

Yao syndrome: A potential role and association of vasoactive intestinal peptide with *NOD2*

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Abstract

Nucleotide-binding oligomerization domain containing protein 2 (*NOD2*) is a cytosolic receptor. Both *NOD2* and vasoactive intestinal peptide (VIP) are critical in regulation of immune and inflammatory response. Yao syndrome (YAOS, OMIM 617321) is an autoinflammatory disease associated with specified *NOD2* mutations. Herein, we report a well-studied case of YAOS masquerading as mast cell disorder and neuroendocrine tumors to support the involvement of VIP in YAOS. For the first time, this case study suggests a potential relationship between *NOD2* and VIP. This could provide a novel avenue for mechanistic study of *NOD2*-associated disease.

Keywords

NOD2 • *NOD2*-associated autoinflammatory disease • rash • vasoactive intestinal peptide • Yao syndrome

Introduction

Nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*) is a cytosolic receptor and plays a critical role in defense against microbial infections, regulation of the inflammatory process, and maintenance of immune homeostasis.^[1] *NOD2* gene mutations are linked to Crohn's disease, Blau syndrome, and Yao syndrome (YAOS, OMIM 617321).^[1, 2] YAOS, formerly termed *NOD2*-associated autoinflammatory disease, is characterized by periodic fever, dermatitis, arthritis, and swelling of the distal extremities, as well as gastrointestinal and sicca-like symptoms.^[2]

Vasoactive intestinal peptide (VIP) is synthesized by various cells to inhibit the inflammatory and immune response.^[3] Herein, we report a well-studied case of YAOS masquerading as mast cell disorder and neuroendocrine tumors to suggest the involvement of VIP in YAOS and its potential association with *NOD2*.

Case Presentation

A 39-year-old Caucasian female was essentially healthy until 3 months after the uneventful delivery of her daughter 1 year ago, when she presented with intermittent bouts of cutaneous flushing and diarrhea. Skin flushing and

rash occurred on her face, neck, upper chest, and upper arms. The skin flushing was intermittent and related to hot/high heat, and her rash was nonpruritic and described by a dermatologist as erythematous macules with a sharply demarcated border (Figure 1). Her diarrhea was episodic and non-bloody, loose to watery. There was abdominal bloating without abdominal pain. Her facial flushing and diarrhea started each morning and occurred up to 10 times daily. Her diarrhea did not wake her up in the middle of the night or have any relation to food intake. The patient reported near syncopal symptoms feeling dizzy and lightheaded, which lasted 2–3 h with each episode. Also, she endorsed low-grade fever, weight loss of 10 pounds, mild pain in her fingers/ankles with minimal swelling, and dry eyes/mouth.



Figure 1. Rash: cutaneous flushing on the face and neck, patchy erythema on upper chest and macules

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Table 1. Laboratory, imaging, and pathology data

Category	Item	Result
I. Routine	Erythrocyte sedimentation rate, C-reactive protein, immunoglobulins (IgG, IgA, IgM) (mg/dL), UA	Normal
II. Allergic	Environmental allergens (IgE), immunoglobulin E (IU/mL) Serum tryptase ($\mu\text{g/L}$), 24-h urine N-methyl histamine (mcg/g Cr), 2, 3-dinor 11beta prostaglandin F2alpha (pg/mg Cr), leukotriene E4 (pg/mg Cr); galactose1-3 alpha galactose (kU/L), CKIT D816V mutation (PCR)	Normal or negative except N-methylhistamine: 243 (30–200)
III. Endocrine	Serum gastrin (pg/mL), calcitonin (pg/mL), vitamin D (ng/mL), metanephrine, 24-h urine 5HIAA VIP (serial measurements by radioimmunoassay) (pg/mL)	Normal except gastrin: 156 (0–115) calcitonin: 5.6 (0–5) vitamin D: 11 (30–100) VIP: 91.7, 66.9, 41.4, 123.2, 90.0 (0–58.5)
IV. Imaging	Chest radiograph, CT of the chest, abdomen and pelvis with contrast, Dotatate PET/CT, CT of the pancreas, upper endoscopy with EUS, brain MRI/MRA, tilt table, EEG, echocardiogram, Holter monitor	Negative except small umbilical hernia
V. Endoscopy and pathology	Esophagogastroduodenoscopy/colonoscopy/capsule endoscopy Skin biopsy Bone marrow biopsy with flow cytometry Peripheral blood flow cytometry	Normal except mild chronic gastritis Superficial perivascular inflammatory cell infiltrate (predominantly lymphocytes), negative DIF Normal Normal
VI. Genetic testing	<i>NOD2</i> mutation (whole-gene sequencing)	<i>NOD2</i> : c.2798+158C>T (IVS8+158), homozygous <i>NOD2</i> : c.2104C>T (R702W), heterozygous

Abbreviations: CT, computed tomography; DIF, direct immunofluorescence; EEG, electroencephalogram; EUS, endoscopic ultrasound; HIAA, hydroxyindoleacetic acid; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; *NOD2*, nucleotide-binding oligomerization domain-containing protein 2; PCR, polymerase chain reaction; PET, positron emission tomography; UA, uric acid; VIP, vasoactive intestinal peptide.

The patient reported several episodes of throat closing or spasmodic feeling, palpitations, and constricted breathing during disease flares with normal oxygen saturation. As a result, she visited emergency rooms/clinics frequently, and she was hospitalized several times and underwent extensive multidisciplinary workup in several medical centers. Her home medications included fludrocortisone, cetirizine, loratadine, cromolyn, famotidine, montelukast, and epinephrine autoinjector. She received four doses of omalizumab with minimal symptomatic improvement. She had a history of mild asthma since childhood with no known drug allergy and had a family history of YAOS in her sister. The patient's relevant laboratory, imaging, and pathologic study results are summarized in Table 1.

Discussion

YAOS is a systemic inflammatory disease and can mimic autoimmune, allergic, and other disorders.^[4] Patients often undergo a multidisciplinary workup for relevant disorders including systemic mastocytosis and neuroendocrine tumors as in our case. During the diagnostic process, our patient has been found to have elevated VIP levels in serial measurements of plasma by radioimmunoassay. In the end, the patient

was diagnosed with YAOS based on the diagnostic criteria, i.e., characteristic clinical phenotype and genotype (*NOD2* variants, IVS8+158 and R702W), and exclusion of relevant diseases.^[2] After the failure to respond to sulfasalazine, the patient received canakinumab 150 mg subcutaneously every 2 months for two doses, with significant improvement of her symptoms and physical functional ability, because the drug is effective for the disease.^[5]

The finding of VIP elevation in our patient with YAOS is intriguing. VIP secretions are typified by Vipomas, in which VIP acts via binding to VPAC1 receptors leading to hypersecretions and cutaneous flushing as in our case.^[3, 6, 7] Our case raises an important question. Would VIP have any association with *NOD2*? To our knowledge, there have been no studies of their relationship in the literature. Our case study is the first to show a potential relationship since VIP elevation has been observed in the context of YAOS with the presence of *NOD2* mutations as a major feature. All YAOS patients carry *NOD2* mutations; nearly all patients carry *NOD2* IVS8+158 variant and up to 30% of patients have concurrent *NOD2* R702W as in our case.^[8] *NOD2* is primarily present in monocytes, macrophages, dendritic cells, and the intestinal endothelium. It detects a bacterial cell wall component, muramyl dipeptide,

and causes *NOD2* signal transduction cascades, which in turn activates mitogen-activated kinases (MAPKs) and NF- κ B, eventually leading to proinflammatory cytokine secretions.^[1] While the pathogenesis of YAOS is still elusive, our prior study of the *NOD2* pathway has shown that *NOD2* transcriptional levels and its signal pathway are aberrant in YAOS, with overproduction of proinflammatory cytokines like IL-6.^[9] VIP is a natural anti-inflammatory agent able to

inhibit proinflammatory cytokines such as TNF α , IL-6, and IL-12. In addition, it is also known to inhibit the P38 MAPK pathway and NF- κ B.^[10] Taken together, VIP may participate in the *NOD2* activation pathway and contributes to YAOS. The most important implication of this novel finding is the potential association between *NOD2* and VIP. Further study of their interrelationship would provide a new avenue for mechanistic study of relevant diseases.

Conflict of Interest

The authors declare no conflicts of interest.

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Informed Consent

Informed consents have been obtained.

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