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RESEARCH

Original paper

Brain-Gut axis in management of Parkinson Disease – utility in medical practice

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Rezumat

Parkinson's disease (PD) is one of the most important movement disorder in the spectrum of the neurodegenerative pathologies, associating extrapyramidal signs as tremor, rigidity, postural instability with autonomic nervous system dysfunction as gastro-intestinal disbalance, hypotension; cognitive impairment; mood changes- anxiety, sleep disturbances; anosmia. Patients experience a gradual yet significant change in their daily routine, from mild unilateral tremor to the inability to sustain themselves. It is often diagnosed in the sixth decade of life. At this time, due to possible comorbidities, patients require a meticulous and individualized therapeutical plan, best given by their general practitioners (GPs).
Material and method: We performed an observational study, on a cohort of 30 patients, diagnosed with PD, admitted in the Neurology Department of the Clinical Emergency County Hospital Constanta, Romania, who fulfilled the inclusion criteria and the Movement Disorder Society (MDS) Clinical Diagnostic Criteria, for a period of 6 months. Patients undergo clinical evaluation for the motor function using UPDRS motor part III scale and biological samples were collected. We measured calprotectin levels means and standard deviations (SD). The data collected was analysed using descriptive statistics (mean, range and percentage) and inferential statistics (correlations and regressions).
Results: The results provided a weak association between faecal calprotectin and UPDRS score in Parkinson's patients, (practically with the advanced stages) and no relevant corelation with serum calprotectin levels. The utility of calprotectin testing remains useful, being an inflammatory biomarker, with valuable association with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels.
Conclusions: The correlations found in our study underscore the utility of calprotectin not only as a sensitive indicator of intestinal inflammation but also as a complementary tool in evaluating systemic inflammatory activity in Parkinson disease. For a better understanding of the microbiota–gut–brain axis and the possible common ethology of PD and Inflammatory bowel disease (IBD) further studies are required, highlighting the genetic pathway and using a larger spectrum of IBD tests for a targeted and adaptative therapeutical management.

Keywords: *Parkinson's disease, general practice, calprotectin, inflammation, microbiota*

CERCETARE

Articole originale

Axa creier-intestin în managementul bolii Parkinson – utilitatea în practica medicală

Rezumat

Boala Parkinson (BP) face parte din spectrul bolilor neurodegenerative, invalidantă, caracterizată prin semne și simptome motorii (bradikinezie, instabilitate posturală, tremor inițial unilateral) dar și non-motorii (în spectrul tulburărilor anxios-depresive, tulburări gastro-intestinale) progresive, resimțite de pacient pe măsură ce boala avansează. Are un impact semnificativ asupra calității vieții pacienților, predominant cu vârsta de peste 65 de ani.

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Îngrijirea specializată în boala Parkinson este necesară pentru acești pacienți, în contextul comorbidităților multiple și al particularităților individuale, medicii de familie (MF) pot oferi o abordare holistică, importantă în managementul acestor pacienți.
Material și metodă: Am realizat un studiu observațional pe o perioadă de 6 luni în cadrul Spitalului Clinic Județean de Urgență Constanța, Clinica de Neurologie. Au fost incluși în studiu 30 de pacienți diagnosticați cu BP, care au îndeplinit criteriile de diagnostic clinic ale Movement Disorder Society (MDS).Am măsurat nivelurile de calprotectină, exprimate ca medii și deviații standard (SD). Statistica descriptivă a fost utilizată pentru a sumariza și organiza datele colectate, folosind măsuri precum media, mediana și deviația standard. Statistica inferențială a fost aplicată pentru a trage concluzii despre populație, utilizând teste de ipoteze și intervale de încredere.
Rezultate: Rezultatele arată o corelație slabă între calprotectina fecală și scorul UPDRS la pacienții cu Parkinson, fără o corelație semnificativă cu calprotectina serică. Totuși, calprotectina rămâne un biomarker util pentru inflamația intestinală și activitatea inflamatorie sistemică, fiind semnificativ corelată cu CRP și VSH.
Concluzii: Corelațiile identificate în studiul nostru subliniază utilitatea calprotectinei nu doar ca un indicator sensibil al inflamației intestinale, ci și ca un instrument complementar în evaluarea activității inflamatorii sistemice în boala Parkinson. O înțelegere cuprinzătoare a axei microbiota–intestin–creier va fi esențială pentru dezvoltarea unor strategii terapeutice eficiente în gestionarea tulburărilor neurodegenerative.

Cuvinte cheie: *boala Parkinson, medicină de familie, calprotectină, inflamație, microbiota*

Introduction

Parkinson's disease (PD) is the most extensively studied neurodegenerative movement disorder worldwide, characterized by progressive deterioration of motor function and the gradual onset of both motor and non-motor clinical signs and symptoms initially unilateral, and then progressively global. Because of the decreased level of dopamine from the substantia nigra pars compacta and mesostriatal system deficiency by the progressive loss of dopaminergic neurons with the accumulation of protein aggregates of alpha synuclein, also known as "Lewy bodies", patients develop motor symptoms such as tremor, difficulty in maintaining and initiating movements (gait instability, freezing), and nevertheless loss of the smooth controlled voluntary movement. Due to the loss of dopamine, patients may experience non motor symptoms like anxiety, change in disposition, depression, sleep disorder.

Starting from the beginning, "The shaking palsy" disease, as initially described by James Parkinson in 1817, started with unilateral tremor, bradykinesia, rigidity and postural instability, later Jean- Martin Charcot in 1860s, gave this pathology a distinctive clinical term "Parkinson's disease", reaching out to the connections between progressive motor symptoms and the underling cerebral and systemic pathologic mechanisms. Later, in 2003, Heiko Braak came with the "gut-brain-axis" theory, explain that the underlying cause of PD may be given environmental agents/ pathogens/toxins that are inhaled and deposited in the nasal cavity and the olfactory sensory neurons are activated. The pathogens reach out the olfactory bulb and then they can induce the aggregation of alpha syn nuclein proteins. These aggregates propagate to the mid brain and eventually the neo cortex. By similar mechanisms, ingesting a toxin, can also activate trough the ENS the oxidative stress and mitochondrial dysfunction and the alfa syn nuclein can propagate to the CNS with the vagus nerve reaching the dorsal motor nucleus of the vagus in the brainstem. These explains the early signs of PD such as hyposmia and constipation.

Since then, researchers have the important mission of discovering the subsequent molecular, genetic, inflammatory and immunological ethology or link between PD and IBD for an optimised therapeutic plan in the aim of rising the quality of life for these patients.

Most PD develops in the age between 60–65, though juvenile PD forms, encountered in very young patients (21 years), can be devastating not being diagnosed in early stages, having a rapidly progression with poor rate or recovery of the motor function no matter the treatment (1). This is another reason why the role of the GP in managing Parkinson's disease is crucial in adopting a holistic care approach, promoting self-management, and supporting patient autonomy in decision-making, particularly during the early and moderate stages of the disease. Stepwise and comprehensive follow-up by GPs is essential to optimize outcomes of this special group of patients (2). Other practitioners may face challenges in the successful, holistic management of the patient, due to incomplete knowledge of a its medical history or familial context, increasing the risk of misdiagnosis, polypharmacy, or conflicting treatment regimens. Misdiagnosis or delayed diagnosis often leads to referrals to specialties such as rheumatology, otolaryngology (ENT), or orthopaedics, which may result in inappropriate management and lack of clinical improvement.

Neuroinflammation is another process involved in the pathogenesis of PD. Different biomarkers are used in the diagnosis and prognosis of PD. It has been postulated that calprotectin, which highlights intestinal inflammation and gut barrier injury, may be involved in the aetiology of some neurodegenerative pathologies including PD (3).

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Calprotectin, discovered in early '80s, as an antimicrobial protein via zinc sequestration, represents 60% of cytosolic proteins of neutrophils, and in lower concentration in macrophages and monocytes, being involved in the inflammatory reactions. Calprotectin is detected in both blood and feces, and fecal calprotectin is mainly increased in inflammatory bowel diseases, being considered as a biomarker of disease activity. It is derived from shedding leukocyte into gut lumen, therefore, increasing faecal calprotectin represents intestinal inflammation. Most representative appears to be faecal calprotectin testing, as a biomarker for gut inflammation (4).

Material and Method

Participants, Data Collection and Ethical Statement

We conducted an observational study in the interval of time of 6 months, from 2nd of January 2024 to 1st of July 2024. Participants were recruited from PD patients of Clinical Emergency County Hospital Constanta, Romania, Neurology Clinic. This study was approved by the hospital ethics committee (decision no. 12/29.12.2023). Written informed consent was obtained from all participants for the study enrolment. All patients were selected passing the inclusion criteria and fulfilling the Movement Disorder Society (MDS) clinical diagnostic criteria. Exclusion criteria were gastro-intestinal comorbidities, like acute enterocolitis, inflammatory bowel diseases, colonic cancer, chronic pancreatitis, celiac disease, recent surgical interventions.

All the patients were properly assessed by a neurology physician, and all the data from the personal medical history was collected. For the motor function evaluation, Unified Parkinson's Disease Rating Scale (UPDRS) motor part III scale was applied. (5).

Specimen Collection

Participants collected their own stool samples, from spontaneously emitted stool. Stool samples were processed to measure calprotectin levels by enzyme-linked immunosorbent assay (ELISA) using the commercially available calprotectin ELISA Kit REF EH4140 (produced by FineTest, Wuhan, China) which is intended for the detection of calprotectin molecules in a sample by a sandwich type of the ELISA method with ADALTIS Analyzer—GEN—4 and Victor X4 according to the kits' manufacturer's instructions. The labelled antibody (conjugate) is an animal immunoglobulin fraction conjugated with horseradish peroxidase. Peroxidase activity is determined in the test by a substrate containing TMB. Stool sample extraction was performed using a 980 IU extraction buffer along with 20 mg of stool, stirred for 30 sec and then centrifuged at 2000xg for 10 min using the Thermo Scientific SL16R centrifuge. The dilution of the samples was then performed with a 980 IU of sample buffer and a 20 IU of extraction supernatant.

Statistical Analyses

For the study group we applied descriptive statistical indices and illustrative figures, and we analysed the relationships between variables used inferential statistical methods, including correlation tests to identify significant associations and regression models to determine predictive relationships between variables at a significance level of 0. 05 and 95% confidence interval. Analysis of the data using the software GraphPad Prism version 8.4.3.

The present study may be influenced by bias factors, such as non-homogeneous study group, measurement variability with very high dispersion and the presence of other comorbidities and medications that may bias the results, affecting the validity of the conclusions. Extreme values of measured data were not excluded as they were considered necessary for clinical practice.

Results

Socio-demographic characteristics of the patients

In our study, 30 PD patients were included.

The demographic and paraclinical characteristics are presented in Table 1. The follow-up period was 3 months, 22 patients showed clinical improvement, 7 participants were stable, and 1 patient died.

The mean age of the patients was 64.67 years (SD 12.44). The youngest patient in the PD group was represented by a 22-year-old female who had fecal calprotectin levels of 583.5 µg/ml and originating from an urban area. Among the oldest patients in the PD group, there were two individuals, one male aged 84, rural area, respectively a female 85 years-old, from urban area, with low fecal calprotectin levels< 50 µg/ml.

Table 1. Social and paraclinical characteristics of study cases

Parameter	**Social Data Paraclinical Data**	
Provenience area	Rural	7
	Urban	23
Age - mean		64,67 (12,44)
Gender	Female	18
	Male	12
Fecal Calprotectin (µg/ml) - mean value (SD)		357,31 (331,19)
Fecal Calprotectin - number of cases	<50 µg/ml	10
	50-200 µg/ml	6
	>200 µg/ml	14

Gender representation among patients was nearly equal, with a slight predominance of female patients (18 patients, accounting for 60% of the total PD cases).

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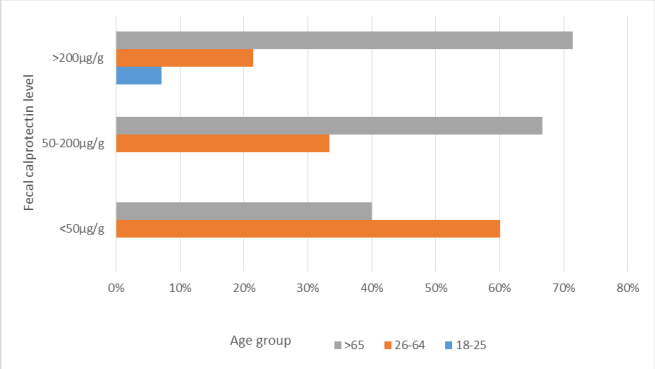
The predominance of urban origin among the enrolled patients is significant: 76.67% (23 patients) were from urban areas, while only 23.33% (7 patients) were from rural areas (Table 1). The location of a hospital in a city may introduce a risk of bias because urban patients have easier access to health services and are therefore more numerous in the study, while rural patients with more difficult access may be under-represented.

Correlations between fecal and serum calprotectin levels in PD patients

The mean fecal calprotectin level was 356.15 µg/g (SD 325.21). When divided by age groups, the highest mean value of fecal calprotectin was observed in the <25 years group (4 patients) (mean value: 517.5 µg/g), followed by the >65 years group (mean value: 388.02 µg/g, SD 376.26), while the 26-64 years group had the lowest mean fecal calprotectin level, but it was very close to that of the >65 years group (326.18 µg/g, SD 319.71).

Figure 1. Distribution of patients by fecal calprotectin level and age group



Most patients with high fecal calprotectin levels (>200 µg/g) were over the age of 60 (Figure 1). From the analysis of the measured fecal calprotectin levels in the PD patients included in the study, the values of calprotectin increased with advancing age (Figure 1).

Analyzing the entire PD group, 33.33% (10 patients) had fecal calprotectin levels <50 µg/g, 20% (6 patients) between 50-200 µg/g, and 46.67% (14 patients) above 200 µg/g.

In the 26-64 years age group, 6/11 patients (54.5%) had fecal calprotectin level< 50 µg/g, while in the >65 years group, 10/18 patients (55.5%) had fecal calprotectin> 200 µg/g (Figure 2).

The regression analysis presented in Figure 3 shows a weak relationship between fecal calprotectin and the UPDRS score in Parkinson's patients, with an R^2 of 0.12, indicating that only ~12.2% of the variation in UPDRS scores is explained by calprotectin levels.

Figure 2. Percentage of patients according to age ranges and measured fecal calprotectin values in the PD patient group

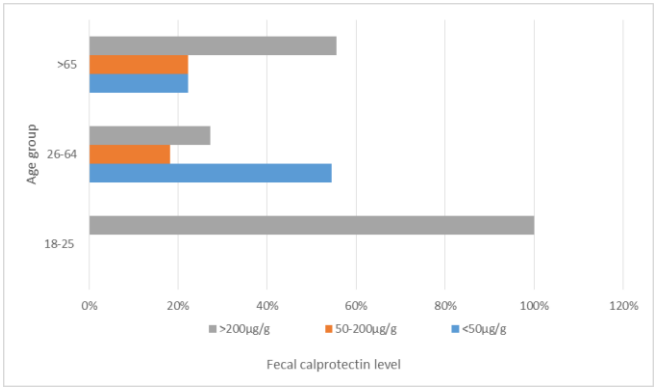
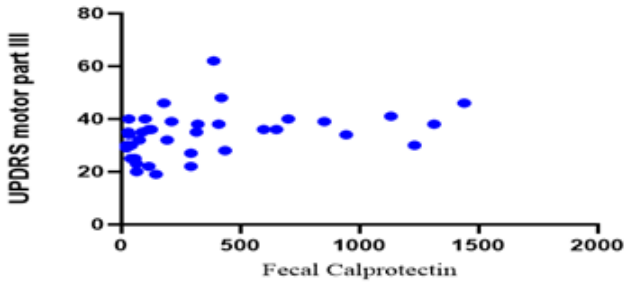


Figure 3. Correlation and regression between fecal calprotectin levels and motor UDRS score part III



The slope is statistically significant (P = 0.03), suggesting a potential association, but the effect size is small (slope = 0.007). Further studies with additional variables and a larger sample size are necessary to draw more definitive conclusions about this correlation. Also, there is no statistically significant correlation between serum calprotectin and UPDRS motor part III submission (α = 0.05).

The results show a weak correlation between fecal calprotectin and UPDRS score in Parkinson's patients with no significant correlation with serum calprotectin. However, calprotectin remains a useful biomarker for intestinal inflammation and systemic inflammatory activity, being significantly correlated with CRP and ESR.

Fecal and serum calprotectin, recognized as key biomarkers in the positive diagnostic of I IBD, are statistically significant correlated with well-known systemic inflammatory markers, including CRP (p = 0.02) and ESR (p = 0.001), whereas with fibrinogen levels no corelations were found.

These correlations underline the utility of calprotectin not only as a sensitive indicator of intestinal inflammation but also as a complementary tool in evaluating systemic inflammatory activity in Parkinson disease.

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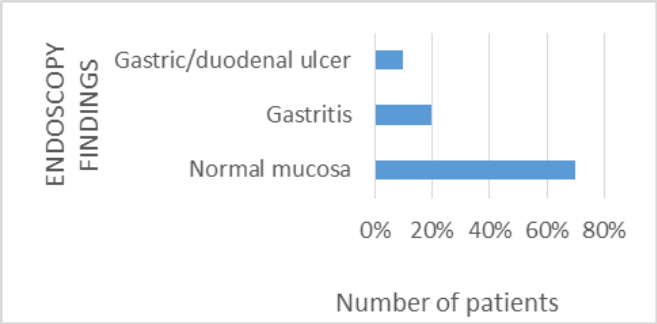
Figure 4. Distribution of PD patients according to endoscopy findings



The correlation of endoscopy with inflammatory bowel disease (IBD) in patients with Parkinson's disease was investigated, resulting in a statistically insignificant p-value. Although the findings do not establish a clear link, they highlight intriguing trends that warrant further study. Larger longitudinal studies are needed to better understand potential common mechanisms or risks. Advanced endoscopic techniques may provide deeper insights in future research. Understanding this correlation could improve patient management and diagnostic strategies.

Discussion

Over time, faecal calprotectin is moderately increased to 50-100 µg/g in patients diagnosed with PD. Research performed by Heinzel et al. showed no associations between fecal calprotectin and initial stages of neurodegenerative diseases (6). A case-control study performed in Poland, compared faecal calprotectin levels obtained from 35 PD patients and 20 healthy controls. The result concluded that fecal calprotectin was increased in 43% of PD patients compared to healthy controls (4).

In recent literature is mentioned another case-control study, in 34 PD patients and 28 controls (group-matched for age), were authors quantitatively analyzed, using enzyme-linked immunosorbent assay (ELISA) kit, calprotectin level, as a faecal marker of intestinal inflammation, along with two other faecal markers for increased intestinal permeability (α-1-antitrypsin and zonulin). They concluded that all the parameters obtained were significantly elevated in PD patients, comparing to the age-matched control-group. The study also shown a correlation between fecal calprotectin levels and PD, with no distribution for severity stages (7).

A recent study compared 77 participants with diagnosed PD, and 113 without PD, and studying dietary habits, faecal metabolome, serum cytokines/chemokines, and intestinal inflammation, and colonic transit time. The results showed that a longer colonic transit was linked to deficits in faecal short-chain-fatty acids outside PD, in individuals associated with tryptophan deficit, linked to higher maltose intake, and benzoic acid deficit, the latest linked to lower caffeine and alcohol intakes (8).

Our study, also conducted on a small sample of 30 patients, identified a similar increase in absolute values of calprotectin with advancing patient age. It is interesting to note that although the diagnostic age for PD is recognized as being predominantly between 60 and 65 years, younger patients were present in our study group.

Another relatively large case-control study, having a cohort of 71 PD patients and 38 patients with multiple system atrophy (MSA), matched with 60 controls without neurological disorders, highlighting the idea that faecal calprotectin levels were also at high levels in both PD and MSA patients comparing to controls. A significant correlation was obtained for fecal calprotectin in elder patients, aged over 61 years, as well with immune blood biomarkers (9).

By now, researchers aim to conclude the importance of microbiota-gut-brain axis as a critical regulator of glial functions, establishing it as a prerequisite for an optimal management for the prevention and treatment of neurodegenerative disorders, including PD and Alzheimer's disease. Gastrointestinal (GI) imbalance and changes in the of the gut microbiota are common in people with Parkinson's disease (PD), but the underlying mechanisms linking the gut microbiome to PD have not been fully elucidated. A study by Sampson et al. (10) demonstrated that "the gut microbiome exerts an influence on α-synuclein pathology, microglial activation and motor deficits in mice that overexpress α-synuclein. Specific-pathogen-free (SPF) ASO mice exhibited a greater prevalence of Parkinson's disease (PD)-related pathologies compared to germ-free (GF) or antibiotic-treated counterparts". Notably, fecal microbiota transplantation (FMT) from PD patients to GF ASO mice restored disease features, including motor dysfunction (11). Additionally, the microbiota dependency in PD models demonstrated that GI dysfunction and motor symptoms occurring after chronic rotenone administration were exclusive to conventionally raised mice, and not observed in germ-free mice. This further substantiates the microbiota's role in PD development (12). All these studies collectively highlight the critical involvement of the microbiota–gut–brain axis in PD pathogenesis, the precise mechanisms remain unclear. A recent study using a comprehensive multi-omics analysis approach found two "novel proteins," SULT1A1 and FDPS, that seem strongly associated with IBD and PD (13).

Current observational studies suggested the existence of associations between variable functional gastrointestinal disorders (FGIDs) and variations in the cerebral cortex and neurodegenerative disorders. The collective insights for the causality of these bidirectional relationship, brain-gut, remains unclear, confounded by anxiety, depression and multiple comorbidities, affecting considerably their quality of life (QoL) (14,15).

Interventional studies targeting specific microbial taxa are needed to determine causality and offering insights into potential therapeutic avenues targeting the gut microbiome.

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Conclusion

PD patients have higher calprotectin levels compared to the general population, but this does not endow this marker with prognostic power for disease progression, as it displays significant variations uncorrelated with the disease evolution stage but rather with advanced age.

Continuously researchers are in progress, pivotal for future health and benefit for these patients, for understanding the unique importance of the microbiota–gut–brain in advancing management for neurodegenerative disorders. The GPs role in patient-centred care for Parkinson's disease remains significant in forming a more nurturing approach for these patients starting from diagnosis and leading to a follow up plan in a multidisciplinary view.

Abreviations

CRP – C-protein reactive
ENT – Otolaryngology
ESR – Erythrocytes sedimentation speed
IBD - Inflammatory Bowel Disease
PD – Parkinson Disease

Conflicts of Interest: none/**Conflict de interese:** nu există

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