Case Report

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Two Novel Variants in the LRR Domain of *NLRP3* Causing Leukoencephalopathy: A Case Report

Zhibo Feng[1,2,3,†], Na Wu[1,2,4,†], Yuxia Shao[1,2,5], Nan Lin[6], Min Shen[1,2,*]

[1]Department of Rare Diseases, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences & Peking Union Medical College; State Key Laboratory of Complex Severe and Rare Diseases, PUMCH, 100730 Beijing, China
[2]Department of Rheumatology and Clinical Immunology, PUMCH; 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, 100730 Beijing, China
[3]Department of Rheumatology and Immunology, Daqing Oilfield General Hospital, 163000 Daqing, Heilongjiang, China
[4]Department of Nuclear Medicine, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua Medicine, Tsinghua University, 102218 Beijing, China
[5]Department of Rheumatology and Immunology, Binzhou People's Hospital, 256610 Binzhou, Shandong, China
[6]Department of Neurology, Peking Union Medical College Hospital (PUMCH), 100730 Beijing, China
*Correspondence: shenmpumch@163.com (Min Shen)
[†]These authors contributed equally.
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Aim: The NLR family pyrin domain containing 3-associated autoinflammatory disease (*NLRP3*-AID) is a rare and heterogeneous hereditary inflammatory disorder caused by variants in the *NLRP3* gene on chromosome 1q44. This condition encompasses a broad spectrum of clinical phenotypes, including urticarial rash, fever, ocular disorders, hearing loss, and musculoskeletal and central nervous system (CNS) involvement. This study reports the clinical features and newly identified *NLRP3* gene variants in two Chinese Han patients with *NLRP3*-AID presenting with leukoencephalopathy.

Case Presentation: The study includes two adult male patients aged 25 and 24 years. Both patients experienced recurrent fevers with elevated C-reactive protein levels during febrile episodes, which normalized during asymptomatic intervals. Elevated cerebrospinal fluid protein levels and magnetic resonance imaging (MRI) findings of intracranial calcification and white matter damage were observed in both cases. Genetic testing revealed novel heterozygous *NLRP3* variants: p.L798M in Patient 1 and p.K829T in Patient 2. Both patients received treatment with adalimumab and canakinumab, resulting in significant clinical improvement.

Results: The clinical and genetic features of two *NLRP3*-AID patients were characterized. Functional studies demonstrated overactivation of the NLRP3 inflammasome in these patients.

Conclusions: Neurological involvement in *NLRP3*-AID patients is variable. This study expands the clinical spectrum of CNS damage in *NLRP3*-AID to include intracranial calcification and leukoencephalopathy. Additionally, two novel *NLRP3* variants, L798M and K829T, were identified and associated with the disease.

Keywords: autoinflammatory disease; cryopyrin-associated periodic syndrome; NLRP3-associated autoinflammatory disease; leukoencephalopathy

Introduction

The NLR family pyrin domain containing 3-associated autoinflammatory disease (*NLRP3*-AID), also known as cryopyrin-associated periodic syndrome (CAPS), is categorized into three clinical entities: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), also referred to as chronic infantile neurological cutaneous articular (CINCA) syndrome) [1]. The primary clinical features of *NLRP3*-AID include periodic fever, urticaria-like rash, bone and joint manifestations, and central nervous system (CNS) involvement [2]. Neurological manifestations of *NLRP3*-AID are diverse and include headaches, sensorineural hearing loss, dizziness, cerebral infarction or hemorrhage, intracranial hypertension, and papilledema. Severe neurological damage may manifest as brain atrophy, hydrocephalus, complete hearing loss, chronic aseptic meningitis, and optic neuritis [3–5].

NLRP3-AID is caused by variants in the *NLRP3* gene on chromosome 1q44. In this study, we describe two patients with *NLRP3*-AID who primarily presented with CNS involvement, including intracranial calcification and white matter damage, alongside other clinical features. Both patients exhibited novel *NLRP3* variants associated with the leucine-rich repeat (LRR) domain of the gene.

Materials and Methods

Patients and Healthy Control

Two patients with *NLRP3*-AID and leukoencephalopathy were diagnosed and followed up at our tertiary medical center between 2019 and 2023. We added the care checklist to the **Supplementary material**. During the follow-up period, comprehensive medical records, laboratory data, and imaging results were collected and documented. Genomic DNA was extracted from whole peripheral blood, and whole-exome sequencing (WES) was performed for each patient using next-generation sequencing (Joy Orient Translational Medicine Research Centre Co., Ltd., Beijing, China). The inclusion criteria for the healthy control (HC) were males aged 18 to 30 years in good health with no history of autoinflammatory or autoimmune diseases. One HC was included in the study.

Isolation and Treatment of PBMCs

Venous blood samples were collected from the *NLRP3*-AID patients and the healthy control, and peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation. PBMCs were re-suspended in Roswell Park Memorial Institute (RPMI) 1640 medium (C11875500BT, Gibco, Waltham, MA, USA), supplemented with 100 U/mL penicillin, 100 µg/mL streptomycin, and 10% fetal bovine serum (FBS, A5670701, Gibco), at a final concentration of 1×10^6 cells/well. Cells were incubated with 1 µg/mL lipopolysaccharide (LPS) (L4391, Sigma-Aldrich, St. Louis, MO, USA) for 3 hours. After stimulation, the supernatants were collected, and proteins were extracted for further analysis.

Enzyme-Linked Immunosorbent Assay (ELISA)

The levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) in the PBMC supernatants were measured using commercial ELISA kits (EXCELL Bio, EH001; EH004; EH009, Suzhou, China) according to the manufacturer's instructions.

Western Blot

Proteins were separated using gradient polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene fluoride or polyvinylidene difluoride (PVDF) membranes. Membranes were blocked with 5% skim milk for 1 hour at room temperature and incubated overnight at 4 °C with the following primary antibodies: NLRP3 rabbit antibody (Cell Signaling Technology, 15101, Beverly, MA, USA), caspase-1 rabbit antibody (Cell Signaling Technology, 2225), IL-1β rabbit antibody (Cell Signaling Technology, 12703), apoptosis-associated speck-like protein containing a CARD (ASC) mouse antibody (Santa Cruz Biotechnology, 514414, Santa Cruz, CA, USA), and β-actin mouse antibody (Beijing Zhong Shan-Golden Bridge Biological Technology, TA-09, Beijing, China). After rinsing with Tris Buffered Saline with Tween 20 (TBS-T), membranes were incubated with goat anti-rabbit Immunoglobulin G (IgG)-horseradish peroxidase (HRP) (Beijing Zhong Shan-Golden Bridge Biological Technology, ZB-2301, Beijing, China) or goat anti-mouse IgG-HRP (Beijing Zhong Shan-Golden Bridge Biological Technology, ZB-2305) at room temperature for 1 hour. The membranes were then rinsed with TBS-T, and an Enhanced chemiluminescence (ECL) substrate (34095, Thermo Fisher Scientific, Waltham, MA, USA) was applied for image development.

ASC Oligomerization

After stimulation with 1 µg/mL LPS for 3 hours, cells were washed with cold phosphate-buffered saline (PBS) and lysed with NP-40 lysis buffer (P0013F, Beyotime, Shanghai, China). The protein pellet was washed twice with 500 µL PBS and re-suspended in 400 µL NP-40. Chemical crosslinking was performed with 2 mM disuccinimidyl suberate (Thermo Fisher Scientific, 21655) at 37 °C in a metal bath for 40 minutes. The crosslinked pellets were centrifuged at 500 g for 15 minutes and re-suspended in 40 µL NP-40 containing 1$\times$ SDS protein loading buffer. ASC oligomerization was detected by western blotting.

Statistical Analysis

Data are expressed as mean $\pm$ standard error of the mean (SEM). Statistical analyses were performed using GraphPad 8.0 software (GraphPad Software Inc., San Diego, CA, USA). Statistical evaluation involved one-way analysis of variance (ANOVA) followed by the Bonferroni multiple comparison test. p value of <0.05 was considered statistically significant ($^*p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$).

Results

Case Presentation

Patient 1

A 25-year-old Han Chinese man presented with slurred speech lasting six years, recurrent convulsions, and fever for five years. The patient first experienced indistinct speech at 19 years of age, accompanied by myalgia, arthralgia, difficulty climbing stairs, and recurrent oral ulcers. At 20 years old, he developed recurrent convulsions and intermittent fever. Over time, he exhibited progressive symptoms, including abnormal mental behavior, memory impairment, urinary incontinence, dizziness upon waking, and a complete inability to speak. He did not report genital ulcers, rashes, hearing loss, or red eyes. His father was healthy, while his mother experienced joint pain and deformation. Of his three sisters, the eldest and her daughter had intellectual disabilities, whereas the other two sisters were asymptomatic.

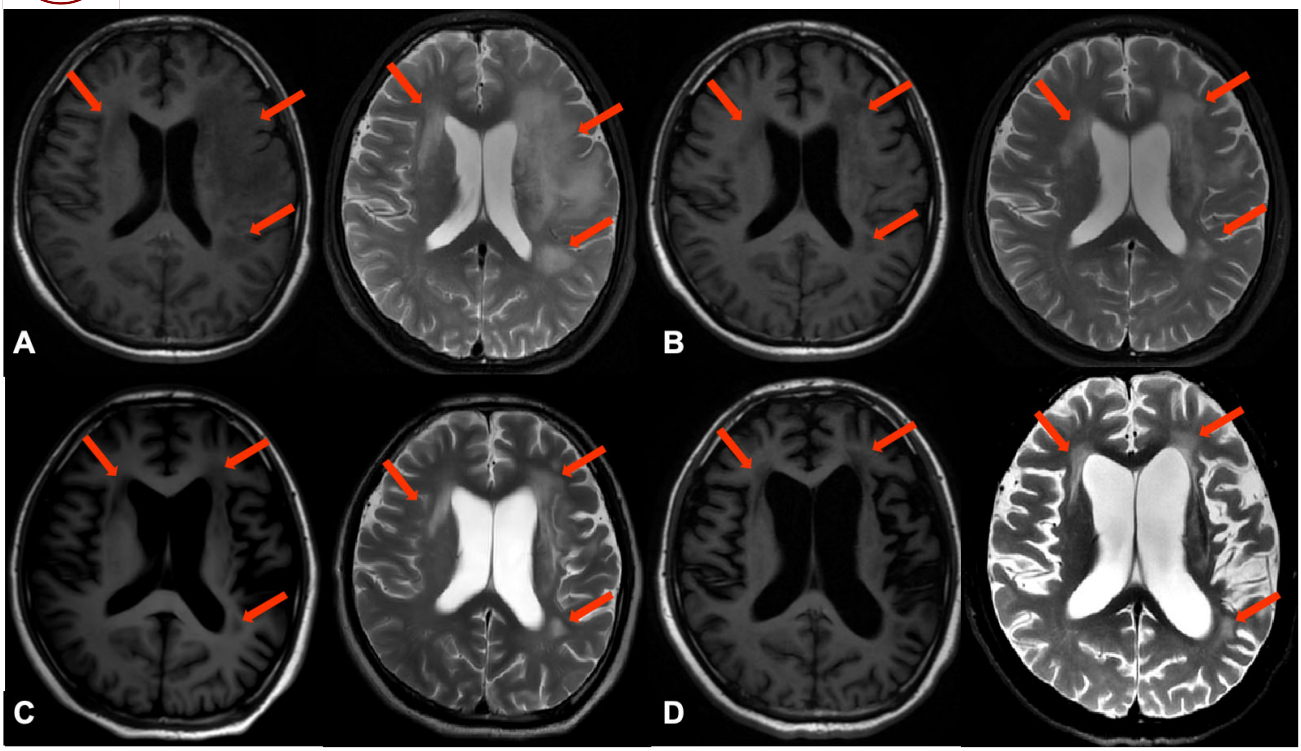

Fig. 1. Brain magnetic resonance imaging (MRI) of Patient 1. (A) Multiple patchy abnormal signals were observed in the left fronto-parietal white matter, basal ganglia, internal and external capsules, and bilateral lateral ventricles before treatment. (B,C) Improvement of white matter damage after steroid therapy. (D) After steroid reduction, the symptoms relapsed, the encephalopathy range increased, and brain atrophy aggravated. The red arrows indicate the lesions of Patient 1's brain.

Blood tests revealed normal complete blood count (CBC), biochemistry panel, urine analysis, and immunoglobulin levels. Autoimmune-related markers, including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, and autoimmune encephalitis antibodies, were negative. Infectious and malignancy-related workups yielded negative results. Audiometry, audiological, and ophthalmic examinations were normal. The patient's serum C-reactive protein (CRP) level was elevated (30 mg/L), while RNA expression of interferon-stimulated genes (ISGs) was within normal limits.

Brain-enhanced magnetic resonance imaging (MRI) revealed multiple patchy abnormal signals in the left fronto-parietal white matter, basal ganglia, internal and external capsules, and bilateral paraventricular regions (Fig. 1A). Cerebrospinal fluid (CSF) analysis showed elevated protein levels consistent with aseptic meningitis, and cytology indicated lymphocytic and neutrophilic inflammation. A 24-hour electroencephalogram revealed epileptiform discharges in the left frontotemporal region.

The patient was initially suspected of having primary CNS vasculitis and was treated with pulse therapy using methylprednisolone and oxcarbazepine. This led to significant improvement in fever, convulsions, mental state, and memory, and his CRP level normalized. Follow-up brain MRI showed notable improvement (Fig. 1B,C). However, symptoms recurred during steroid tapering, despite combination therapy with cyclophosphamide.

Subsequent brain MRI revealed worsening findings, including multiple patchy long T1 and T2 signals in the left fronto-parietal temporal lobe, right corona radiata, right frontal lobe, left basal ganglia area, and internal and external capsules, with high Fluid Attenuated Inversion Recovery (FLAIR) signals mainly involving white matter and subcortical arch fibers (Fig. 1D). Compared with the previous MRI (Fig. 1C), the affected area had expanded, and brain atrophy had worsened.

Genetic testing identified a maternal heterozygous c.2392C>A, p.L798M mutation in the *NLRP3* gene (NM_001243133), confirming the diagnosis of *NLRP3*-AID.

The patient was initiated on subcutaneous adalimumab (0.4 mL every other week). After 18 months of follow-up, his symptoms stabilized, steroids and oxcarbazepine were tapered off, and the dosing of adalimumab was adjusted to every four weeks.

Patient 2

The patient was a 24-year-old Han Chinese man who had experienced recurrent fever without an apparent cause since the age of 2 years. His fever episodes were accompanied by rashes, sore throats, pharyngitis, tonsillitis, occasional oral ulcers, and enlarged lymph nodes. Despite un-

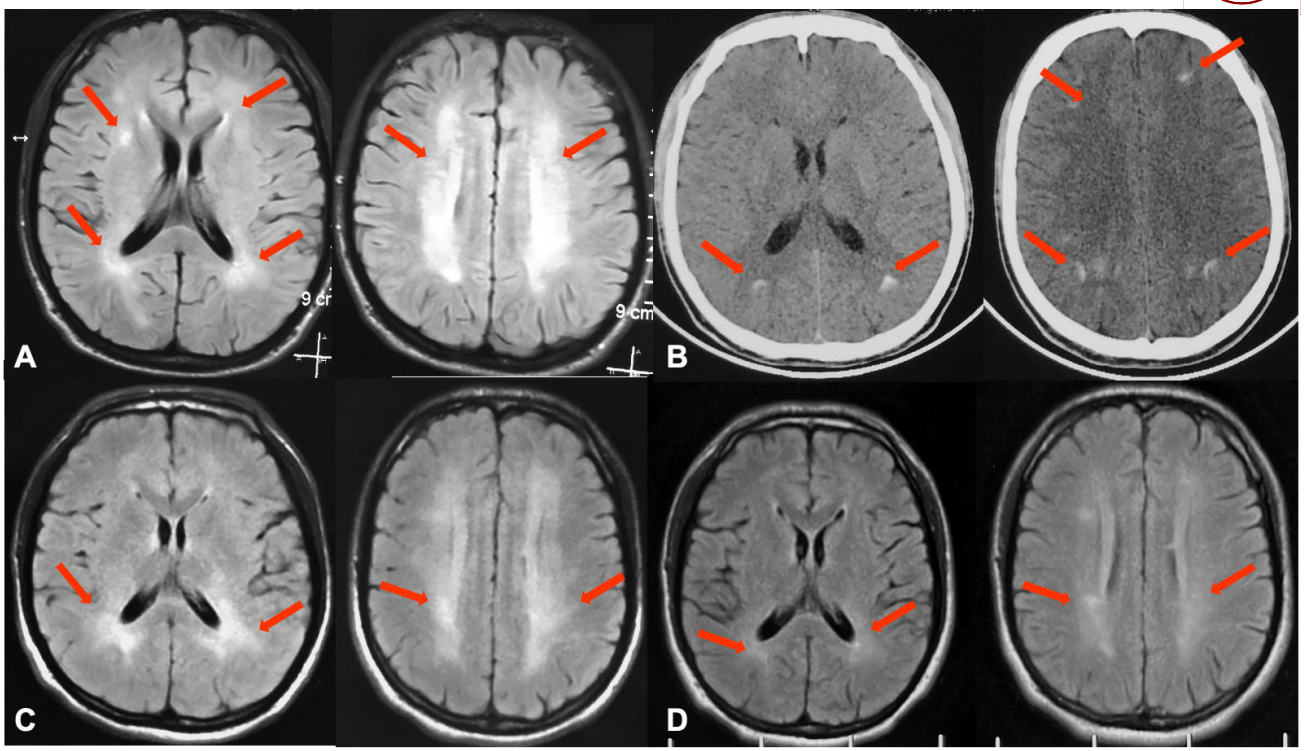

Fig. 2. Brain MRI and computed tomography (CT) of Patient 2. (A) MRI showed bilateral patchy, long T2 signal and calcification in the white matter in December 2018. (B) MRI re-examination after 3 months of adalimumab treatment in July 2020. (C) MRI re-examination after 1 year of treatment with canakinumab in July 2022. (D) The patient's initial brain CT scan was in October 2018 when he first developed neurological symptoms in which intracranial calcification could be seen. The red arrows indicate the lesions of Patient 2's brain.

dergoing a tonsillectomy, the recurrent fever persisted. At 10 years of age, he was suspected of having encephalitis at a local hospital. At 15 years old, he developed bilateral sensorineural hearing loss and was diagnosed with deafness. By the age of 19, his symptoms progressed to include dizziness, nausea, vomiting, fatigue, poor appetite, and myalgia. There was no family history of inflammatory disease.

Brain MRI revealed intracranial calcifications and bilateral patchy long T2 signals in the white matter (Fig. 2A). Brain computed tomography (CT) showed multiple patchy high-density shadows at the cortical-medullary junction of the bilateral lentiform nuclei, thalamus, and corona radiata, with clear boundaries (Fig. 2B). Lumbar puncture results indicated elevated intracranial pressure and mild elevation of cerebrospinal fluid (CSF) protein levels. CSF cytology showed a predominant neutrophilic reaction and increased activated mononuclear cells.

Serum IgG levels were slightly elevated (18 g/L), while white blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels increased during febrile episodes and normalized between episodes. Autoimmune markers, including ANA, ANCA, and anti-proliferative leukemia (APL) antibodies, were negative.

Genetic testing identified a *de novo* heterozygous *NLRP3* variant (c.2486A > C, p.K829T). Based on these findings, the patient was diagnosed with *NLRP3*-AID.

The patient was started on subcutaneous adalimumab injections (0.4 mL every two weeks). His symptoms partially improved, and a follow-up brain MRI demonstrated a reduction in the extent of leukoencephalopathy (Fig. 2C). After one year of treatment with adalimumab, the patient was transitioned to canakinumab (150 mg subcutaneously every 8 weeks).

At the two-year follow-up, the patient's symptoms had substantially improved, as did the findings on brain MRI (Fig. 2D). His ESR and CRP levels remained within normal ranges, indicating effective disease control.

Pathogenicity Validation of Novel NLRP3 Variants

L798M and K829T are novel *NLRP3* missense variants that occur in the leucine-rich repeat (LRR) domain and are positioned outside exon 3. To evaluate their association with the phenotypes observed in our patients, we isolated PBMCs from the patients and healthy control (HC), treated the cells with or without lipopolysaccharide (LPS) for 3 hours *in vitro*, and assessed the levels of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, in the supernatants.

Stimulation with LPS induced a significantly higher release of IL-1β and IL-6 from PBMCs of the patients compared to the HC, while the difference in TNF-α levels between the patients and the HC was less pronounced

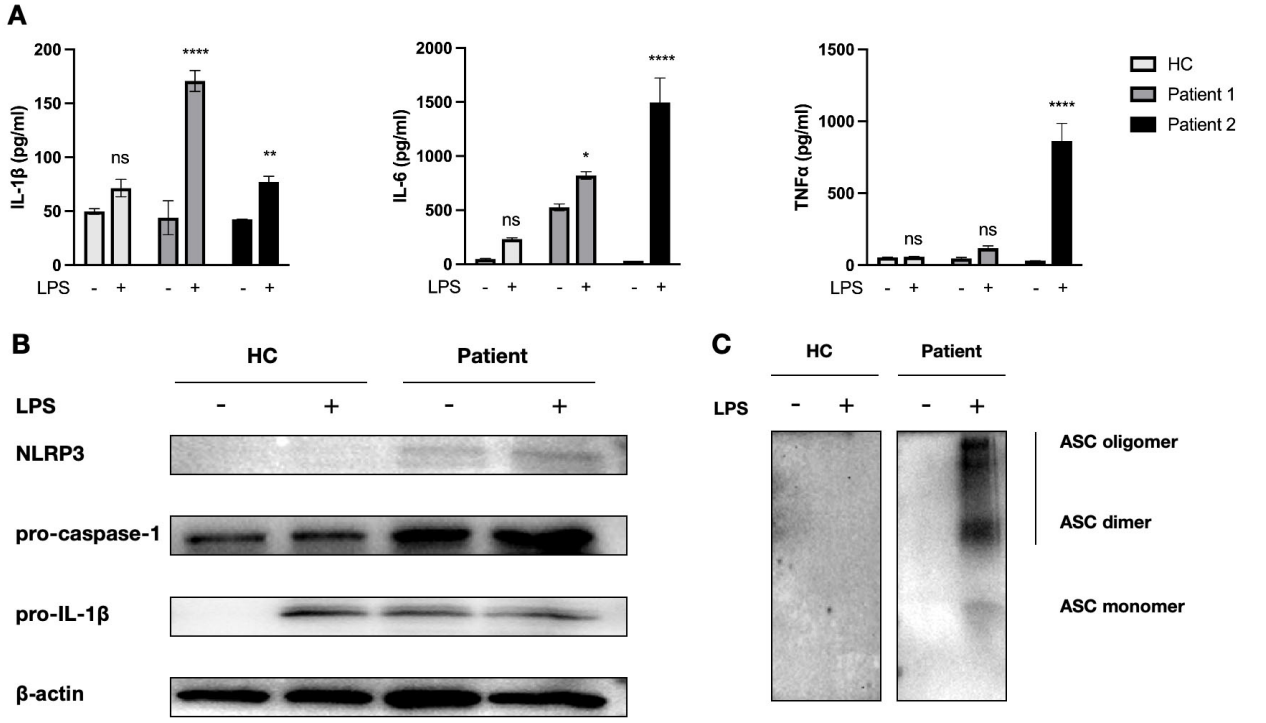

Fig. 3. Effects of NLR family pyrin domain containing 3 (*NLRP3*) variants on inflammasome activation in peripheral blood mononuclear cells (PBMCs). (A) The levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) in the supernatant of PBMCs from patients and an age-gender-matched healthy control after treatment with/without lipopolysaccharide (LPS) (1 µg/mL, 3 h). (B) Immunoblot analysis of protein NLRP3, pro-caspase-1, and pro-IL-1β in cell lysates from Patient 1. (C) Immunoblot analysis of apoptosis-associated speck-like protein containing a CARD (ASC) oligomerization in the lysates of PBMCs from Patient 1. The experiments were replicated three times. The significance markers are intended to compare Patients + LPS vs HC + LPS. HC, healthy control; ns, no significance, *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

(Fig. 3A). Additionally, immunoblot analysis revealed increased expression of NLRP3 and pro-caspase-1, both components of the NLRP3 inflammasome, in PBMC lysates from Patient 1, regardless of LPS treatment (Fig. 3B).

ASC oligomerization, an upstream event in NLRP3 inflammasome activation, was also assessed. Following LPS treatment, remarkable ASC oligomerization was detected in PBMC lysates from Patient 1 (Fig. 3C). These findings suggest that the L798M and K829T variants lead to overactivation of the NLRP3 inflammasome, contributing to the observed inflammatory phenotype in the patients.

Discussion

NLRP3-AID is an autosomal dominant inherited disorder that often leads to neurological inflammation, presenting symptoms such as hearing loss, ophthalmological inflammation, and chronic meningitis. However, leukoencephalopathy and intracranial calcifications are relatively rare features of *NLRP3*-AID [6]. In this study, we report two adult patients with *NLRP3*-AID from unrelated families who were treated at our hospital. Both patients exhibited intermittent fever, oral ulcers, aseptic meningitis, and white matter lesions in the brain.

Patient 1 primarily presented with neurological symptoms, including speech disorders, paroxysmal convulsions, epilepsy, and brain atrophy, in addition to the common phenotypes of periodic fever and aseptic meningitis. In contrast, Patient 2 presented with recurrent fever followed by progressive sensorineural hearing loss, leukoencephalopathy, and intracranial calcifications. Genetic testing revealed heterozygous *NLRP3* variants in both patients. Based on clinical diagnostic criteria and genetic testing results, both were diagnosed with *NLRP3*-AID. Notably, both patients showed rare manifestations of leukoencephalopathy, a feature not previously reported in patients with *NLRP3*-AID.

Interestingly, the progression of symptoms varied between the two patients. Patient 1 first exhibited CNS symptoms, followed by periodic fever, whereas Patient 2 experienced periodic fever initially and later developed CNS symptoms. However, the diagnosis was delayed for 5 years in Patient 1 and 19 years in Patient 2. After treatment with adalimumab or canakinumab, both patients showed improvements in fever, myalgia, arthralgia, and oral ulcers. Despite these improvements, both patients experienced varying degrees of CNS sequelae, such as intellectual disability and deafness. These findings underscore the importance of considering autoinflammatory diseases, par-

ticularly *NLRP3*-AID, in cases of unexplained CNS inflammation or leukoencephalopathy accompanied by periodic fever and other systemic manifestations. Early diagnosis and timely treatment are critical for improving prognosis and preventing serious organ damage and sequelae.

Most pathogenic *NLRP3* mutations are located in exon 4, which encodes the nucleotide-binding and oligomerization (NACHT) domain responsible for adenosine triphosphatase (ATPase) activity that facilitates NLRP3 self-oligomerization [6–8]. According to the Infevers database (https://infevers.umai-montpellier.fr/web/), 275 *NLRP3* variants have been identified to date. The K829T variant was reported in our previous *NLRP3*-AID cohort study and is included in the Infevers database [9]. However, the L798M variant has not been previously identified in any patient. Both variants are located in exon 6, which encodes the leucine-rich repeat (LRR) domain. The LRR domain has been demonstrated to contribute to the hyperactivity of the NLRP3 inflammasome [7]. Mutations in the LRR domain are relatively rare, and substitutions in this domain may lead to atypical inflammatory syndromes [10].

Previous studies have shown that LRR domain mutations, such as R920Q, Y861C, and Y861H, enhance the binding affinity between NLRP3 and NIMA-related kinase 7 (NEK7), thereby activating the NLRP3 inflammasome [10,11]. Gain-of-function mutations in *NLRP3* result in hyperactivation of the inflammasome in affected patients [7]. In this study, *in vitro,* functional experiments demonstrated that LPS stimulation led to activation of the NLRP3 inflammasome in patient PBMCs, as evidenced by elevated levels of IL-1β, IL-6, and TNF-α, along with increased expression of inflammasome-related proteins.

ASC oligomerization, a key event in inflammasome activation, was also observed in PBMCs from Patient 1 following LPS stimulation, further confirming NLRP3 inflammasome activation in this patient [12]. These findings validate the pathogenicity of the L798M and K829T variants to some extent.

Interestingly, these two novel variants are located close to each other within the LRR domain. Whether the location of these variants is related to the patients' specific CNS manifestations, such as leukoencephalopathy and intracranial calcifications, warrants further investigation. These findings open new avenues for research into the relationship between variant location and phenotypic variability in *NLRP3*-AID.

Conclusions

In conclusion, the diverse clinical manifestations of *NLRP3*-AID make its diagnosis challenging. Early diagnostic sensitivity can be improved through a combination of clinical phenotype recognition, laboratory evaluations, and genetic analyses. By reporting unique neurological manifestations and identifying novel *NLRP3* gene mutations in two *NLRP3*-AID patients, this study aims to enhance clinicians' awareness of *NLRP3*-AID, particularly in autoinflammatory patients with CNS involvement. Early diagnosis and timely intervention are crucial for improving patient outcomes and preventing severe complications.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

MS designed and supervised the study; ZBF and NW made contributions to data curation, methodology, and drafting of this manuscript; NW collected samples and performed experiments; NW and YXS analyzed the data; YXS, NL and MS conceptualized this study and critically revised the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and was performed in accordance with the Declaration of Helsinki. The reference number for the ethics approval is ZS-3272. Informed consents were obtained from both participants.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202537194.51.

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