



Unspecified Polyneuropathy, Vitamin B12 Deficiency, and Atrophic Gastritis. When is Collaboration Between a Neurologist and A Gastroenterologist Necessary?

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Abstract

Background/Aim: Polyneuropathies comprise a heterogeneous group of peripheral nervous system disorders with diverse etiologies, among which vitamin B12 deficiency represents one of the most important treatable causes. Auto-immune Atrophic Gastritis (AIG), is a leading cause of vitamin B12 deficiency. This study investigated the prevalence of AIG and vitamin B12 deficiency among patients with clinically diagnosed unspecified polyneuropathy.

Material and methods: Fifty-one consecutive patients with unspecified polyneuropathy were prospectively evaluated. Clinical characteristics, neurological findings, cognitive function, psychological status, and gastrointestinal symptoms were assessed using validated clinical instruments. Gastric mucosal status was evaluated by GastroPanel® biomarker testing, and active vitamin B12 concentrations were measured using the HoloTC assay.

Results: Active *Helicobacter Pylori* (Hp) gastritis was diagnosed in 21 patients (41.2%), Atrophic Corpus Gastritis (AGC) in nine (17.7%), and Atrophic Antrum Gastritis (AGA) in one patient (1.9%). Seven patients (13.7%) had probable vitamin B12 deficiency according to HoloTC testing. Patients with AGC were significantly more likely to exhibit anxiety according to the Hospital Anxiety and Depression Scale than patients without AG (OR=3.57, 95% CI=1.18-10.4, p<0.05).

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Conclusion: AGC is common among patients with unspecified polyneuropathy. Because empirical vitamin supplementation may obscure biochemical evidence of vitamin B12 deficiency, assessment of gastric mucosal status should complement routine neurological evaluation. Close collaboration between neurologists and gastroenterologists may facilitate earlier diagnosis and optimize long-term management.

Introduction

Polyneuropathies typically present with a diffuse, multiple involvement of the peripheral nerves, primarily in the distal parts of the extremities [1]. The manifestations include sensory- (paresthesia, a “burning” sensation, pain in the feet and hands, “glove” and “sock” patterns of hypoesthesia or hyperesthesia), motor- (peripheral paresis, muscle atrophy, decreased tendon reflexes up to areflexia), and autonomic disturbances [1]. Due to a wide variety of causes, non-specific clinical picture, and difficulty of diagnosis, the etiology of polyneuropathy typically remains clinically unrecognized (polyneuropathies of unknown origin). However, vitamin B12 deficiency is among the most common causes of polyneuropathy [1].

Vitamin B12 deficiency is among the most common and, importantly, one of the few readily treatable causes of peripheral neuropathy [2,3]. Cobalamin deficiency may result from inadequate dietary intake, impaired gastrointestinal absorption, defects in transport or intracellular metabolism, or increased physiological requirements. Reported prevalence varies considerably according to the population studied and the diagnostic criteria applied, ranging from approximately 3% to 16% [4,5]. The most common causes of vitamin B12 deficiency are gastrointestinal diseases: chronic atrophic gastritis associated with *Helicobacter pylori* (*H. pylori*) and/or an autoimmune process, small intestine diseases (celiac disease, Crohn’s disease, etc.), bacterial overgrowth syndrome, chronic pancreatitis with exocrine insufficiency, as well as helminthiasis [6].

Vitamin B12 is essential for normal hematopoiesis and neurological function. Within the nervous system, it plays a crucial role in myelin synthesis, axonal maintenance, and Schwann cell function. Consequently, deficiency may result in a wide spectrum of neurological and neuropsychiatric manifestations, including peripheral neuropathy, cognitive impairment, gait disturbance, depression, and spinal cord degeneration, whereas classical megaloblastic anemia develops in only a minority of affected patients [6,7]. In patients with neurological symptoms, diagnosis of vitamin B12 deficiency is often complicated by empirical administration of vitamin B preparations before the underlying cause has been established. Such treatment may normalize circulating vitamin B12 concentrations while leaving the primary cause of malabsorption undetected.

Among gastrointestinal disorders, Atrophic Corpus Gastritis (AGC) represents one of the principal causes of impaired vitamin B12 absorption because progressive destruction of the oxyntic mucosa leads to loss of Intrinsic Factor (IF) secretion [8]. In many patients, AGC develops as a consequence of Autoimmune Gastritis (AIG), although chronic *Hp*-infection may also contribute to the development of gastric atrophy or even initiate the autoimmune mechanisms [8-10]. Population-based studies estimate the prevalence of AIG or AGC to range between approximately 0.5% and 5%, depending on the diagnostic criteria and study population [9,10].

Progressive loss of oxyntic glands results in reduced secretion of hydrochloric acid, pepsinogen I, and IF, accompanied by compensatory hypergastrinemia due to increased Gastrin-17 (G-17) secretion from antral G cells [11,12]. These characteristic physiological alterations form the basis for serological assessment of gastric mucosal status.

The diagnostic gold standard for atrophic gastritis remains upper gastrointestinal endoscopy (EGD) with systematic gastric biopsies [13]. However, because endoscopy is invasive and unsuitable for large-scale screening, validated serological biomarker assays have become increasingly important in clinical practice. GastroPanel® (Biohit Oyj, Helsinki, Finland) combines measurements of pepsinogen I, pepsinogen II, gastrin-17, and IgG antibodies against *Hp*, allowing non-invasive assessment of gastric mucosal status and reliable detection of different forms of AG, AIG included [10,14].

The present study was undertaken to determine the prevalence of AGC and vitamin B12 deficiency among patients with clinically diagnosed unspecified polyneuropathy using the GastroPanel® biomarker assay and measurement of active vitamin B12 (holotranscobalamin). In addition, we evaluated the neurological, cognitive, psychological, and gastrointestinal characteristics of these patients to clarify the need for multidisciplinary collaboration between neurologists and gastroenterologists.

Materials and methods

Study design and patients

This prospective observational study included 51 consecutive patients admitted for elective inpatient treatment to the Departments of Neurology, Peter the Great Clinic, North-Western State Medical University named after I.I. Mechnikov (St. Petersburg, Russia), between 2024 and 2025.

All participants had a clinical diagnosis of unspecified polyneuropathy established before enrolment according to routine neurological practice. Patients with confirmed alternative causes of peripheral neuropathy were not included in the study.

The study population comprised 16 men and 35 women (male-to-female ratio, 1:2.2), with a median age of 66 years (interquartile range=53-73 years). According to body mass index (BMI), 23 patients (45.1%) were overweight, four (7.8%) had class I obesity, two (3.9%) had class II obesity, one (2.0%) had class III obesity, 15 (29.4%) had normal body weight, five (9.8%) were underweight, and one (2.0%) was severely underweight.

The study protocol was approved by the local Ethics Committee (approval protocol No. 2, dated March 5, 2024), and written informed consent was obtained from all participants before inclusion in the study.

Methods

Clinical evaluation: All patients underwent a standardized neurological examination. Clinical manifestations of peripheral neuropathy were assessed using the Michigan Neuropathy Screening Instrument (MNSI), which consists of a symptom questionnaire and a standardized physical examination including evaluation of foot appearance, Achilles tendon reflexes, vibration sensation using a 128-Hz tuning fork, and tactile sensation assessed with a Semmes-Weinstein monofilament [15]. According to the original validation, an overall MNSI score of ≥ 7 indicates a high probability of polyneuropathy [15]. Alternatively, lower cutoff scores can be used: ≥ 4 for the questionnaire

and ≥ 2 points for the physical examination [15].

Cognitive function was evaluated using both the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) [16-19]. A MoCA score below 26 points was considered indicative of cognitive impairment. In addition to the MoCA, screening for cognitive impairment in routine clinical practice was conducted using the MMSE. As compared to MMSE, the MoCA scale has a higher sensitivity in detecting mild cognitive impairment [18,19].

Psychological status was assessed using the Hospital Anxiety and Depression Scale (HADS), consisting of separate anxiety and depression subscales [20,21]. A score of 0-7 is considered normal; subclinical anxiety or depression is diagnosed with a score of 8-10; and clinically significant anxiety or depression is diagnosed with a score of 11 or higher [20,21].

Health-related quality of life was evaluated using the WHO Brief Quality of Life Questionnaire (WHOQOL-BREF), which assesses four domains including physical health, psychological well-being, social relationships, and environmental factors [22]. The results are interpreted as follows: 0-20% – low; 21-40% – below average; 41-60% – average; 61-80% – above average; 81-100% – high [22].

The Gastrointestinal Symptom Rating Scale (GSRS) questionnaire was developed to assess the quality of life of patients with complaints associated with the digestive system. The questionnaire consists of 15 items grouped into 6 scales: abdominal pain, gastroesophageal reflux (reflux syndrome), diarrhea syndrome, dyspeptic syndrome, constipation syndrome, and a total score scale. On each scale, a patient can score between 0 and 6 points. A higher score corresponds to more severe symptoms and a poorer quality of life [23].

Laboratory tests. Additional laboratory tests included serological testing for AIG and measurement of serum levels of the active form of vitamin B12 [10,14]. Serum analysis was performed using an automated GastroPanel® ELISA (enzyme-linked immunosorbent assay) test (Biohit Oyj, Helsinki, Finland), and the results were interpreted using the GastroSoft® application [24]. The manufacturer recommended reference range for the 4 markers were used as follows: PG I (30-160 $\mu\text{g/L}$), PG II (3-15 $\mu\text{g/L}$), PG I/PG II ratio [3-20], G-17 (1-7 pmol/L), anti-*H. pylori* IgG antibodies (<30 EIU) [24-28]. Based on these biomarker profiles (Table 1), gastric mucosal status was classified into five predefined diagnostic categories: normal gastric mucosa, non-atrophic *H. pylori* gastritis, atrophic gastritis of the antrum (AGA), Atrophic Gastritis of the Corpus (AGC), and Atrophic Pangastritis (AGP) according to the validated GastroPanel® diagnostic algorithm [10,14,24-28].

Assessment of vitamin B12 status. Active vitamin B12 status was determined by measuring serum holotranscobalamin concentrations using an ELISA-based assay (HoloTC, Biohit Oyj, Helsinki, Finland) [10]. According to the manufacturer's recommendations, HoloTC concentrations <25 pmol/L indicated vitamin B12 deficiency, concentrations between 25 and 69.9 pmol/L indicated probable vitamin B12 deficiency, and concentrations ≥ 70 pmol/L were considered normal [10].

Statistical analysis

Statistical analyses were performed using Microsoft Excel and STATISTICA version 10 (StatSoft Inc., Tulsa, OK, USA). Continuous variables showed a non-normal distribution and

are presented as median and Interquartile Range (IQR) unless otherwise indicated. Comparisons between groups were performed using appropriate non-parametric statistical tests. Correlations between continuous variables were evaluated using Spearman's rank correlation coefficient. Odds Ratios (ORs) with 95% confidence intervals (95% CIs) were calculated where appropriate. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant.

Results

Gastric mucosal status

The GastroPanel® biomarker profiles for each diagnostic category are presented in Table 2. The principal finding of the present study was the detection of AGC in nine of the 51 patients (17.7%), by a classical biomarker profile (down-regulated PGI and PGI/PGII ratio, up-regulated G-17, and high Hp ELISA antibody titer). Only one patient (1.9%) was diagnosed with AGA, whereas none fulfilled the serological criteria for (AGP).

Overall, GastroPanel® biomarker testing classified 20 patients (39.2%) as having a normal gastric mucosa, while 21 patients (41.2%) had active *Hp*-gastritis without evidence of mucosal atrophy. Thus, nearly one in every five patients with unspecified polyneuropathy exhibited AGC, a prevalence substantially higher than that reported for the general population. Women predominated among the patients with AGC, accounting for seven of the nine cases (77.8%), whereas two patients (22.2%) were men.

Active vitamin B12 status

Interpretation of vitamin B12 status required particular caution because all study participants had received oral and/or parenteral vitamin B supplementation, including cyanocobalamin, during the preceding three months. Serum holotranscobalamin concentrations were ≥ 70 pmol/L in 44 patients (86.3%), indicating normal active vitamin B12 status. Seven patients (13.7%) had HoloTC concentrations between 25 and 69.9 pmol/L, consistent with probable vitamin B12 deficiency, whereas no patient fulfilled the criterion for definite vitamin B12 deficiency (<25 pmol/L).

Among the seven patients with probable vitamin B12 deficiency, AGC was identified in two patients (28.6%), active *H. pylori* gastritis in two (28.6%), and normal gastric mucosa in three (42.9%). No statistically significant association was observed between serum holotranscobalamin concentrations and gastric mucosal status (Table 3). Despite the relatively high prevalence of AGC, biochemical evidence of vitamin B12 deficiency remained uncommon, most likely reflecting recent empirical vitamin B12 supplementation before enrolment.

Neurological and psychological assessment

The Michigan Neuropathy Screening Instrument confirmed a high probability of polyneuropathy in 44 patients (86.3%), whereas only seven patients (13.7%) scored below the diagnostic threshold. Assessment of cognitive function using the Montreal Cognitive Assessment identified cognitive impairment in 27 patients (52.9%), while normal cognitive performance was observed in 24 patients (47.1%).

According to the Hospital Anxiety and Depression Scale (HADS), clinically significant anxiety was present in 12 patients (23.5%), whereas borderline anxiety was observed in 11 patients (21.6%). Clinically significant depression was identified in

12 patients (23.5%), and borderline depression in five patients (9.8%). A clinically relevant association emerged between gastric pathology and psychological well-being. Patients with AGC were significantly more likely to have anxiety than those without atrophic gastritis (OR=3.57, 95%CI=1.18-10.4; $p<0.05$).

Quality of life

The results of the WHOQOL-BREF questionnaire are summarized in Table 4. According to the WHO questionnaire on quality-of-life assessment, patients had a relatively good quality of life in all four assessed domains (in most cases, average or above average). However, scores were lower in the domain of physical and psychological well-being, and higher in the domains of self-perception, microsocial support, and social welfare. These findings suggest that, despite the presence of a neurological disorder, the patients' mental and emotional state was significantly intact, leading to harmonious interactions with the external environment, including their social circle.

Gastrointestinal symptoms

Assessment using the GSRS questionnaire demonstrated that constipation was the predominant gastrointestinal com-

plaint, affecting 25 patients (49.0%) (Table 5). Epigastric discomfort was reported by 14 patients (27.5%), gastroesophageal reflux symptoms by 10 (19.6%), epigastric pain by nine (17.6%), whereas diarrhea was reported by only five patients (9.8%). The median overall GSRS score was 22 (range=15-31). Among the individual symptom domains, the highest median scores were obtained for the constipation: 4 (range 3-15), and dyspeptic symptoms: 4 (range 3-8), indicating that upper gastrointestinal symptoms were common in this cohort.

Sex-related differences

Sex-specific comparisons are summarized in Table 6. Women (n=35) reported significantly higher GSRS scores for abdominal pain, constipation, and overall gastrointestinal symptom burden than men (n=16). Conversely, men achieved significantly higher WHOQOL-BREF scores for physical and psychological well-being. Men also demonstrated a higher prevalence of serological *H. pylori* infection and significantly higher anti-*Hp* IgG antibody concentrations than women. Overall, the observed sex-related differences did not influence the principal finding of the study, namely the unexpectedly high prevalence of AGC in these patients with clinically diagnosed unspecified polyneuropathy.

Table 1: Gastric status classified on the basis of GastroPanel biomarker profiles.

Gastric Status	PG I 30-160 µcg/L	PG II 3-15 µcg/L	PG I/ PG II 3-20	G -171-7 pmol/L	Hp IgG< 30 EIU
Normal	N	N	N	N	N
Active Hp gastritis	N/↑	N/↑	N	N/↑	↑
AGC		↓	↓	↑	N/↑
AGA	N	N	N	↓	↑
AGP	↓	↓	↓	↓	N/↑

Hp: *Helicobacter Pylori*; AGC: Atrophic Gastritis of the Corpus; AGA: Atrophic Gastritis of the Antrum; AGP: Atrophic Gastritis of the Antrum and corpus (pangastritis)

Table 2: GastroPanel biomarker values stratified by the five diagnostic GP categories.

Diagnostic Category	No of Cases	PG I (µg/L) (M ±SD)	PG II (µg/L) (M ±SD)	PGI/PG II (M ±SD)	G -17 (pmol/L) (M ±SD)	Hp IgG (EIU) (M ±SD)
Normal	20	116.82±47.08	14.07±8.77	9.01±2.18	6.68±9.06	14.41±9.53
Hp-infection	21	137.62±47.68	26.73±13.51	5.89±2.56	11.49±12.14	218.01±145.47
AGA	1	70.1±0.00	11.5±0.00	6.09±0.00	0.3±0.00	31.3±0.00
AGC	9	23.29±25.07	15.38±9.72	1.58±1.63	23.64±11.77	155.31±185.84
AGP	0	-	-	-	-	-
TOTAL	51	107.96±59.76	19.46±12.47	6.36±3.45	11.53±12.27	123.44±151.29

GP: GastroPanel® test; Hp: *Helicobacter Pylori*; AGC: Atrophic Gastritis of the Corpus; AGA: Atrophic Gastritis of the Antrum; AGP: Atrophic Gastritis of the antrum and Corpus (pangastritis); EIU: Enzyme Immunoassay Unit

Table 3: The levels of active vitamin B12 stratified by the five diagnostic GP categories.

Diagnostic Category	No of Cases	Vitamin B12 levels (pmol/L) (M ±SD)
Normal	20	107.72±30.29
Hp-infection	21	110.21±27.65
AGA	1	84.82±0.00
AGC	9	102.2±38.26
AGP	0	-
TOTAL	51	107.32±30.11

GP: GastroPanel® test; Hp: *Helicobacter Pylori*; AGC: Atrophic Gastritis of the Corpus; AGA: Atrophic Gastritis of the Antrum; AGP: Atrophic Gastritis of the Antrum and corpus (pangastritis).

Table 4: Results of the WHO questionnaire on quality-of-life assessment.

Well-being sphere	Low rate (0-20%)		Reduced rate (21-40%)		Average rate (41-60%)		Increased rate (61-80%)		High rate (81-100%)	
	N	%	N	%	N	%	N	%	N	%
Physical and psychological well-being	0	0.0	4	7.84	23	45.1	23	45.1	1	1.96
Self-perception	0	0.0	0	0.0	20	39.22	20	39.22	11	21.57
Microsocial support	2	3.9	0	0.0	16	31.37	18	35.29	15	29.41
Social welfare	0	0.0	0	0.0	13	25.49	23	45.1	15	29.41

Table 5: Results of the GSRS questionnaire.

Indicators	Points Median [Range]
Abdominal pain	2 [2; 4]
Reflux syndrome	3 [3; 5]
Diarrheal syndrome	3 [3; 4]
Dyspeptic syndrome	4 [4; 8]
Constipation syndrome	4 [3; 15]
GSRS questionnaire, average total score (max. 36)	22 [15; 31]

GSRS: Gastrointestinal Symptom Rating Scale

Table 6: Statistically significant differences between the male and female patients.

Indicators	Men (n=16)	Women (n=35)	p
Complaints from the digestive system (GSRS questionnaire)(points)			
Abdominal pain	2 [2; 2]	2 [2; 5]	0.04
Constipation syndrome	3 [3; 8]	10 [3; 15]	0.02
Overall GSRS score	15 [15; 26.5]	26 [15; 19]	0.02
WHO Quality of Life Questionnaire			
The sphere of physical and mental well-being	23.5 [20.5; 26]	21 [17; 23]	0.02
GastroPanel® test results			
IgG to H. pylori (EIU)	158.2 [21.6; 398]	27.4 [12.5; 125.3]	0.03
Increased Hp IgG antibody levels	11 (68.75%)	16 (45.71%)	p<0.05

GSRS: Gastrointestinal Symptom Rating Scale; EIU: Enzyme Immunoassay Unit

Discussion

The principal finding of the present study was the unexpectedly high prevalence of AGC among patients with clinically diagnosed unspecified polyneuropathy. GastroPanel® biomarker testing identified AGC in 17.7% of the study population (Table 2), a prevalence considerably higher than that reported among the general population, where AIG or AGC has generally been estimated to occur in approximately 0.5-5% of adults [8-10,13,25,28,33,36]. Although our study population was relatively small and recruited from a tertiary neurological referral center, this observation strongly suggests that AGC may represent an underrecognized comorbidity in patients with unspecified polyneuropathy.

Vitamin B12 deficiency is a well-established and potentially reversible cause of peripheral neuropathy [2-7,31,39]. Nevertheless, determining the underlying cause of cobalamin deficiency frequently remains challenging in routine clinical practice because patients often receive empirical vitamin B supplementation before an appropriate diagnostic evaluation has been completed [3,4,6,31]. This phenomenon was clearly reflected in the present study, in which all participants had received vitamin B supplementation during the preceding three months. Consequently, circulating vitamin B12 concentrations

may normalize despite persistent impairment of gastric vitamin B12 absorption. This observation is supported by the HoloTC findings summarized in Table 3.

Previous studies analysing the levels of vitamin B12 in patients with polyneuropathy are relatively scarce. In a study by Saperstein et al. (2003) focused on patients with idiopathic sensory polyneuropathy, 8% were found to have a vitamin B12 deficiency, and 22.2% were diagnosed with pernicious anemia resulting from AIG [30]. In a study from China, the relationship between serum vitamin B12 levels and peripheral neuropathy was analysed in patients with chronic AG [32]. The prevalence of *Hp*-infection and CAG was higher in patients with peripheral neuropathy, while Body Mass Index (BMI) and plasma concentrations of vitamin A, folic acid, and vitamin B12 were lower than in the control group [32]. Lahner et al. (2009) concluded that in patients with cryptogenic polyneuropathy, AIG must be ruled out as a cause of neurological disorders [33].

A number of studies have confirmed that vitamin B12 deficiency develops in 15-50% of the patients with AIG, and in 80% of those who have a chronic course of the disease. In the study by Hershko et al. (2006), subclinical vitamin B12 deficiency was identified in 25% of the patients with AIG [34], and even in patients with normal hemoglobin levels [35,36]. In the present

study, only 2 (22.2%) of 9 patients with AGC and polyneuropathy had a probable deficiency of active vitamin B12, whereas in 77.8% of the patients, the HoloTC testing resulted in B12 levels within the reference range (Table 3). The normal levels of holotranscobalamin in these patients with AGC are explained by the routine, empirical administration of B vitamins to all patients with various neurological disorders, including polyneuropathies. In such a setting, short-term courses of vitamin B12 increase the plasma vitamin concentrations but do not resolve the symptoms of polyneuropathy. According to the current consensus guidelines, vitamin B12 supplementation in patients with AG and B12 deficiency should be lifelong [12].

The biological relationship between AGC and neurological manifestations is well established. Progressive destruction of the oxyntic mucosa leads to loss of gastric acid secretion together with impaired IF production, ultimately resulting in defective vitamin B12 absorption [8,13,33-36]. Progressive cobalamin depletion may subsequently impair myelin synthesis, axonal integrity, and neuronal metabolism, thereby contributing to the development of peripheral neuropathy and other neurological disorders [2,4,31,39]. Although the present study was not designed to investigate these pathogenic mechanisms directly, the observed association is biologically plausible and consistent with previous clinical observations. The coexistence of AGC with largely normal vitamin B12 concentrations (Tables 2 and 3) illustrates the diagnostic challenge created by routinely instituted vitamin B12 supplementation.

An important secondary finding was the significant association between AGC and anxiety. Patients with AGC were more than three times as likely to exhibit clinically relevant anxiety scores than patients without AG. Although the underlying mechanisms remain uncertain, neuropsychiatric manifestations have long been recognized among patients with vitamin B12 deficiency and AIG [2,7,31,33]. Chronic disease burden, nutritional deficiency, autoimmune mechanisms, or combinations of these factors may all contribute to the observed association.

The present study also supports the clinical utility of the GastroPanel® biomarker assay as a non-invasive method for evaluating gastric mucosal status [10,14,24-28]. Several validation studies have demonstrated high diagnostic accuracy of GastroPanel® for detecting AG and *Hp*-infection, making it a practical first-line diagnostic tool before referral for upper Gastrointestinal Endoscopy (EGD) [10,14,24-28]. The characteristic biomarker profiles observed in the present study (Table 2) are in good agreement with these previous validation studies. In patients with biomarker profiles indicating AGC, endoscopic examination with systematic biopsies should subsequently be performed to confirm the diagnosis and determine the extent of gastric mucosal damage, i.e., the grade of AG [13,14,33,36].

Interestingly, gastrointestinal symptoms were common in the present cohort, constipation and dyspeptic symptoms being the predominant complaints (Table 5). Although these symptoms are non-specific and cannot be attributed solely to gastric pathology, they emphasize that gastrointestinal manifestations frequently coexist with neurological symptoms in patients with unspecified polyneuropathy. The combination of gastrointestinal symptom assessment and serological evaluation of gastric mucosal status may therefore help identify patients who would benefit from further gastroenterological investigation.

From a clinical perspective, our findings support a multidisciplinary diagnostic strategy. Neurological evaluation should be

complemented by assessment of gastric mucosal status whenever vitamin B12 deficiency is suspected or when the etiology of unspecified polyneuropathy remains uncertain. Measurement of serum vitamin B12 or holotranscobalamin alone may be insufficient because previous supplementation can normalize circulating concentrations despite persistent malabsorption [29-31,33,34,39]. Combining active vitamin B12 measurement with GastroPanel® biomarker testing provides complementary diagnostic information that may facilitate earlier recognition of clinically significant gastric disease and identify patients requiring gastroenterological follow-up. The complementary diagnostic value of these investigations is illustrated by the combined findings presented in Tables 2 and 3.

Sex-specific analyses revealed significant differences in gastrointestinal symptom burden and quality of life, women reporting higher GSRS scores whereas men demonstrated higher anti-*Helicobacter pylori* IgG antibody concentrations (Table 6). Although these observations were secondary findings and the study was not adequately powered for sex-stratified analyses, they suggest that sex-related differences in the clinical presentation of unspecified polyneuropathy deserve further investigation in larger prospective studies.

The present study has several strengths. All patients underwent standardized neurological examination together with validated assessment of cognitive function, psychological well-being, gastrointestinal symptoms, gastric mucosal status, and active vitamin B12 concentrations (Tables 2-6). To our knowledge, only few previous studies have simultaneously evaluated these complementary clinical and laboratory parameters in patients with unspecified polyneuropathy [10,24,25,29,30,32-36].

Some potential limitations should also be mentioned. First, the study population was relatively small, limiting the statistical power of subgroup analyses. Second, autoimmune gastritis could not be confirmed by systematic histopathological examination or determination of PC and IF antibodies in all patients. Consequently, the diagnosis was based primarily on the characteristic serological profile of AGC identified by the GastroPanel® biomarker assay [10,14,24-28]. Third, previous empirical vitamin B12 supplementation complicated interpretation of serum holotranscobalamin concentrations (Table 3).

Future prospective multicenter studies combining GastroPanel® testing with systematic endoscopic biopsies classified according to the USS, and comprehensive autoimmune antibody testing are warranted to determine the true prevalence of AIG among patients with unspecified polyneuropathy [13,32-36]. Such studies should also investigate whether earlier diagnosis and treatment of gastric pathology (e.g. *Hp*-infection) improve neurological outcomes and reduce long-term complications associated with chronic vitamin B12 deficiency.

Conclusion

The present study demonstrates that AGC is unexpectedly common among patients with clinically diagnosed unspecified polyneuropathy, with a prevalence considerably exceeding that reported for the general population (Table 2). This finding suggests that gastric pathology may represent an underrecognized contributor to neurological disease in this patient population.

Because empirical vitamin B12 supplementation may normalize circulating vitamin B12 and holotranscobalamin concentrations despite persistent impairment of gastric absorption (due to AGC), biochemical assessment alone may not be suffi-

cient to identify the underlying cause of vitamin B12 deficiency. The discrepancy between the prevalence of AGC and the relatively low frequency of biochemical vitamin B12 deficiency observed in the present study (Tables 2 and 3) underscores this important clinical limitation.

Evaluation of gastric mucosal status using the GastroPanel® biomarker assay provides valuable complementary diagnostic information and may facilitate identification of patients who require confirmatory upper gastrointestinal endoscopy. When AGC is identified in patients with unspecified polyneuropathies, specific treatment to correct vitamin B12 deficiency is necessary, which involves the parenteral or sublingual administration of high doses of cyanocobalamin [40].

The findings support closer collaboration between neurologists and gastroenterologists in the diagnostic work-up of patients with unspecified polyneuropathy. A multidisciplinary approach combining neurological evaluation, assessment of active vitamin B12 status, and non-invasive serological evaluation of gastric mucosal structure and function may improve diagnostic accuracy, optimize patient management, and permit earlier recognition of clinically significant gastric disease.

Author declarations

Conflicts of interest

Of the Authors, KS is the retired Chief Medical Director of Biohit Oyj. None of the other Authors have any conflict of interest to declare in relation to this study.

Authors' contributions

All Authors have met all the following four criteria: i) substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, ii) drafting of the work or revising it critically for important intellectual content, and iii) final approval of the manuscript version submitted.

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Artificial intelligence (AI) disclosure

An artificial Intelligence (AI) tool (ChatGPT) was used to make the translation of the original Russian text to English and only for the language checking of the final English text version written by the authors (not AI).

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