Parkinsonism and Related Disorders 15 (2009) 692–696

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Evaluation of gastric emptying in familial and sporadic Parkinson disease☆

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ARTICLE INFO

Article history:
Received 15 November 2008
Received in revised form
27 March 2009
Accepted 11 April 2009

Keywords:
Gastric emptying
Familial
Parkinson disease
Radionuclide imaging

ABSTRACT

Objective: To assess for the presence of gastric dysmotility in familial and sporadic Parkinson disease (PD).

Methods: 10 subjects with familial Parkinson disease (fPD), 35 subjects with sporadic Parkinson disease (sPD), and 15 controls, all from academic tertiary care movement disorders centers, were studied. fPD was defined as the presence of at least 2 affected individuals within 2–3 consecutive generations in a family. Molecular genetic analysis has not revealed, thus far, any known genomic abnormality in these families. Gastric emptying was assessed by dynamic abdominal scintigraphy over 92 min following ingestion of a solid meal containing 99mTc-labeled colloid of 40 MBq activity. The main outcome measures were gastric emptying half-time and radiotracer activity over the gastric area at 46 and at 92 min.

Results: Gastric emptying time was delayed in 60% of subjects with PD. In comparison to mean $t_{1/2}$ of 38 ± 7 min in controls, mean $t_{1/2}$ was 58 ± 25 min in fPD ($p = 0.02$) and 46 ± 25 min in sPD ($p = 0.10$). Both fPD and sPD groups included subjects with delayed gastric emptying at an early stage of disease.

Conclusions: Patients with fPD showed significantly delayed gastric emptying in comparison to normal age-matched individuals. Further studies of gastrointestinal dysfunction in PD, particularly fPD, are warranted.

1. Introduction

Gastrointestinal dysfunction is an important nonmotor manifestation of Parkinson disease (PD) [1–4]. Pooling saliva, pharyngeal or esophageal dysphagia, delayed gastric emptying, constipation and difficulty defecating are common in PD [5–7]. The commonest gastrointestinal disturbance is constipation, which may precede motor signs [8–10].

Several studies have reported reduced gastric motility in PD, up to 100% of individuals with PD may show some gastric emptying abnormality during the course of the disease [7,11–14]. The clinical presentation of delayed gastric emptying is complex and includes erratic absorption of antiparkinsonian drugs with its pharmacokinetic implications.

It is not clear whether impaired gastric emptying only develops in PD patients with advanced disease. Some studies have suggested that gastroparesis increases with PD progression [11,13,14], but others have failed to demonstrate any relationship between gastroparesis and PD duration or severity [12].

It has been shown that familial (fPD) due to mutations in the *α-synuclein* (*SNCA*) and *Parkin* (*PRKN*) genes have different patterns of autonomic involvement [15–17]. To our knowledge, no previous studies have specifically examined, whether or to what degree gastric emptying is impaired in patients with fPD.

Therefore, we investigated gastric emptying in patients with fPD and sporadic PD (sPD) of varying disease duration using abdominal scintigraphy and compared the results to those from a control group.

☆ The review of this paper was entirely handled by the Co-Editor-in-Chief, Ronald Pfeiffer.

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doi:10.1016/j.parkreldis.2009.04.003

2. Methods

The study group comprised 45 subjects, which included 10 subjects with fPD (3 females and 7 males) aged 59.0 ± 8.2 years (range: 49–77 years) and 35 subjects with sPD (13 females and 22 males) aged 60.5 ± 9.9 years (range: 38–78 years). Separation of cases into fPD and sPD group was done retrospectively. The control group included 15 healthy volunteers (6 females and 9 males) aged 59.5 ± 9.7 years (range: 48–76 years) matched by age, sex and body weight. The study population was Caucasian and of Polish extraction. All individuals gave written informed consent, and the study was approved by the Ethics Committee of the Collegium Medicum Jagiellonian University.

The diagnosis of PD was established according to the UK Parkinson's Disease Society Brain Bank criteria (family history was not used as an exclusion criterion). Severity of parkinsonism was assessed using the Hoehn&Yahr scale (H&Y) and Unified Parkinson's Disease Rating Scale (UPDRS). Cognitive dysfunction was evaluated by the Mini Mental State Examination (MMSE). fPD was defined as the presence of at least two affected individuals within 2–3 consecutive generations in a family. In 7 out of 9 families there were 3 or more affected individuals, including 1 family with 10 and 1 family with 7 affected individuals. Families presented with a dominant pattern of disease inheritance, however known genetic causes of PD were excluded. The phenotype of fPD was consistent with typical levodopa-responsive parkinsonism.

Age at onset of symptoms was 37–70 years in fPD and 30–70 years in sPD. Duration of PD was 4–18 years in fPD (mean 8.4 ± 5.2 years) and 2–17 years in sPD (mean 7.1 ± 4.3 years). Duration of PD was defined as the time from the onset of first motor symptom to the time of entry into the study. The clinical features of both groups are presented in Tables 1a and 1b.

All subjects were on levodopa/benserazide therapy and 17 subjects were also treated with amantadine. No subjects were taking dopamine agonists, MAO-B inhibitors, COMT inhibitors, metoclopramide or domperidone. Patients on any concurrent drug treatment that could potentially impair autonomic nervous system function or gastrointestinal motility were excluded from the study. No subject in the study had a history of major gastrointestinal disease, gastrointestinal surgery (except appendectomy), or concomitant gastrointestinal symptoms and diabetes mellitus.

Gastric emptying was estimated by dynamic abdominal scintigraphy started immediately after the complete ingestion of a standardized 200 kcal solid meal containing ^{99m} Tc-labeled colloid of 40 MBq activity. All subjects fasted for at least 8 h prior to the examination, and the time taken to ingest the meal was less than 10 min. Scintigraphy was performed at a rate of 23 images at 4-min intervals for a total of 92 min. Gastric emptying curves were analyzed with the computer program of the gamma-camera ZLC Digitrac 7500 (Siemens, Erlangen, Germany) connected to acquisition station Mirage and processed by ICON computer programming. Mean gastric emptying half-time and mean radiotracer activity over the gastric area at 46 min and at 92 min of the procedure were analyzed for both fPD and sPD group. The same parameters of gastric emptying function were assessed in healthy control subjects and the results were compared to those of the fPD and sPD groups. The results of dynamic gastric scintigraphy performed in an individual with fPD, one with sPD, and in a healthy control subject are presented in Fig. 1.

Molecular genetic analysis was performed in all PD subjects. Genomic DNA was extracted from peripheral blood and prepared according to standard methods. Genetic studies included screening of the *leucine-rich repeat kinase 2* (*LRRK2*) p.G2019S mutation using Taqman chemistry, following the manufacturer's protocol (Applied Biosystem, Foster City, CA), screening of the Lrrk2 p.R1441C/G/H substitutions using a restriction enzyme digest (BstU1 enzyme, New England Biolabs, Ipswich, MA), sequencing of 12 exons and intron–exon boundaries of *PRKN* using Big Dye chemistry (Applied Biosystem, Foster City, CA), and quantitative analysis of *SNCA*, *PTEN-induced kinase 1* (*PINK1*), *PRKN*, *DJ1* with SALSA® MLPA® kit P051, according to the manufacturer's protocol (MRC-Holland, Amsterdam, Netherlands). Spinocerebellar ataxia type 2 (*SCA2*) and spinocerebellar ataxia type 3 (*SCA3*) genes were also screened for trinucleotide repeat expansions.

Statistical analysis of the data was performed using Statistica 5.1 software (StatSoft, Tulsa, OK, USA). All variables were distributed normally and so are presented as mean ± SD. The normal distribution permitted the use of Student's *t*-test for comparisons between groups and Pearson's test to determine possible correlations between tested variables. Gastric emptying in the PD groups was considered abnormal when prolonged more than two standard deviations above the mean value for controls. Calculated p values less than 0.05 were considered statistically significant.

3. Results

Gastric emptying time was delayed in 60% of subjects with PD and was manifested by prolonged gastric emptying half-time or increased gastric retention at 46 or 92 min as compared to data obtained in normal subjects.

When fPD and sPD were examined separately, gastric emptying was found to be delayed in 70% of subjects with fPD and in 55% of subjects with sPD. A statistically significant difference was shown for fPD as compared to controls ($p = 0.02$). In contrast, the differences in gastric emptying time for the sPD group as compared to controls did not reach statistical significance ($p = 0.10$).

In the PD study groups, mean gastric emptying half-time was 58 (range 23–92) min in the individuals with fPD ($fPDt_{½}$) and 46 (range 7–92) min in those with sPD ($sPDt_{½}$), while the normal value established in healthy individuals was only 38 (range 29–46) min. The mean values of radiotracer activity over the gastric area after 46 min of the test were found to be 64% in fPD (range 10–98, $fPD\%_{46min}$), 51% in sPD (range 1–86, $sPD\%_{46min}$) and 43% in controls (range 31–58). The mean values of radiotracer activity over the gastric area after 92 min were 23% in fPD (range 0–89, $fPD\%_{92min}$), 24% in sPD (range 0–81, $sPD\%_{92min}$) and below 10% in controls. Tables 1a, 1b and 2 show the gastric emptying rates for subjects with fDP and sPD as well as for control subjects.

Both fPD and sPD groups included cases of impaired gastric emptying at an early stage of disease as defined by H&Y and UPDRS. Demographics and clinical characteristics are presented in Tables 1a and 1b.

Mutation screening, gene sequencing and dosage analysis did not reveal any known genomic abnormality in fPD or sPD subjects.

4. Disscusion

Using dynamic abdominal scintigraphy we have demonstrated that gastric emptying in fPD is significantly delayed when compared

Table 1a
Clinical data and results of scintigraphy examination in individuals with familial Parkinson disease.

	Sex	Age (years)	H&Y (stage)	Disease duration (years)	Age at onset (years)	Response to l-dopa	$S_{46min[\%]}$ (%)	$S_{92min[\%]}$ (%)	$St_{1/2}$ (min)
1	M	62	I	4	58	+	85	60	92
2	M	49	I	6	43	+	30	6	30
3	M	51	II	14	37	+	86	8	61
4	F	54	II	6	48	+	70	3	57
5	M	66	II	18	48	+	92	31	77
6	F	56	II	9	47	+	68	27	58
7	M	77	II	7	70	+	98	89	92
8	M	55	II/III	4	51	+	79	0	59
9	M	58	II	14	44	+	10	5	35
10	F	62	I	2	60	+	25	0	23
Mean	N/A	59.0	N/A	8.4	50.6	N/A	64	23	58
SD	N/A	8.2	N/A	5.2	9.6	N/A	32	30	25

$S_{46min[\%]}$, radiotracer activity over the gastric area at 46 min; $S_{92min[\%]}$, radiotracer activity over the gastric area at 92 min; $St_{1/2}$, gastric emptying half-time; H&Y, Hoehn&Yahr scale; M, male; F, female; SD, standard deviation; N/A, nonapplicable.