Review paper

Gullo's syndrome – what do we know?

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Abstract

Benign pancreatic hyperenzymemia (Gullo's syndrome) is characterized by a more than threefold increase of the serum pancreatic enzymes lipase and amylase activity in the absence of any pancreatic disease. Recently, there is an increase in describing cases of Gullo's syndrome in medical literature. Gullo's syndrome is a diagnosis of exclusion, and clinicians should be aware of various other conditions which can cause elevation of pancreatic enzymes. However, the diagnostic pathway should be done with the right accuracy to avoid unnecessary examinations.

A persistent elevation of pancreatic enzymes activity in the absence of any evidence of pancreatic disease is known as benign pancreatic hyperenzymemia (BPH) [1]. The disorder was first described by Gullo in 1996 and since then it has also been called Gullo's syndrome [2]. The proper diagnosis is based on the exclusion of other causes of pancreatic hyperenzymemia that include duodenal ulcer, acute cholecystitis, neoplastic diseases, hypertriglyceridemia, macroamylasemia, virus infection, intestinal infarction, ectopic pregnancy, inflammatory bowel disease, and liver or renal diseases [3, 4]. There are not many cases of this syndrome described in the medical literature [4]. According to some researchers BPH may become the first manifestation of a pancreatic cancer, which involves screening in this group of patients [4, 5]. It is reported to appear in every age, including children [5]. Its frequency is higher in men than women with a ratio of 1.5 to 1 [5]. The diagnosis of Gullo's syndrome is based on the confirmation of increased pancreatic enzymes activity without any available evidence indicating pancreatic disorder, observed for at least 1 year [6]. The pathogenesis of Gullo's syndrome remains unknown [1, 4]. It is believed that there is a cellular defect leading to amylase or lipase outflow into the blood circulation rather than to PE secretion in the duodenum [3, 4, 6]. However, it is only a hypothesis that needs to be proven [6].

Scientists who examine patients with Gullo's syndrome frequently note daily fluctuation of enzyme activity levels [7–9]. Gullo described such day-to-day fluctuations in more than 75% of patients who participated in his research while only 2.4% of them showed normal serum enzyme levels [1]. Some researchers believe that there is a defect in the pathway of pancreatic enzymes from the trans-Golgi network to the cell membrane [1]. This hypothesis assumes that fluctuating behavior depends on the degree of the defect [1]. Mostly, all pancreatic enzymes are elevated while in some cases only one enzyme is elevated [10]. Blood tests as a single tool without abdominal imaging are not recommended for the diagnostic approach to the patient with the suspicion of this disease. At the beginning, the pancreatic disease should be excluded using ultrasonography of the abdomen [11].

However, magnetic resonance cholangio-pancreatography (MRCP) is the preferred diagnostic tool in case of the suspicion of pancreatic ductal system obstruction due to the better visualization of the ducts [11]. Furthermore, endoscopic ultrasonography (EUS) also improves the pancreatic tract imaging in comparison to standard ultrasound scans [11]. Both aforementioned techniques, MRCP and EUS, are useful in the differentiation of organic pancreatic abnormalities with pancreatic hyperenzymemia from BPH [12]. Di Leo *et al.* showed that combining these two methods improves pancreatic imaging in 25% of the patients with pancreatic hyperenzymemia and in 75% of them both examinations

are sufficient to make the proper diagnosis [12]. MRCP and EUS are regarded as the second choice pancreatic imaging and indicated as the confirmation tools for the subgroup of patients with chronic asymptomatic pancreatic hyperenzymemia [13].

About 10 years ago scientists believed that secretin-enhanced MRCP (s-MRCP) was more sensitive than standard MRCP [14]. Nevertheless, results of several studies revealed that s-MRCP showed normal pancreatic morphology in a lower number of patients in comparison with standard MRCP [14]. Amodio *et al.* (2012) analyzed a group of 160 patients and found pancreatic abnormalities in 27.5% of their patients on standard MRCP while the secretin administration helped to reveal pancreatic alterations in 50% of these patients [15]. However, the meta-analysis of 521 patients with pancreatic hyperenzymemia performed by Vanella *et al.* (2019) showed that standard MRCP (contrast-enhanced) can be as effective as s-MRCP and it does not miss important pancreatic pathologies [13]. Amodio *et al.* continued their research in patients with BPH and conducted a 5-year follow-up study using s-MRCP to exclude the development and/or progression of pancreatic disease [16]. They discovered that their initial diagnosis of BPH could be confirmed on s-MRCP imaging in 90% of patients [16]. It shows that secretin-enhanced MRCP is an effective diagnostic method not only in the diagnostic approach, but also in the follow-up of BPH patients.

On the other hand, many researchers emphasize the economic aspect of repeated procedures in order to establish the proper diagnosis of BPH [17, 18]. They admit that due to the fact of the weak awareness, doctors perform too many procedures in this group of patients [17]. Therefore, it seems crucial to establish the BPH diagnosis to avoid additional costs related to unnecessary tests or hospital admissions [19]. The majority of BPH cases present with elevation of both pancreatic enzymes and only in 5% of them can isolated increase of amylase or less frequently lipase be seen [20]. The researchers agree that no matter which enzyme activity is increased, both of them require further investigation [21]. Pezzilli *et al.* described 37 patients with benign pancreatic hyperenzymemia and 3 of them presented with the familial type of the disorder [21]. Gullo *et al.* excluded a possible association between serine protease inhibitor Kazal-type 1 (SPINK1)/serine protease 1 (PRSS1) mutations and benign pancreatic hyperenzymemia [22]. They examined 68 BPH patients and found that only 13% of them had PRSS1 or SPINK1 mutations; i.e. the prevalence was very similar to the healthy population [22].

Currently, no correlations between benign pancreatic hyperenzymemia and other medical conditions are confirmed. However, 1 case of an ulcerative colitis patient with elevated pancreatic enzymes while on azathioprine treatment was reported in the literature and suspected to be Gullo's syndrome [23], although adverse effects of azathioprine should be taken into account in that patient as well. We should always keep in mind that medical awareness of possible patient comorbidities and careful differential diagnosis are extremely important in order to avoid any risk of misinterpretation of results obtained from laboratory tests and diagnostic procedures.

Conflict of interest

The authors declare no conflict of interest.

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