset, years | 6 | 0 | 10 | 2 | 2 | 2 | 15 | 0 | 3 | 6 | 49 | 2 | 7 | 46 | 46 | 7 | 37 | 1 | 19 | 5 |
| Interval between symptoms onset and diagnosis, years | 26 | 19 | 12 | 29 | 37 | 18 | 17 | 20 | 9 | 39 | 3 | 21 | 11 | 1 | 0 | 20 | 5 | 20 | 3 | 19 |
| Family history | + | − | − | − | + | − | − | + | + | + | − | − | − | − | − | − | − | + | − | + |
| *NLRP3* mutation | G326E | T348M | T348M | T348M | T348M | K829T | L632F | D303G | A439V | A439V | V198M | V70M | Negative | Q703K | K131R | M116I | P38S | V442I | L798M | S196N |
| Fever | + | + | + | + | + | + | − | + | + | + | + | + | + | + | − | + | + | + | + | + |
| Rash | + | + | + | + | + | − | + | + | − | + | + | + | + | + | + | − | − | + | − | + |
| Oral ulcers | − | − | − | − | − | + | + | − | + | + | − | + | + | − | − | − | + | + | + | − |
| Arthralgia/arthritis | + | + | + | + | + | − | + | + | + | + | + | + | + | + | − | + | − | + | − | + |
| Hearing loss | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | + | − | − | − | − |
| CNS involvement | + | + | + | + | + | + | − | + | + | + | − | − | − | − | − | − | − | − | + | − |
| Lymphadenopathy | − | − | − | + | + | + | − | − | − | − | − | − | − | − | + | − | − | − | − | − |
| Lower limbs edema | − | − | − | − | + | − | − | − | − | − | − | − | + | − | − | − | −− | − | − | − |
| Myalgia | + | − | + | − | − | + | − | − | − | + | + | + | − | + | + | + | − | + | − | + |
| Abdominal pain | − | − | − | − | − | − | − | − | − | − | − | − | − | + | − | + | + | − | − | + |
| Fatigue | + | − | + | + | + | − | − | + | − | − | − | − | + | − | − | − | − | − | − | + |
| Ocular involvement | + | + | + | + | + | + | + | + | + | + | + | + | + | − | − | − | − | − | − | − |
| Treatments | | | | | | | | | | | | | | | | | | | | |
| Glucocorticoids | − | − | − | + | + | − | − | − | + | − | + | + | + | + | + | − | − | + | + | + |
| TNF-α inhibitors | − | − | + | + | − | + | + | + | − | − | − | − | − | − | − | + | + | − | + | − |
| IL-1 inhibitors | − | − | + | − | − | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − |

*NLRP3*-AID: *NLRP3*-associated autoinflammatory disease.
CNS involvement refers to the manifestation of meningitis or imaging findings, such as brain atrophy or calcification.
*Patients with optic disc changes.

with ODS than in those without ($p=0.043$, $p=0.001$, and $p=0.034$) (Table 6).

### *Effect of treatment on ODC*

As shown in Table 1, eleven patients received oral corticosteroids(prednisone) treatment (qd, varying dosage of 20–60 mg per day, tapering). Eight patients received subcutaneous TNF-α inhibitors, with five patients receiving etanercept (q.w., 50 mg per dose) and three patients receiving adalimumab (q.2w., 40 mg per dose). Patients were followed up every three months, and they exhibited partial improvement in ocular conditions, primarily in conjunctivitis and uveitis, but no significant improvement in ODC. Furthermore, no significant systemic adverse effects were reported. Two patients (#3 and #6) receiving regular subcutaneous IL-1 inhibitor (canakinumab, q.8w., 150 mg per dose) treatment demonstrated improvements in ODC, and no adverse effects were observed. Patient 3 showed an improvement in the visual field of the left eye after 6 months of canakinumab treatment (Figures 2A and B). Patient 6 reported a significant improvement in blurred vision after treatment, and OCT showed reduced ODS after canakinumab treatment for 18 months. Average peripapillary RNFL thickness of patient 6 reduced from 116 to 89 µm in the right eye and from 104 to 92 µm in the left eye. Follow-up after 18 months of canakinumab treatment showed that the serum inflammatory markers of patient 6 had normalized for at least 1 year, but the ODS had not completely resolved compared to the healthy control (Figures 2C–H).

**Table 2.** Clinical characteristics of *NLRP3*-AID patients with/without ocular involvement.

| Category | With ocular involvement ($n=13$) | Without ocular involvement ($n=7$) | $p$-Value |
|---|---|---|---|
| Gender (male), *n* (%) | 7 (53.9) | 4 (57.1) | $p>0.999$ |
| Age at onset, years | 8.00 ± 13.04 | 23.00 ± 19.72 | $p=0.055$ |
| Interval between symptoms onset and diagnosis, years | 20.08 ± 10.56 | 9.714 ± 9.45 | $p=0.044$ |
| Family history, *n* (%) | 5 (38.5) | 2 (28.6) | $p>0.999$ |
| *NLRP3* mutation (T348M), *n* (%) | 4 (30.8) | 0 (–) | $p=0.249$ |
| Fever, *n* (%) | 12 (92.3) | 6 (92.3) | $p>0.999$ |
| Rash, *n* (%) | 11 (84.6) | 4 (57.1) | $p=0.290$ |
| Oral ulcers, *n* (%) | 6 (46.2) | 3 (42.9) | $p>0.999$ |
| Arthralgia/arthritis, *n* (%) | 12 (92.3) | 4 (57.1) | $p=0.101$ |
| Hearing loss, *n* (%) | 10 (76.9) | 1 (14.3) | $p=0.017$ |
| CNS involvement, *n* (%) | 9 (69.2) | 1 (14.3) | $p=0.057$ |
| Lymphadenopathy, *n* (%) | 3 (23.1) | 1 (14.3) | $p>0.999$ |
| Lower limbs edema, *n* (%) | 2 (15.4) | 0 (–) | $p=0.521$ |
| Myalgia, *n* (%) | 6 (46.2) | 5 (71.4) | $p=0.374$ |
| Abdominal pain, *n* (%) | 0 (–) | 4 (57.1) | $p=0.007$ |
| Fatigue, *n* (%) | 6 (46.2) | 1 (14.3) | $p=0.329$ |

*NLRP3*-AID: *NLRP3*-associated autoinflammatory disease.
CNS involvement refers to the manifestation of meningitis or imaging findings, such as brain atrophy or calcification.

## Discussion

Our study provides a detailed description of ODC in a cohort of Chinese patients with MWS. ODC are common in these patients and often present as a delayed diagnosis, with ODS being the most common manifestation. Hearing loss and CNS involvement often accompany the occurrence of ODS. Most patients with ODS have IH, and their WBC, ESR, and CRP levels are significantly higher than those in patients without ODS. In our study cohort, among the 15 NLRP3 mutations, the T348M mutation is the only one that recurrently appears, and it is more likely to result in ODC with visual-field defects.

The proportion of our patients with ODC (50%) was lower than that of the CINCA group (83%) [6]—a previous clinical study of *NLRP3*-AID. This discrepancy may be related to racial and phenotypic differences. The CINCA group comprised patients of Caucasian ethnicity with NOMIC/CINCA, while our study included Chinese patients with MWS. Mehr et al. found that in

**Table 3.** Ocular involvements and examinations of *NLRP3*-AID patients.

| Patients | 1* | 2* | 3* | 4* | 5* | 6* | 7* | 8* | 9* | 10 | 11* | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Keratopathy | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Conjunctivitis | + | + | – | + | + | – | + | + | + | + | – | + | + |
| Glaucoma | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Cataract | – | – | – | – | – | – | – | + | – | – | – | – | – |
| Optic disc swelling | + | + | + | + | + | + | + | + | – | – | – | – | – |
| Optic atrophy | – | – | + | + | – | – | – | – | + | – | + | – | – |
| Uveitis | – | – | – | – | – | – | – | + | – | + | – | – | – |
| Retinopathy | + | – | – | – | + | + | – | – | + | – | – | – | + |
| BCVA | OD 20/20 OS 20/16 | OD 20/20 OS 20/20 | OD HM OS 20/150 | OD 20/20 OS FC/50cm | OD 20/20 OS 20/20 | OD 20/20 OS 20/20 | OD 20/16 OS 20/20 | OD 20/20 OS 20/20 | OD 20/200 OS 20/33 | OD 20/25 OS 20/25 | NA | NA | OD 20/20 OS 20/20 |
| Visual field defects | + | + | + | + | + | – | – | – | + | + | + | NA | – |
| Optic disc hyperfluorescence on FFA | + | NA | NA | NA | + | + | + | + | NA | NA | NA | NA | – |

*NLRP3*-AID: *NLRP3*-associated autoinflammatory disease; BCVA: best correct visual acuity; FFA: fundus fluorescein angiography; NA: not available.
*Patients with optic disc changes.

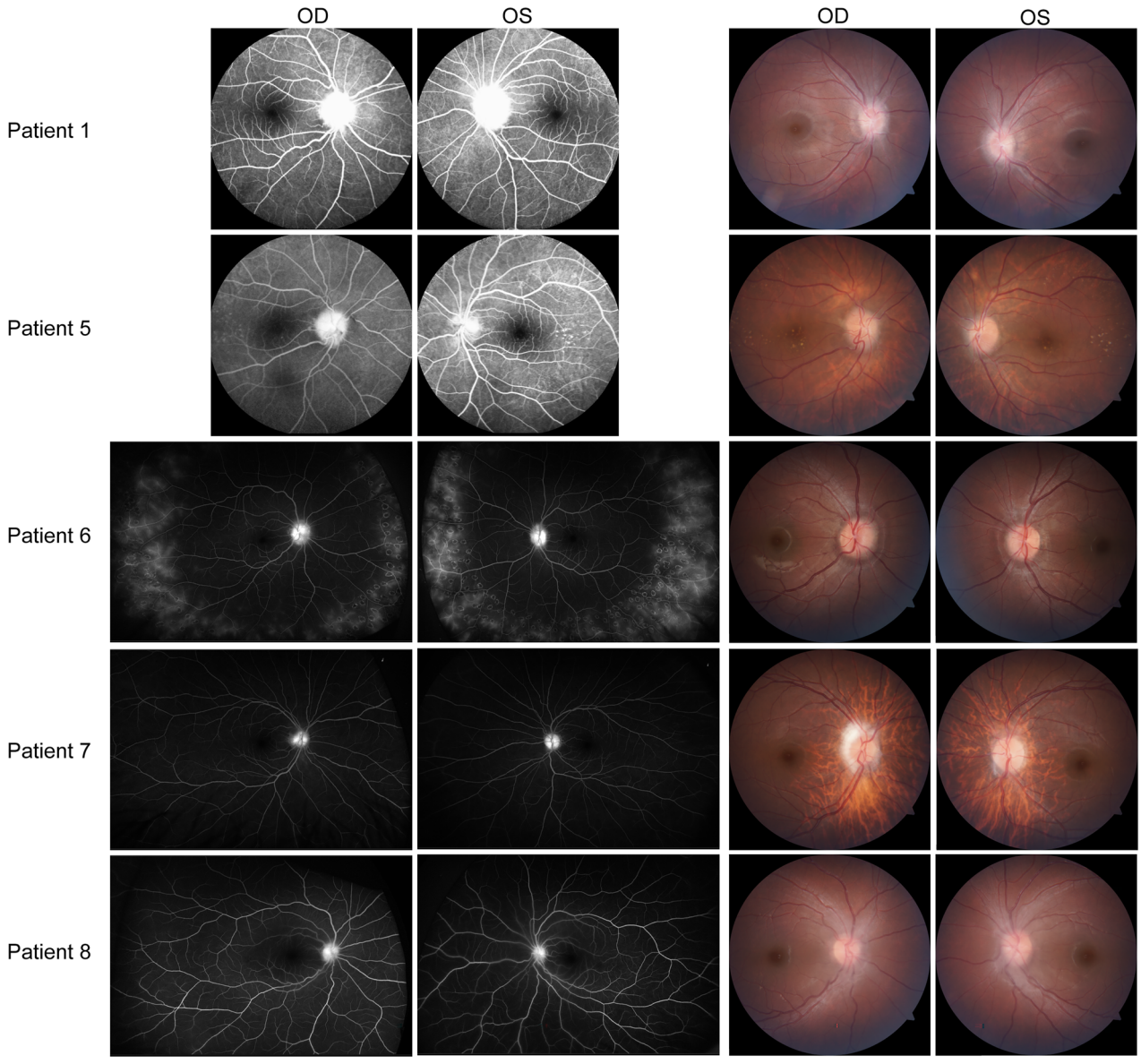


**Figure 1.** Multimodal images showed the ODS of *NLRP3*-AID patients. The late stage fundus fluorescein angiography showed leakage of the dye at the optic disc in both eye. Fundus photograph showed circumferential halo with decreased translucency of optic disc in both eyes. ODS: optic disc swelling; *NLRP3*-AID: *NLRP3*-associated autoinflammatory disease.

an Australian population, patients with NOMID/CINCA were more likely to develop papilledema than those with MWS or FCAS [16]. Besides ethnic differences, our result, when compared with the CINCA group, further supports the conclusion of Mehr et al. According to a systemic review involving 1353 patients with autoinflammatory diseases[17], although NLRP3-AID patients exhibit a higher incidence of ODC, it is not unique to NLRP3-AID. It can also manifest in other autoinflammatory diseases, such as Blau syndrome, Familial Mediterranean Fever (FMF), Deficiency of Adenosine Deaminase 2 (DADA2), and Aicardi-Goutieres syndrome. Therefore, in clinical practice, physicians need to differentiate by considering the patient's systemic clinical presentation. In addition to ODC, the patients in our study showed manifestations of conjunctivitis, uveitis, cataract, and retinopathy but not keratitis or primary glaucoma, as reported in previous studies [10,18].

Our previous study has reported a strong association between T348M and severe ocular damage [12]. All the four patients with the T348M mutation in this study had varying degrees of visual-field defects. Compared with other gene mutations, the T348M mutation may be more likely to contribute to optic disc pathology and visual-field defects. The two patients with the worst vision in this series also had T348M mutations, suggesting that this mutation could

potentially be associated with a higher risk of significant visual impairment. These findings indicate that patients with the T348M mutation might need careful monitoring to potentially prevent permanent and irreversible visual damage caused by ODC. Individuals with this mutation are reportedly at risk of neurological complications [8,10,19]. Our conclusion further supports the genotype-phenotype relationship, as the optic nerve is considered an extension of the CNS. Furthermore, both hearing loss and CNS involvement are associated with ODS in *NLRP3*-AID patients, a discovery made for the first time in our research. We found that *NLRP3*-AID patients with ODS are more likely to have hearing loss and CNS involvement than patients without. Both ODS and hearing loss can be considered part of CNS damage, suggesting a tendency for comprehensive CNS neurological involvement in this disease.

Through the presentation of multimodal imaging, including fundus photography, FA, and the comparison of RNFL thickness in OCT, we confirmed the presence of ODS in some *NLRP3*-AID patients. However, the underlying mechanisms of ODS remain unclear. All patients in our study with previously recorded IH levels had ODS. Therefore, we reasonably speculate that IH is part of the cause of ODS in *NLRP3*-AID. However, in this study, IH was not found in patients 6 and 8, but ODS persisted. A survey conducted by Dollfus in pediatric patients with NOMID/CINCA showed that most patients with ODC do not have IH [6]. Among our eight patients with ODS, seven had chronic aseptic meningitis with increased protein (four patients) and leukocyte (five patients) levels in the CSF. The serum WBC, ESR and CRP levels of the patients with ODS were significantly higher than those of patients without ODS, suggesting that chronic inflammation of the optic nerve may contribute to ODS. There is evidence of the involvement of inflammatory factors in this process [6,20]. Optic atrophy was also observed in this study. We could not provide a reasonable explanation for the cause of optic atrophy owing to the small sample size. Optic atrophy may be a late manifestation of optic neuritis, ischemic optic neuropathy, or IH. However, when patient 9 was diagnosed, she was only 12 years old, did not have IH, and had no elevated inflammatory markers in the CSF and serum; nevertheless, optic atrophy still existed, suggesting that optic atrophy in *NLRP3*-AID may not necessarily be due to ODS progression.

Several studies have reported the effectiveness of IL-1 inhibitors in treating *NLRP3*-AID-related ODC [16,20,21]. However, the reported efficacy of canakinumab for ocular involvement is not consistent [22]. Owing to the unavailability of IL-1 inhibitors in China, most of our patients were unable to avail them. According to our observations, medications, such as

**Table 4.** Clinical characteristics of *NLRP3*-AID patients with/without optic disc swelling.

| Category | With ODS ($n=8$) | Without ODS ($n=12$) | $p$-Value |
|---|---|---|---|
| Gender (male), *n* (%) | 5 (62.5) | 6 (50.0) | $p=0.670$ |
| Age at onset, years | 4.63 ± 5.37 | 19.00 ± 19.55 | $p=0.059$ |
| Interval between symptoms onset and diagnosis, years | 22.25 ± 7.96 | 12.58 ± 11.56 | $p=0.055$ |
| Family history, *n* (%) | 3 (37.5) | 4 (33.3) | $p>0.999$ |
| *NLRP3* mutation (T348M), *n* (%) | 4 (50.0) | 0 (–) | $p=0.014$ |
| Fever, *n* (%) | 7 (87.5) | 11(91.7) | $p>0.999$ |
| Rash, *n* (%) | 7 (87.5) | 8 (66.7) | $p=0.603$ |
| Oral ulcers, *n* (%) | 2 (25.0) | 7 (58.3) | $p=0.197$ |
| Arthralgia/arthritis, *n* (%) | 7 (87.5) | 9 (75.0) | $p=0.619$ |
| Hearing loss, *n* (%) | 8 (100.0) | 3 (25.0) | $p=0.001$ |
| CNS involvement, *n* (%) | 7 (87.5) | 3 (25.0) | $p=0.020$ |
| Lymphadenopathy, *n* (%) | 3 (37.5) | 1 (8.3) | $p=0.255$ |
| Lower limbs edema, *n* (%) | 1 (12.5) | 1 (8.3) | $p>0.999$ |
| Myalgia, *n* (%) | 3 (37.5) | 8 (66.7) | $p=0.362$ |
| Abdominal pain, *n* (%) | 0 (–) | 4 (33.3) | $p=0.117$ |
| Fatigue, *n* (%) | 5 (62.5) | 2 (16.7) | $p=0.062$ |

*NLRP3*-AID: *NLRP3*-associated autoinflammatory disease; ODS: optic disc swelling.
CNS involvement refers to the manifestation of meningitis or imaging findings, such as brain atrophy or calcification.

**Table 6.** Serum inflammation markers of *NLRP3*-AID patients.

| Group patients | Patients with ODS 1 2 3 4 5 6 7 8 | Patients without ODS 9 10 11 12 13 14 15 16 17 18 19 20 | $p$-Value | Normal values |
|---|---|---|---|---|
| WBC, $\times10^9$/L | 20.67 ± 12.38 | 12.09 ± 3.674 | $p=0.043$ | 3.50–9.50 |
| ESR, mm/h | 73.88 ± 16.46 | 30.50 ± 28.55 | $p=0.001$ | 0–15 |
| CRP, mg/L | 98.34 ± 41.17 | 54.76 ± 38.28 | $p=0.034$ | 0–10 |

*NLRP3*-AID: *NLRP3*-associated autoinflammatory disease; ODS: optic disc swelling; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

**Table 5.** Lumber puncture examination of 8 *NLRP3*-AID patients.

| Patients | 2 | 3 | 4 | 5 | 6 | 8 | 9 | 10 | Normal values |
|---|---|---|---|---|---|---|---|---|---|
| ICP, $mmH_2O$ | 270↑ | 320↑/270↑ | 305↑ | 300↑ | 245↑/Normal$^+$ | 160 | Normal$^+$ | 135 | 80–180 |
| CSF protein count, g/L | 1.300↑ | 0.591↑ | 0.580↑ | 0.330 | 0.620↑ | 0.279 | Normal$^+$ | Normal$^+$ | 0.150–0.450 |
| CSF leukocyte count, $\times10^6$/L | 2300↑ | 35↑ | 40↑ | 20↑ | 1 | 29↑ | NA | Normal$^+$ | 0–8 |

ICP: intracranial pressure; CSF: cerebrospinal fluid; NA: not available.
/The patient underwent the examination twice.
$^+$The exact value is unknown.

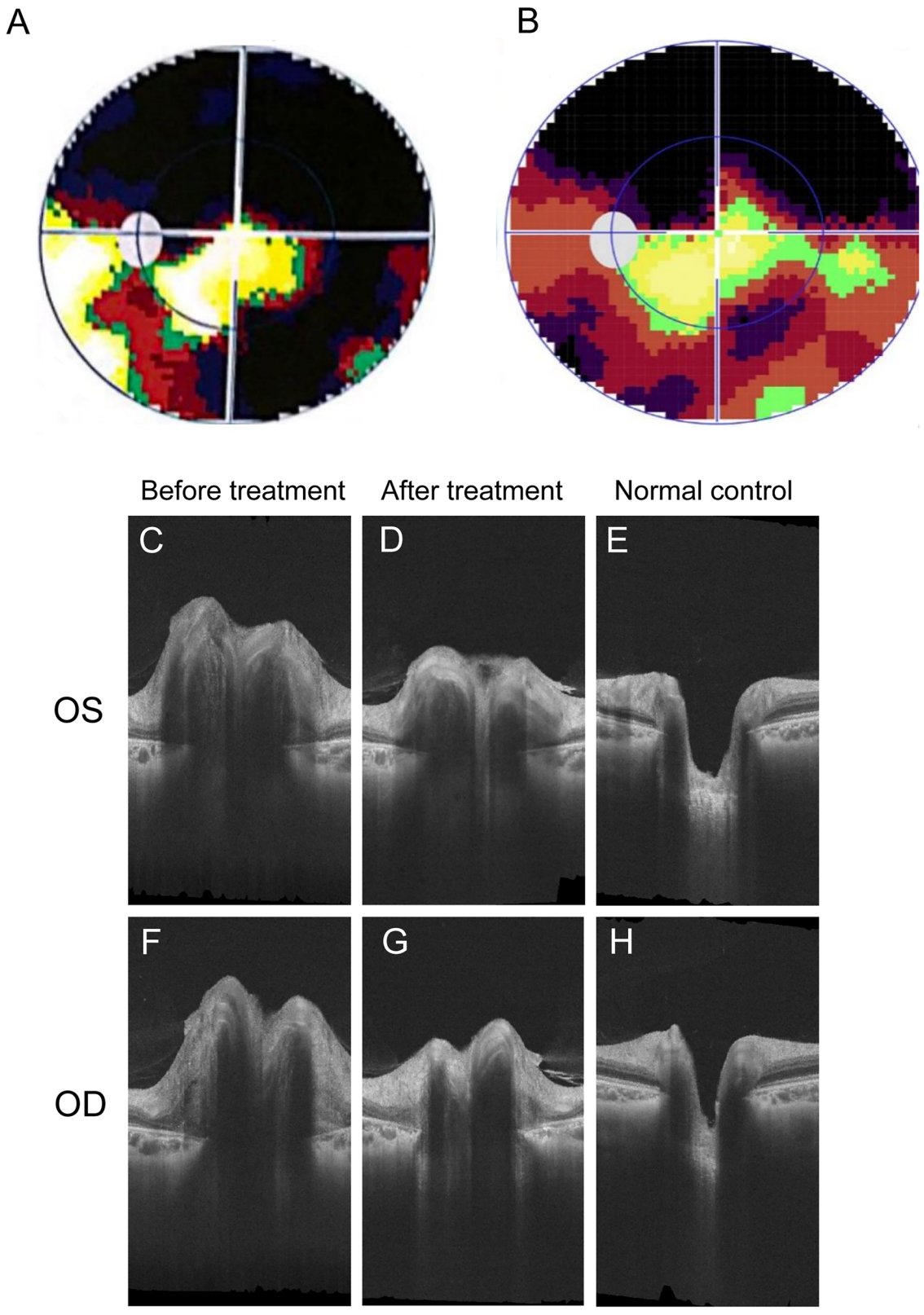


**Figure 2.** Improvement in visual field defect of left eye, patient 3. (A) Before and (B) 6 months after regular canakinumab treatment; OCT examination showed the remission of ODS in both eyes after regular canakinumab treatment for 18 months, patient 6. (C) Left eye before treatment. (D) Left eye after treatment. (E) Left eye of normal control. (F) Right eye before treatment. (G) Right eye after treatment. (H) Right eye of normal control. OCT: optical coherence tomography; ODS: optic disc swelling.

steroids and immunosuppressants have limited efficacy in treating *NLRP3*-AID optic disc lesions. In contrast, the two patients who received IL-1 inhibitors showed improvement in these lesions. Patient 6 had been receiving regular canakinumab treatment for 1 year, during which time his inflammatory markers remained normal. Therefore, we inferred that the patient no longer had active inflammation, but his ODS, although better, persisted. Previous studies have confirmed the effect of IL-1 inhibitors in reducing ICP [23]. As we were unable to obtain ICP results after treatment in patient 6, we hypothesize that his ODS did not resolve completely because of adhesion of arachnoid granules and increased CSF viscosity caused by long-term and repeated aseptic meningitis [24], which might have resulted in limited effectiveness of canakinumab and diuretic agents in reducing ICP, and thus, incomplete resolution of ODS. This suggests that in the early stages of the disease when aseptic meningitis has not yet led to arachnoid adhesion, prompt diagnosis, and intervention with IL-1 inhibitors may have better anti-inflammatory and ICP-lowering effects [19]. Therefore, early diagnosis and intervention are critical. Furthermore, the T348M mutation appears to support an increased dosage regimen for systemic treatment [22], which needs to be verified in more cases for treating ODC.

Some limitations still existed. Firstly, the study was retrospective, which may introduce bias and limit the ability to draw casual conclusions. Secondly, *NLRP3*-AID is a rare disease, and the sample size was small, which may affect the generalizability of the findings and ability to detect rare events or associations. Finally, the study had been conducted at a single center, which may limit the diversity of the patient population and the external validity of findings.

In conclusion, ODC is common in *NLRP3*-AID patients and often presents as a delayed diagnosis, with ODS being the most common manifestation. Hearing loss and CNS involvement often accompany the occurrence of ODS. Most patients with ODS have IH, and their WBC, ESR, and CRP levels are significantly higher than those in patients without ODS. The T348M mutation is more likely to lead to ODC with visual-field defects. Increased awareness among ophthalmologists regarding this rare but treatable auto-inflammatory syndrome could help prevent permanent visual impairment and aid in diagnosis.

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## Ethical approval

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Peking Union Medical College Hospital. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

Yuezhu Lu and Min Shen completed the entire process, including study design, data collection, data analysis, and manuscript drafting. Weihong Yu, Min Shen, Yuezhu Lu, Zhikun Yang, Xiao Zhang, Donghui Li, Zhangwanyu Wei, Bing Li, Xufeng Zhao, Na Wu, and Bingxuan Wu made the data collection. Weihong Yu and Yong Zhong made the revision and guided the study. All authors have read and approved the final manuscript.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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