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Original Article

Potential role of Nickel Allergy in Disorders of Gut-Brain Interaction

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ABSTRACT

Introduction and objectives. Disorders of Gut-Brain Interaction (DGBIs), also known as functional gastrointestinal disorders (including functional dyspepsia and irritable bowel syndrome [IBS]), share overlapping symptoms with food allergies, such as diarrhoea, nausea, bloating, and abdominal pain. Nickel is the most common contact allergen, responsible for sensitising up to 20% of the general population, with possible systemic involvement (Systemic Nickel Allergy Syndrome, SNAS), often characterised by gastrointestinal (GI) symptoms. The aim of this study was to assess the prevalence of nickel allergy in paediatric and adult patients with GI symptoms consistent with DGBIs and to evaluate the diagnostic accuracy of the nickel atopy patch test (APT).

Materials and methods. This prospective observational study involved patients of both sexes (aged 4-65 years) with GI symptoms consistent with functional dyspepsia or IBS according to the Rome IV criteria. Upon enrolment, patients underwent medical history review, clinical and auxological assessments, and a nickel sulphate patch test (APT). Subsequently, all patients followed a nickel-free diet and, after 4 weeks, underwent an oral food challenge (OFC).

Results. Between January 2025 and January 2026, 200 patients (mean age 16 ± 5 years; 125 were female) with gastrointestinal symptoms consistent with DGBIs were consecutively assessed at two tertiary centres for allergic and gastrointestinal disorders. At the end of the diagnostic process, a definitive diagnosis of SNAS was established in 77 of the 200 patients. The nickel APT was positive in 90 subjects (45%). Seventy-five of the 90 patients with a positive nickel APT showed regression of GI symptoms on a nickel-free diet and recurrence of symptoms during the OFC. Two patients with negative APT results experienced resolution of GI symptoms on a nickel-free diet and recurrence during the OFC with nickel. The overall diagnostic accuracy of the nickel sulphate APT was as follows: PPV 83.3%, NPV 98.2%, sensitivity 97.4%, and specificity 87.8%.

Conclusions. Nickel allergy is common in subjects with GI symptoms consistent with functional dyspepsia or IBS. The APT has good diagnostic sensitivity in these patients and may be a useful screening test for identifying SNAS. The inclusion of an allergy work-up in patients with functional dyspepsia or IBS could open up new diagnostic and therapeutic possibilities.

KEYWORDS: nickel, functional dyspepsia, irritable bowel syndrome

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INTRODUCTION

The gut-brain axis is the bidirectional communication network linking the enteric and central nervous systems. Disruptions in this pathway — driven by altered microbiota, stress, and

immune dysfunction – are the primary cause of disorders of gut-brain interaction (DGBI), formerly known as functional gastrointestinal diseases. DGBIs can affect any part of the digestive tract. The most frequent conditions include functional dyspepsia and irritable bowel syndrome (IBS) [1].

Food allergy (FA) is one of the most common chronic conditions at a worldwide level, affecting up to 5% of adults and 8% of children [2,3]. DGBIs and the FAs share overlapping symptoms (i.e., diarrhea, nausea, bloating, and abdominal pain) and pathogenic mechanisms (i.e., dysbiosis, increased intestinal permeability, immune dysfunction) [4].

Nickel is a very common metal contained in many everyday objects and is the leading cause of allergic contact dermatitis (ACD). Nickel is also present in many constituents of a normal diet, with some foods containing higher amounts of this metal. It is responsible for sensitizing up to 20% of the general population, and up to 10% of children [5] with possible systemic involvement (SNAS) often characterized by gastrointestinal (GI) symptoms [6-8].

The aim of this study was to assess the prevalence of nickel hypersensitivity in pediatric and adult patients with GI symptoms consistent with a diagnosis of DGBI according to Rome IV criteria [9] and to assess the diagnostic accuracy of the atopy patch test (APT) for nickel.

METHODS

All subjects consecutively observed at the Adult and Pediatric Gastroenterology and Allergy Units of the Academic Hospital "Federico II" of Naples for the presence of symptoms of functional dyspepsia or IBS according to the validated criteria [9] were evaluated for the study by a research team (RT) composed of a pediatrician, gastroenterologist, allergists and nutritionists.

During the first visit (T0), anamnestic, demographic, anthropometric, and clinical data were collected in a specific data collection form. All subjects underwent a complete clinical examination and patch test (APT) with nickel sulfate. All patients received written information regarding the APT procedures (occlusion time for 48 hours, reading at 72 hours, and avoiding washing the back for 72 hours). Questionnaires related to the evaluation of symptoms and quality of life for functional dyspepsia and IBS were also collected [10-13]. At the second visit (T1), 72 hours after the APT application, patients attended the centers for assessment of APT results and received nutritional counseling with written information on a nickel-free diet for 28 days. At the end of the 28 days of a elimination diet, a third visit was performed (T2) for assessment of the response using validated clinical scores [10-13]. During the same visit a nickel oral food challenge (NOC) was performed at hospital and in the absence of immediate reactions, and patients were instructed to continue the NOC every day for the subsequent 6 days at home. At the end of the 6-day home NOC period, a visit was planned at the center for the interpretation of NOC.

The NOC consisted of administering a capsule containing talc (placebo), followed one hour later by a capsule containing 0.6 mg of nickel sulfate; if the test was still negative, an additional dose of 1.25 mg of nickel was administered one hour later. Symptoms (cutaneous and systemic) were assessed 24 hours later (positive reactions include: skin rashes in previously unaffected areas, flare-ups in previous sites of contact dermatitis, hives, and any systemic symptoms such as headache, marked fatigue, and gastrointestinal symptoms). If the test was negative, nickel was reintroduced into the patient's diet for the next 6 consecutive days.

The design of the study is reported in Figure 1.

This study was approved by the Ethics Committee of the University of Naples 'Federico II' (reference number 219/2025). Participants gave informed consent to participate in the study before patricipating.

RESULTS

Between January 2025 and January 2026, a total of 200 patients (70 aged <18 years and 130 aged ≥18 years) presenting with gastrointestinal manifestations suggestive of functional dyspepsia or IBS were evaluated. The main anamnestic and clinical features are depicted in Table I.

At the end of the diagnostic work-up, a definitive diagnosis of SNAS was established in 77 of 200 patients. The nickel APT was positive in 90 subjects, corresponding to 45% of the overall cohort. Among 90 individuals with a positive nickel APT, 75 experienced significant improvement or complete resolution of gastrointestinal symptoms after adherence to a nickel-free diet. Importantly, symptom recurrence was subsequently observed during NOC, confirming the diagnosis of SNAS.

Notably, two additional patients that resulted negative at the nickel APT showed a clear clinical response to the elimination diet, with disappearance of gastrointestinal symptoms during the nickel-free diet and reappearance following NOC. Table II summarizes the APT results related to the SNAS presence. Thus, the overall diagnostic accuracy of the nickel sulfate APT was: PPV 83.3%, NPV 98.2%, sensitivity 97.4%, specificity 87.8%.

DISCUSSION

In this prospective observational study, we demonstrated a 38.5% prevalence of SNAS in a cohort of pediatric and adult patients presenting with functional dyspepsia and IBS. These findings support growing evidence suggesting that nickel hypersensitivity may represent an underrecognized contributor to gastrointestinal symptoms commonly classified as functional disorders [14].

In recent years, increasing attention has been focused on SNAS, and our results are in line with previous adult studies reporting an increased prevalence of nickel hypersensitivity among patients with functional gastrointestinal symptoms [14]. Rizzi et al. previously demonstrated that a substantial proportion of patients with IBS-like symptoms exhibited nickel hypersensitivity and clinical improvement after nickel dietary

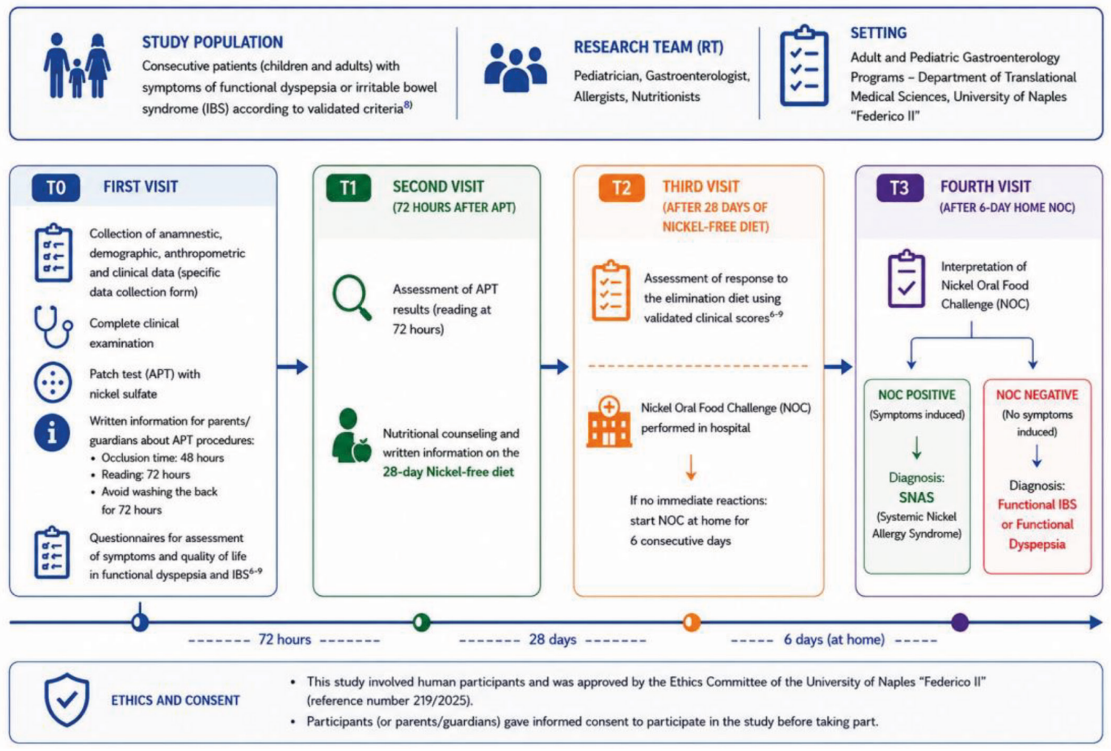

FIGURE 1. Design of the study.

restriction [15]. Similarly, Di Gioacchino et al. reported that low-nickel diets may significantly improve gastrointestinal manifestations in sensitized subjects [16]. However, pediatric evidence remains extremely limited, making our findings particularly relevant [17].

An important aspect emerging from our study is the potential role of nickel APT as a useful diagnostic tool in the identification of SNAS in patients with unexplained gastrointestinal symptoms. Among patients with positive APT, the vast majority experienced symptom improvement during nickel elimination diet and symptom recurrence during oral challenge, supporting the clinical relevance of sensitization. Nevertheless, we also observed two patients with negative APT who responded to nickel restriction and challenge, suggesting that APT alone may not be sufficient to completely exclude SNAS. This observation highlights the importance of integrating clinical history, dietary response, and oral challenge into the diagnostic work-up.

The pathophysiological mechanisms underlying gastrointestinal manifestations in SNAS are still incompletely understood. Nickel exposure has been associated with activation of mucosal immune responses, intestinal permeability alterations, mast cell activation, and low-grade inflammation, all mechanisms potentially implicated in functional gastrointestinal disorders[8]. Furthermore, the overlap between SNAS symptoms and disorders of gut–brain interaction may contribute to underdiagnosis and diagnostic delay.

Our study has several strengths. First, it prospectively evaluated a

TABLE I. Clinical characteristics of the population.

N.	200
Female sex, n (%)	125 (62.5)
Age at the enrollment, years (IQR)	16 (5)
Body mass index (IQR)	18.6 (4.5)
Family allergy risk, n (%)	90 (45)
Patients with IBS, n (%)	105 (52.5)
Patients with functional dyspepsia, n (%)	95 (47.5)

TABLE II. The results of nickel patch tests in the study population.

Nickel Patch Test	SNAS +	SNAS -	Total
Test Positive	75	15	90
Test Negative	2	108	110
Total	77	123	200

relatively large cohort of both pediatric and adult patients within a multidisciplinary setting involving gastroenterologists, allergists, pediatricians, and nutritionists. Second, the diagnosis of SNAS was not based exclusively on sensitization testing, but also incorporated dietary response and oral challenge confirmation, thus increasing diagnostic reliability.

However, some limitations should also be acknowledged. The study was conducted at tertiary referral centers, potentially introducing referral bias and limiting generalizability to the broader population. In addition, longer follow-up studies are needed to evaluate the long-term efficacy and nutritional sustainability of nickel-restricted diets, particularly in pediatric patients.

In conclusion, our findings suggest that nickel hypersensitivity and SNAS may be frequently associated with gastrointestinal symptoms currently classified as functional dyspepsia or IBS. Nickel APT may represent a useful screening tool in selected patients, although clinical evaluation and dietary response remain essential for diagnosis. These results support the need for increased awareness of SNAS among gastroenterologists, allergists, and pediatricians, particularly when evaluating patients with unexplained chronic gastrointestinal symptoms.

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Conflict of interest statement

The authors declare that they have no potential conflicts of interest related to this study

Authors' contributions

Conceptualization: LC, RBC. Original draft, and investigation: LC, RBC. Writing-Review & Editing: LC, VC, EC, RFI, PDA, DM, AM, MS, GF, SC, AA, RBC. Supervision: LC, RBC.

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