

***NOD2*-associated autoinflammatory disease and immune deficiency**

Qingping Yao, MD, PhD^a, Min Shen, MD^a, and
James Fernandez, MD, PhD^b



Clinical Implications

- Nucleotide-binding oligomerization domain containing 2—associated autoinflammatory disease (NAID) is an increasingly recognized emerging disease. This is the first report that NAID may coexist with an underlying immune deficiency, supporting the notion that autoinflammatory disease and immune deficiency may not be mutually exclusive. This study will increase awareness of the new entity in the community of allergy and immunology.

TO THE EDITOR:

Nucleotide-binding oligomerization domain containing 2 (*NOD2*) is a cytoplasmic molecule involved in sensing microbial cell wall components and regulating inflammatory processes and apoptosis. Certain *NOD2* sequence variants (*NOD2* variants) are linked to Crohn disease, Blau syndrome, and *NOD2*-associated autoinflammatory disease (NAID).¹ NAID is one of the systemic autoinflammatory diseases (SAIDs), and is characterized by periodic fever, dermatitis, arthritis, gastrointestinal symptoms, and sicca-like symptoms, and has a genetic association with *NOD2* variants.² The clinical manifestations of NAID have been well characterized since our first report in 2011.²⁻⁴ NAID is phenotypically and genotypically distinct from Crohn disease, Blau syndrome, and other SAIDs.² Unlike hereditary monogenic periodic fever syndromes, NAID is a genetically complex disease and relatively common clinically. SAIDs generally involve abnormal activation of the innate immunity, and reports of associated humoral immune deficiency are uncommon. Here, we report a case series of patients with NAID with recurrent infections and frequent hypogammaglobinemia.

A total of 7 adult patients were recruited from our single tertiary medical center between February 2011 and February 2015. They presented with a periodic disease consisting of fever, rash, and arthralgia among other signs and symptoms. Their blood specimens were collected after informed consent and genotyped for *NOD2* variants. This study was approved by the Institutional Review Board of the Cleveland Clinic.

The diagnostic criteria for NAID were per our previous report.⁴ The clinical phenotype for NAID was considered to be present if patients met the following 2 criteria: (1) *periodic disease occurrence*, defined as 2 or more self-limiting episodes of a few days to several weeks' duration, and (2) recurrent fever of unknown origin and/or dermatitis. In the meantime, the patients had arthritis/arthralgia, abdominal pain/diarrhea, sicca-like symptoms, or serositis. To fulfill the diagnosis of NAID, the

patients also had to carry *NOD2* variants, mostly IVS8⁺¹⁵⁸ or compound IVS8⁺¹⁵⁸ and/or R702W in the absence or presence of low titers (<1:80 by immunofluorescence) of antinuclear antibodies. The exclusion criteria were inflammatory bowel disease, adult sarcoidosis, Sjögren syndrome, and other SAIDs. Continuous variables were expressed as mean $\pm$ SD, range, and frequency for descriptive statistics.

The clinical phenotypes, laboratory findings, and genetic variants of our patients are summarized (Table I). The mean age at the symptom onset was 45.4 $\pm$ 9.6 years. Of the 7 patients, 6 were women and all were white. There was no family history of periodic fever syndromes or immunodeficiency. Dermatitis was present in all patients, fever in 6, polyarthralgia/arthritis in 6, sicca-like symptoms in 6, and gastrointestinal symptoms in 4. All patients carry heterozygous *NOD2* variants, including IVS8⁺¹⁵⁸ in 6 patients and R702W in 1. Immunoglobulin analysis at the initial appointment for NAID revealed low total IgG level in 3, low IgG₁ level in 4, low IgG₄ level in 3, and low IgA/IgM ratio in 1. The abnormal immunoglobulin levels were deemed unrelated to glucocorticoids or immunosuppressive agents. Furthermore, 6 of the 7 patients had a self-reported or documented history of recurrent bacterial or viral infections managed with frequent administration of antibiotics (Table II). Unfortunately, the timing of the infection in relation with NAID-related symptoms was not always ascertained. Four patients had protective titers to both protein and polysaccharide antigen with an average of 12/14 protective pneumococcal serotypes (Table II). Because of recurrent infections, 1 patient received intravenous immunoglobulin infusions and noted unexpected improvement in her NAID-related manifestations as well as infections. She later successfully transitioned to subcutaneous immunoglobulin with continued response.

The recurrent infections and frequent hypogammaglobinemia occurring in the setting of NAID suggest a potential association between the immune dysfunction and autoinflammation. As a cytosolic molecule of the innate immunity, *NOD2* protein is known to protect intestinal mucosa from microbial invasions. Disease-associated *NOD2* variants may predispose to intestinal inflammation as a result of the *NOD2* dysfunction. Common variable immune deficiency (CVID) with hypogammaglobinemia as a hallmark is highly associated with various inflammatory/autoimmune diseases. However, the association of hypogammaglobinemia alone with SAIDs is sparsely reported. For example, there were only 3 cases of hypogammaglobinemia among 50 patients with mevalonate kinase deficiency.⁵ In addition, in support of the association between SAIDs and immunodeficiency are 2 newly recognized SAIDs: deficiency of adenosine deaminase 2, and PLCr2-associated antibody deficiency and immune dysregulation.⁶ Thus far, no reports of hypogammaglobinemia have been seen in other SAIDs such as familial Mediterranean fever, cryopyrin-associated periodic syndrome, or TNF receptor—associated periodic syndrome. In our study, all had abnormal immunoglobulin levels and 6 experienced recurrent infections, suggesting a possible relevance of the disease to CVID-like syndrome. These data suggest that the *NOD2* variant IVS8⁺¹⁵⁸ might play a role in infection, though

TABLE I. Demographic, phenotypic, and genotypic data

Patient	Sex	Age* (y)	Ethnicity	Fever	Rash	Arthritis	Ankle swelling	Sicca-like	GI	ESR†	<i>NOD2</i> variants
1	F	40	White	Yes	Yes	Yes	Yes	Yes	Yes	17	IVS8 ⁺¹⁵⁸
2	M	56	White	Yes	Yes	Yes	No	No	No	100	R702W
3	F	31	White	Yes	Yes	Yes	No	Yes	No	7	IVS8 ⁺¹⁵⁸
4	F	40	White	Yes	Yes	Yes	Yes	Yes	Yes	22	IVS8 ⁺¹⁵⁸
5	F	52	White	Yes	Yes	No	No	Yes	Yes	5	IVS8 ⁺¹⁵⁸
6	F	37	White	No	Yes	Yes	No	Yes	Yes	5	IVS8 ⁺¹⁵⁸
7	F	62	White	Yes	Yes	Yes	Yes	Yes	No	7	IVS8 ⁺¹⁵⁸

ESR, Erythrocyte sedimentation rate; F, female; GI, gastrointestinal; M, male.

*Age of onset of symptoms.

†Normal range (0-15 mm/h).

TABLE II. Laboratory data and clinical complications

Patient	WBC (3.7-11.0 k/μL)	IgG (717-1411 mg/dL)	IgG ₁ (456-1110 mg/dL)	IgG ₄ (11-112 mg/dL)	IgA (78-391 mg/dL)	IgM (53-334 mg/dL)	Infections	Antibody response (T-cell dependent)	Antibody response (T-cell independent)	Other
1*	5.3	783	415	1	149	89	URI, pneumonia×2, UTI	Protective	Protective 13/14 serotypes	↓CD4
2	3.8	1040	698	4	173	324	Atelectasis			↓CD4 splenomegaly
3	5.3	616	—	—	104	97	None reported			
4	4.7	572	415	19	160	97	Pneumonia ×5	Protective	Protective 14/14 serotypes	
5	2.8*	869	—	—	55	22	Viral syndrome	Protective	Protective 12/14 serotypes	
6	5.8	—	428	9	247	—	UTI/pelvic abscess			
7	7.8	536	268	11	161	—	Pneumonia ×1	Protective	Protective 10/14 serotypes	↓CD3

URI, Upper respiratory infection; UTI, urinary tract infection; WBC, white blood cell.
Bold values indicate abnormal numbers.

*Responded to immunoglobulin replacement.

no susceptibility of the 3 common variants of *NOD2* (1007fs, G908R, and R702W) to classical CVID has been shown.⁷

A study of the potential role of *NOD2* in immunity has indicated that *NOD2* plays a critical role in eliciting both T_H1 and T_H2 immunity through synergistic activation of antigen-presenting cells with Toll-like receptor (TLR) and NOD agonists. *NOD2* is required for an optimal IgG₁ and IgG₂ response in the absence of exogenous TLR agonists, and new chimeric *NOD2*/TLR adjuvant drastically increases vaccine immunogenicity.⁸ The pathogenesis of NAID is multifactorial, involving a complex interaction of genetics and cofactors. Our previous study has indicated possible implications in the cytokine IL-17, T_H17 cells, and specific regulatory T cells in the disease.⁹ Our new data have shown that *NOD2* was uniquely dysfunctional.

Coupled with the literature, our data support the current view that the boundaries between autoinflammation, immunodeficiency, and autoimmunity have become blurred and they may not be mutually exclusive. We believe this report also strengthens the need for further studies of immune mechanisms beyond the innate immunity in patients with NAID.

^aDepartment of Rheumatic and Immunologic Disease, Cleveland Clinic, Cleveland, Ohio

^bDepartment of Allergy & Immunology, Cleveland Clinic, Cleveland, Ohio

Conflicts of interest: J. Fernandez has received lecture fees from Baxalta. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 26, 2015; revised February 7, 2016; accepted for publication February 12, 2016.

Available online March 30, 2016.

Corresponding author: Qingping Yao, MD, PhD, Division of Rheumatology, Allergy and Immunology, Stony Brook University, HSC Tower 040, Stony Brook, NY 11794. E-mail: Qingping.yao@stonybrookmedicine.edu.

2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.02.016>

REFERENCES

1. Yao Q. Nucleotide-binding oligomerization domain containing 2: structure, function, and diseases. *Semin Arthritis Rheum* 2013;43:125-30.
2. Yao Q, Su LC, Tomecki KJ, Zhou L, Jayakar B, Shen B. Dermatitis as a characteristic phenotype of a new autoinflammatory disease associated with *NOD2* mutations. *J Am Acad Dermatol* 2013;68:624-31.
3. Yao Q, Zhou L, Cusumano P, Bose N, Piliang M, Jayakar B, et al. A new category of autoinflammatory disease associated with *NOD2* gene mutations. *Arthritis Res Ther* 2011;13:R148.
4. Yao Q, Shen M, McDonald C, Lacbawan F, Moran R, Shen B. *NOD2*-associated autoinflammatory disease: a large cohort study. *Rheumatology (Oxford)* 2015;54:1904-12.
5. Bader-Meunier B, Florkin B, Sibilia J, Acquaviva C, Hachulla E, Grateau G, et al. SOFREMIP (Société Francophone pour la Rhumatologie et les Maladies Inflammatoires en Pédiatrie); CRI (Club Rhumatismes et Inflammations). Mevalonate kinase deficiency: a survey of 50 patients. *Pediatrics* 2011;128:e152-9.

6. Ombrello MJ, Remmers EF, Sun G, Freeman AF, Datta S, Torabi-Parizi P, et al. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. *N Engl J Med* 2012;366:330-8.
7. Packwood K, Drewe E, Staples E, Webster D, Witte T, Litzman J, et al. NOD2 polymorphisms in clinical phenotypes of common variable immunodeficiency disorders. *Clin Exp Immunol* 2010;161:536-41.
8. Pavot V, Rochereau N, Resseguier J, Gutjahr A, Genin C, Tiraby G, et al. Cutting edge: new chimeric NOD2/TLR2 adjuvant drastically increases vaccine immunogenicity. *J Immunol* 2014;193:5781-5.
9. Yao Q, Myles J, Shen B, McDonald C. NOD2-associated autoinflammatory disease: an exploratory study of its pathogenesis. *Rheumatology (Oxford)* 2014; 53:958-60.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.