original article

Wien Klin Wochenschr
DOI 10.1007/s00508-015-0731-9

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Exocrine pancreatic insufficiency is not a cause of abdominal complaints in patients with Fabry disease

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Received: 14 August 2014 / Accepted: 19 January 2015

Summary
Background Fabry disease (FD), also called Anderson–Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. Gastrointestinal (GI) symptoms are very common among male and female individuals, although the age of onset is later among female patients. To our best knowledge, exocrine pancreatic insufficiency (EPI) has not yet been studied in patients with FD as a possible cause of abdominal complaints. The aim of our study was to determine whether exocrine pancreatic function is impaired in patients with FD.

Patients and methods We analysed medical records of patients with FD treated in Fabry Center in Slovenj Gradec General Hospital (Slovenian referral centre for FD) by the evaluation of the following features: gender, age, first symptoms before confirmation of FD diagnosis, time interval between first symptoms and diagnosis, therapy and current abdominal complaints. Diagnosis of FD was established by genetic analysis and confirmation of mutation in the α-galactosidase A gene. Faecal elastase-1 (FE-1) measurements were performed using enzyme-linked immunosorbent assay and the commercial kit ScheBo Biotech, Giessen, Germany.

Results There were 28 adult patients (Slovene, Caucasians) with known FD included in the study: 12 male and 16 female; mean age, 45.6 ± 14.3 (range, 19–75) years. Seventeen patients (63 %) were on enzyme replacement therapy (ERT). In seven (25.9 %) patients, abdominal complaints (diarrhoea, bloating and feeling of satiety) were present before introduction of ERT. In three out of these seven patients, abdominal complaints resolved after ERT, and in four patients, they were still occasionally present. FE-1 was normal in all patients (547.9 ± 104.5 μg/g).

Conclusions Our results show that exocrine pancreatic function is normal in all patients with FD and is most likely not a cause of abdominal complaints in this group of patients. Nevertheless, EPI still could not be completely excluded as an aetiology factor for GI problems in patients with FD because all our patients with GI problems were treated with ERT. Therefore, a potential effect of ERT on EPI cannot be excluded. Further studies are necessary to determine the aetiology, especially in the group of naïve male patients.

Keywords Fabry disease · Exocrine · Pancreatic · Insufficiency · Abdominal complaints

Introduction

Fabry disease (FD), also called Anderson–Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. Due to mutation on X-chromosome, there is decreased or absent activity of lysosomal enzyme α-galactosidase A, which leads to accumulation of glycosphingolipids within lysosomes of various cell types [9].

The prevalence of FD is estimated to be in the range from 1:17,000 to 1:117,000 male individuals in Caucasian populations [12, 18, 20]. The prevalence of FD in Slovenia is among the highest in the world and is estimated to be approximately 2/100,000 (46 patients discovered

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Published online: 03 April 2015

in recent years and 39 still alive in the population of 2,000,000 inhabitants).

Early signs and symptoms of FD involve the nervous system, kidneys, heart, skin, eyes and gastrointestinal (GI) tract [9].

GI symptoms are very common among male and female individuals, although the age of onset is later among female patients. According to the data of the Fabry Registry, female individuals with FD frequently have major organ involvement [25].

Most reports of prevalence of GI symptoms among FD patients are based on small cohorts and case reports [7, 8, 13, 19, 21, 22, 24].

In a large cohort of patients, the overall prevalence of GI symptoms was 52 %, with abdominal pain and diarrhoea being most frequent [11].

The pathophysiology of GI symptoms in FD is still not fully elucidated. In the absence of inflammatory activity in the intestine, the most probable causes are dysfunction of enteric neurons, intestinal dysmotility and microvascular changes [11].

To our best knowledge, exocrine pancreatic insufficiency (EPI) has not been evaluated yet in patients with FD as a possible cause of abdominal complaints. The term EPI is defined as the functional limitation of pancreatic enzyme secretion regardless of its cause and could exist in association with pancreatic illnesses (chronic pancreatitis, hereditary pancreatitis, autoimmune pancreatitis, cystic fibrosis, pancreatic carcinoma and diabetes mellitus) or as a concomitant illness (autoimmunopathy, chronic inflammatory bowel diseases, irritable bowel syndrome, viral infections, postoperative abdominal conditions and coeliac disease) [14, 15].

The main clinical consequence of EPI is fat maldigestion and malabsorbtion resulting in steatorrhoea. Other symptoms may also include abdominal pain, flatulence and weight loss. If left untreated, fat maldigestion may lead to low circulating levels of micronutritiens, fat-soluble vitamins and lipoproteins [23].

The aim of our study was to determine whether exocrine pancreatic function is impaired in patients with FD.

Patients and methods

We analysed medical records of patients with FD treated in the Fabry Center of Slovenj Gradec General Hospital (Slovenian referral centre for FD) by the evaluation of the following features: gender, age, first symptoms before confirmation of FD diagnosis, time interval between first symptoms and diagnosis, therapy and current abdominal complaints.

All patients were invited to participate in a single-centre prospective study and gave their written informed consent. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 157/02/12 of 26 March 2012).

Diagnosis of FD was established by genetic analysis and confirmation of mutation in the α-galactosidase A gene.

Faecal elastase-1 (FE-1) measurements were performed using enzyme-linked immunosorbent assay and the commercial kit ScheBo Biotech, Giessen, Germany. The results of FE-1 were presented in μg/g of stool. Levels of >200 μg/g were considered as normal exocrine pancreatic function. Patients sampled a probe of their morning stool into a labelled stool tube that was transported to the central laboratory. In all patients, the stool sample was solid.

Results

There were 28 adult patients (Slovene, Caucasians) with known FD included in the study: 12 male and 16 female; mean age, 45.6 ± 14.3 (range, 19–75) years. Seventeen patients (63 %) were on enzyme replacement therapy (ERT). Mean time between first symptoms and confirmation of diagnosis was 18.4 ± 12.7 (range, 1–45) years. Seven (25.9 %) included patients (all male) were index patients; in all other patients (five male and all female), diagnosis was made by family screening.

In five (18.5 %) patients, first symptoms appeared after confirmation of the diagnosis (mean time, 4.2 years), while eight (29.6 %) patients were still without any symptoms. In seven (25.9 %) patients, abdominal complaints (diarrhoea, bloating and feeling of satiety) were present before the introduction of ERT. In three out of these seven patients, abdominal complaints resolved after ERT, and in four patients, they were still occasionally present (Table 1). There were no patients with abdominal complains who were not receiving ERT. FE-1 was normal in all patients (547.9 ± 104.5 μg/g).

Discussion

Some of the symptoms of EPI are also present in patients with FD, especially abdominal pain and flatulence. Nevertheless, FE-1 level was normal in all presented patients with FD, and therefore EPI was not confirmed. The prevalence of GI symptoms in the presented cohort of FD patients was significantly lower than in previous reports [11, 17]. This difference could be attributed to underreporting of symptoms and possible selection bias. MacDermot et al. [17] reported a prevalence of approximately 70 % in a group of male patients. Gender differences in the prevalence of GI symptoms were already described in patients with FD and also in the general population (more common among female individuals) [1, 3, 11].

Hoffmann et al. [11] performed a study on 342 patients with FD, with 52 % prevalence of GI symptoms. The most common complaints were abdominal pain, diarrhoea, constipation, nausea and vomiting. The most frequently observed combinations in the same study were abdominal pain and diarrhoea, abdominal pain and nausea, and

Table 1 Demographic and clinical features of patients with Fabry disease in whom gastrointestinal symptoms were present at the time of confirmation of diagnosis

Patient number	Gender	Age (years)	Genotype	Interval	Symptoms	Therapy (years)	Current symptoms
1	F	52	pAsn 272 ser	– 2	Bloating, diarrhoea, feeling of satiety	7	Yes
2	M	44	pAsn 272 ser	3	Bloating, diarrhoea, feeling of satiety	10	Yes
3	F	45	pAsn 272 ser	4	Bloating, diarrhoea, feeling of satiety	2	Yes
4	M	51	c.1025G>A	40	Bloating, diarrhoea, feeling of satiety	4	No
5	M	49	Arg 363 Pro	40	Bloating, diarrhoea, feeling of satiety	9	Yes
6	M	48	R227x	1	Bloating, diarrhoea, feeling of satiety	2	No
7	F	74	R227x	1	Bloating, diarrhoea, feeling of satiety	2	No

F female, *M* male, *Interval* interval from first symptoms to confirmation of diagnosis, *Symptoms* gastrointestinal symptoms at the time of diagnosis, *Therapy* duration of enzyme replacement therapy

abdominal pain and constipation. GI symptoms in our group were the same in all patients: bloating, diarrhoea and feeling of satiety (Table 1).

Numerous direct pancreatic function tests were used in the past for diagnosis of EPI, including secretin–pancreozymin test, endoscopic secretin test and Lundh test. Nevertheless, all direct tests were difficult to perform and were limited to a small number of endoscopic centres. In the past 20 years, non-invasive methods have become a gold standard for EPI detection, with FE-1 being most useful. Using direct pancreatic function tests as a reference standard, FE-1 has approximately 100 % sensitivity for severe, 77–100 % for moderate and 63 % for mild EPI, with approximately 93 % of specificity [2, 5, 10, 16].

Use of FE-1 as a diagnostic tool could also be a limitation factor in the study owing to its lower sensitivity for mild and moderate EPI, which is a common problem with all non-invasive diagnostic methods. The use of 13C breath test (even with metoclopramide) is also an unreliable diagnostic tool due to impaired gastric emptying in patients with FD, which can influence test results. Secretin magnetic retrograde cholangiopancreatography, which is already used in a routine clinical practice, could be useful for a definitive determination of pancreatic morphology and exocrine function in patients with FD.

There were no naïve male patients included in the study. All our patients were on ERT at the time of study. In three out of these seven patients, abdominal complaints resolved after ERT, while they were still occasionally present in the remaining four.

Similar positive effects of ERT were already reported in previous studies after 6, 12 and 24 months of follow-up [4, 11], but the mechanisms by which ERT improves GI symptoms are still not fully elucidated. Improvements were particularly noted for abdominal pain and diarrhoea [11].

In summary, GI complaints are a common and probably under-recognised manifestation of FD with abdominal pain and diarrhoea as the leading symptoms. It seems that all symptoms are at least partially responsive to ERT. EPI determined by FE-1 was not found in our patients with FD.

Conclusions

Our results show that exocrine pancreatic function is normal in all patients with FD and is most likely not a cause of abdominal complaints in this group of patients. Nevertheless, EPI still could not be completely excluded as an aetiological factor for GI problems in patients with FD, as all our patients with GI problems were treated with ERT. Therefore, a potential effect of ERT on EPI cannot be excluded. Further studies are necessary to determine the aetiology, especially in the group of naïve male patients.

Contributors

Miroslav Vujasinovic and Bojan Tepes designed the study and drafted the manuscript; Miroslav Vujasinovic, Bojan Vujkovac, Andreja Cokan Vujkovac and Vesna Korat recruited the patients; and Miroslav Vujasinovic, Bojan Tepes, Bojan Vujkovac, Andreja Cokan Vujkovac and Martin Tretjak wrote the manuscript. All authors approved the final version.

Ethics approval

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 157/02/12 of 26 March 2012).

Funding

None.

Conflict of interest

Miroslav Vujasinovic: Lecture fee: Abbott; Bojan Tepes: none; Bojan Vujkovac: member of the European Advisory Board of the Fabry Registry, sponsored by Genzyme, Lecture fee: Genzyme, Shire; Andreja Cokan Vujkovac: Lecture fee: Genzyme, Shire; Martin Tretjak: Lecture fee: Genzyme, Shire; Vesna Korat: Lecture fee: Shire.

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