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Communication

Diagnosis and Treatment of Acute Pancreatitis Due to Hypertriglyceridemia in Italy: A Survey among Physicians of the Italian Association for the Study of the Pancreas: A Brief Report

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Abstract: Introduction: The Italian Association for the Study of the Pancreas promoted a survey on exploring the point of view of Italian pancreatologists regarding the diagnosis and the treatment of acute pancreatitis (AP) due to hypertriglyceridemia (HAP). Method: A questionnaire was administered, and it contained four sections regarding epidemiological characteristics of the participants, how the participants arrived at a diagnosis of the disease, how they treated familial hypertriglyceridemia, and whether they knew of the new drugs developed for the treatment of this disease. Definition of AP and HAP: In this survey, all participants followed this definition of AP: The diagnosis of AP requires two of the following three features: abdominal pain consistent with acute pancreatitis (acute onset of a persistent and severe epigastric pain, often radiating to the back); serum pancreatic enzymes at least three times greater than the upper limit of normal; and characteristic findings of acute pancreatitis using imaging techniques. On the other hand, HAP is characterized by serum triglyceride concentration of >1000 mg/dL as the diagnostic cut-off, even though a value of >500 mg/dL has been used for a more inclusive definition, since moderately elevated triglyceride levels have also been suggested as a risk factor for AP. Results. Nine percent of all managed patients with AP had HAP; 5.0 ± 7.7 patients per year had a recurrence of HAP, and the number of recurrences was about one. A diagnosis of hypertriglyceridemia was made by the majority of Italian physicians due to the presence of elevated serum triglycerides at a level of ≥880 mg/dL. Twenty-five physicians treated their patients with fibrates, 23 with statins, 11 with omega-3, one with medium-chain triglycerides, and six with plasmapheresis. Finally, fewer than 50% of the physicians knew of the new drugs to treat dyslipidemia. Conclusions: The results of this survey show that an educational program is important, and we also need an Italian National Registry both for improving knowledge regarding this disease and for identifying the causal factors in our country.

Keywords: acute pancreatitis; hypertriglyceridemia; disease recurrence; therapy

1. Introduction

Hypertriglyceridemia is a rare but well-known cause of acute pancreatitis (AP), and there are no effective therapies, except for familial hyperchylomicronemia [1,2]. There is no clear picture of the etiology of AP in Italy, and, during their Annual Meeting on 19–21 September, 2019, the Italian Association for the Study of the Pancreas promoted a survey to explore the points of view of Italian pancreatologists regarding the diagnosis and the treatment of hypertriglyceridemic AP (HAP).

Definition of acute pancreatitis and hypertriglyceridemic acute pancreatitis: In this survey, all participants followed the definition of acute pancreatitis suggested by the Acute Pancreatitis Classification Working Group [3]. In brief, the diagnosis of AP requires two of the following three

features: abdominal pain consistent with acute pancreatitis (acute onset of a persistent and severe epigastric pain, often radiating to the back); serum pancreatic enzymes (lipase or amylase activity) at least three times greater than the upper limit of normal; and characteristic findings of acute pancreatitis using imaging techniques (contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography). The onset of acute pancreatitis is defined as the time of onset of abdominal pain. Clinically, we recognize three degrees of severity: mild acute pancreatitis characterized by absence of organ failure; moderately severe acute pancreatitis characterized by transient organ failure present for <48 h; severe acute pancreatitis characterized by persistent organ failure, defined as organ failure that persists for >48 h.

Regarding HAP, the disease is characterized by a serum triglyceride concentration of >1000 mg/dL as the diagnostic cut-off, even though a value of >500 mg/dL has been used a more inclusive definition, since moderately elevated triglyceride levels have also been suggested as a risk factor for AP. The pathophysiology of hypertriglyceridemic (HTG)-AP remains unclear, but several mechanisms have been proposed. According to one prominent theory, excess serum triglycerides are hydrolyzed by pancreatic lipase, resulting in the formation of free fatty acids; these cause injury to the acinar cells and pancreatic capillaries, thus determining ischemia and acidosis and contributing to the inflammatory response in AP [4].

2. Methods

A questionnaire was administered to 140 participants, and 39 (27.9%) completed it. Five minutes were needed to complete the questionnaire. Each participant gave written informed consent. The questionnaire was divided into four parts, as reported in Table 1: The first section concerned the epidemiological characteristics of the participants, the second section concerned how the participants arrived at a diagnosis of the disease, the third section concerned how they treated familial hypertriglyceridemia, and the last part concerned whether they knew of the new drugs developed for the treatment of this disease. The data are reported as mean, standard deviation, absolute number, and percentage. The statistical analysis was carried out using the chi-square test. A value of $p < 0.05$ was considered significant. All the data were run on SPSS software (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA).

Table 1. Characteristics of the questionnaire. Five minutes was the time necessary to fill it.

Section	Content	Number of Questions
First section	Epidemiological characteristics of the participants	5
Second section	How the participants made the diagnosis of the disease	4
Third section	How the participants treat the hypertriglyceridemia after an attack of acute pancreatitis	2 with multiple choice
Fourth section	If the participants know of the new drugs developed for the treatment of hypertriglyceridemia	1 with multiple choice

3. Results

The epidemiological characteristics of the evaluated population were the following (Figure 1). More than 90% of the participants were members of Italian Associations come from Northern Italy. The average time since graduation from medical school was (mean ± SD) 15.8 ± 11.7 years (range 1–41 years); 25 of the participants were gastroenterologists (64.1%), 11 were surgeons (28.2%), two were internists and gastroenterologists (5.1%), and one was a geriatrician (2.6%). A total of 21 participants worked in public hospitals and 18 in university hospitals. In the last five years, the number of AP patients managed per year by each physician was 47.4 ± 42.5 (mean ± SD; range 0–200), and 4.4 ± 13.3 (mean ± SD; range 0–80) had patients with HAP. In particular, 9% of all managed patients with AP had HAP; 5.0 ± 7.7 patients per year had a recurrence of HAP (range 0–40), and the number of recurrences was 0.9 ± 0.9 (range 0–3). From a practical point of view, the number of recurrences

seems to be less than those reported in the past considering all the etiologies of acute pancreatitis (27% considering all etiologies [5] vs. 9% in the present study regarding only HAP). A diagnosis of hypertriglyceridemia was made by the majority of Italian physicians (38 out of 39, 97.4%) due to the presence of elevated serum triglycerides; however, whereas the majority of physicians considered a limit of triglycerides of >880 mg/dL useful for diagnosis, two considered this value to be ≥1000 mg/dL and one ≥500 mg/dL. Ten physicians (25.6%) considered plasmatic apolipoprotein B determination to be useful for the diagnosis of HAP, and three (7.7%) also utilized genetic tests. Regarding the treatment (Figure 2), 25 physicians treated their patients with various combinations of fibrates (64.1%), 23 (59.0%) with statins, 11 (28.2%) with omega-3, one (2.6%) with medium-chain triglycerides, and six (15.4%) with plasmapheresis in the acute phase of pancreatitis; the differences among the various drugs utilized were not statistically significant ($p = 0.164$). With respect to the follow-up (Figure 3), five physicians managed the hypertriglyceridemia in their post-HAP patients alone (12.8%), 15 (38.5%) worked with one specialist, 12 (30.8%) with two specialists, five (12.8%) with three specialists, one (2.6%) with four specialists, and one (2.6%) with five specialists ($P < 0.001$). The specialists involved in the follow-up of these patients were gastroenterologists (n = 22), endocrinologists (n = 13), dieticians (n = 9), pancreatologists (n = 6), lipidologists (n = 6), cardiologists (n = 5), and psychologists (n = 2). The final question posed by the questionnaire was whether the physician knew of the new drugs for treating familial hypertriglyceridemia (Figure 4); it was found that fewer than 50% of the physicians (17, 43.6%) knew of one or more of these new drugs: Five knew of the microsomal triglyceride transfer protein (MPT) inhibitor, two (5.1%) knew of the Acyl-CoA:diacylglycerol acyltransferase I (DGAT1) inhibitor, and 14 (35.9%) knew of the antisense inhibitor of apolipoprotein CIII (apoC-III); this difference was statistically significant ($p < 0.001$).

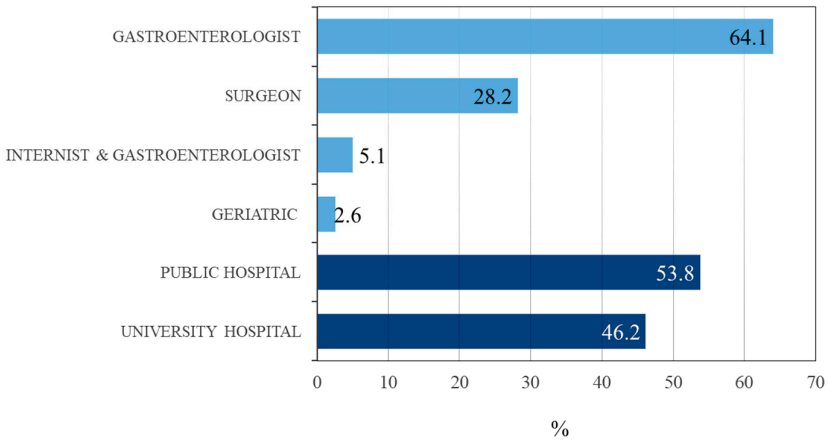

Figure 1. Epidemiological characteristics of the population of physicians evaluated.

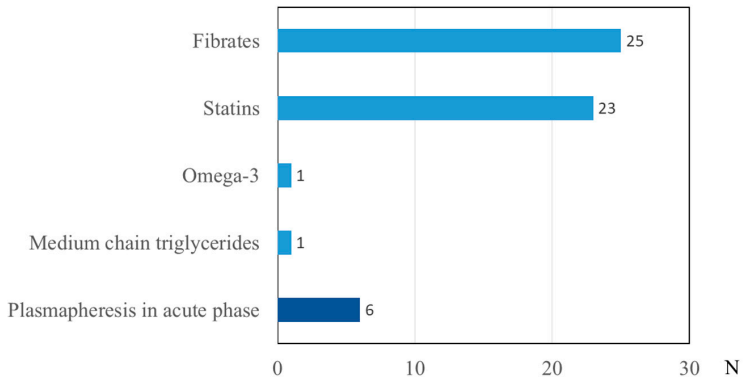

Figure 2. How the Italian physicians treat their patients. They utilized one or various combinations of drugs. The difference among the various drugs utilized is not statistically significant ($p = 0.164$).

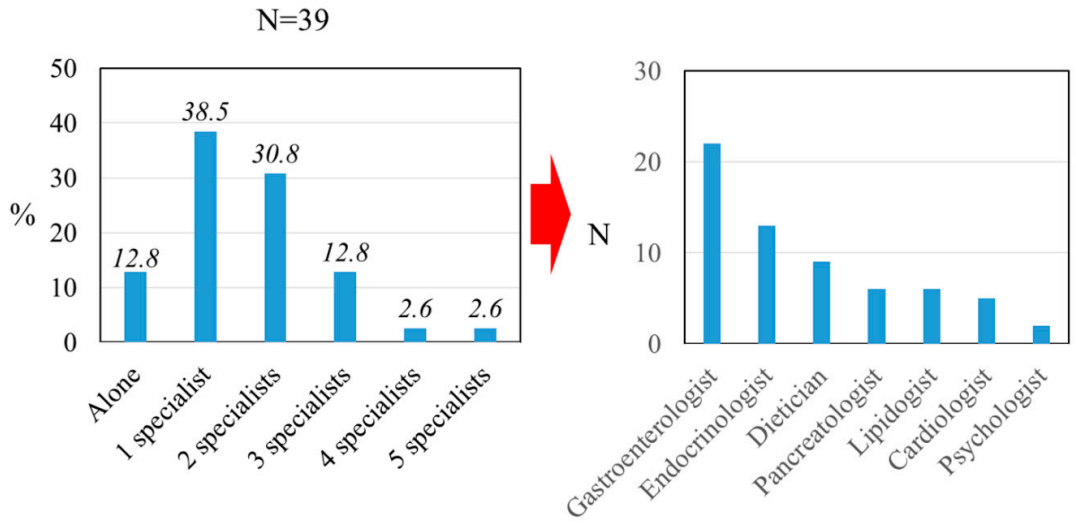

Figure 3. Types of specialists that follow the hypertriglyceridemic patients after the attack of acute pancreatitis.

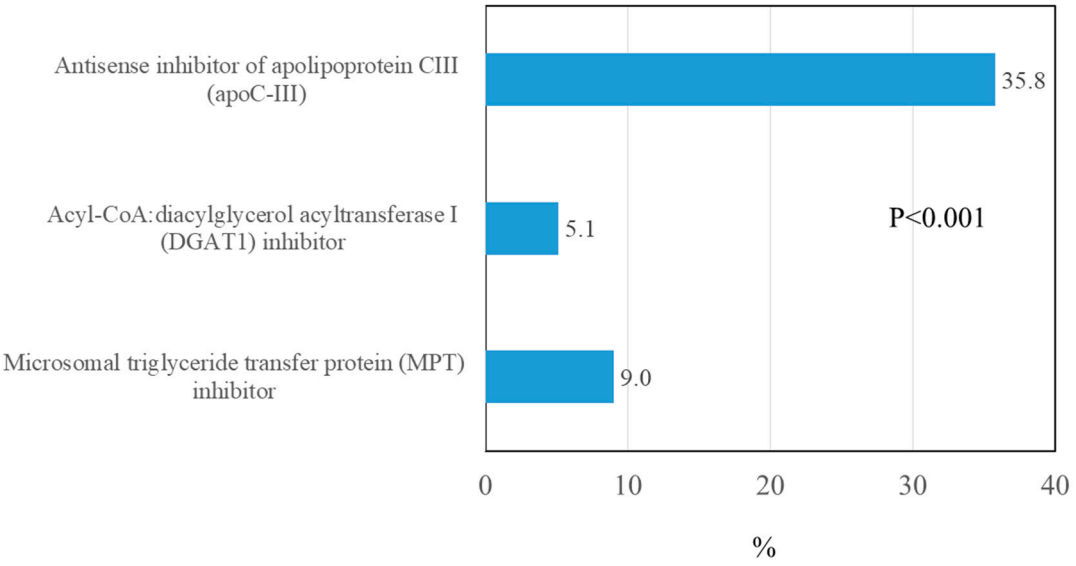

Figure 4. Percentages of knowledge of new drugs for treating hypertriglyceridemia among Italian physicians. Seventeen of the 39 physicians (43.6%) knew of one or more of these new drugs.

4. Discussion

Hypertriglyceridemia is a complex disease, and the etiology may be both genetic (primary hypertriglyceridemia) or due to alimentary factors, which can lead to elevated triglyceride levels in the circulation (secondary hypertriglyceridemia). In about 2% of cases, primary severe hypertriglyceridemia with serum triglycerides equal to or greater than 5.6 mmol/L may arise as a result of autosomal recessive and monogenic familial chylomicronemia syndrome (FCS). However, a majority of severe hypertriglyceridemia cases are multifactorial and have polygenic determinants with additional secondary factors (mixed hypertriglyceridemia). Mild to moderate hypertriglyceridemia cases (2–9.9 mmol/L triglycerides) are similarly polygenic with complex genetic susceptibility [6,7]. Environmental factors, alcohol, positive-energy balanced diet, obesity, non-compensated diabetes mellitus, renal diseases, pregnancy, hypothyroidism, and medications such as estrogens, retinoids, thiazides, and b-blockers are responsible for raised triglyceride levels, with possible interactions with genetic factors [8,9]. Hypertriglyceridemia is a cause of acute pancreatitis [10,11]. The occurrence of AP increases with the increase in triglyceride levels as well as the severity of AP and length of hospitalization, which were

significantly increased by levels of triglycerides; in addition, local complications and organ failure were also significantly increased by increased levels of triglycerides [12]. HAP is important for several reasons: First of all, there is a rising incidence worldwide as a result of increasing obesity-related dyslipidemia [13,14]; secondly, it raises the risk of severe AP and related complications [15–19]; and finally, there is no evidence-based therapy for it [20,21], even though, in the last years, new drugs have been developed for the genetic and non-genetic forms [22]. In Italy, there are no extensive data on HAP, and the Italian Association for the Study of the Pancreas planned a survey involving Italian pancreatologists on this topic.

In Italy, the percentage of acute pancreatitis due to hypertriglyceridemia is similar to that previously reported in international studies [23,24], and the number of AP recurrences is also similar [4,23]. The majority of patients with this disease are correctly identified, but not the presence of hereditary hypertriglyceridemia, since genetic testing is, for the most part, not largely carried out.

Of course, this study has some limitations; first of all, the number of 39 participants is small, even if is indicative of the behavior of Italian physicians; however, in the past, a survey carried out in the United States reported a low incidence of respondents [25]. The second limitation is that in the questionnaire, the age and severity of HAP were been included; finally, for the HAP patients, we did not ask about possible differences in the treatment according to the severity of AP. However, according to the Italian survey on the treatment of acute pancreatitis, differences in treatment of the disease exist [26], and this may have also happened for HAP patients with different severities in the present survey. Regarding the treatment, fewer than 50% of the physicians knew of the new drugs to treat dyslipidemia [27], and the knowledge of drugs did not differ by specialty of the doctors, even if they worked in public hospitals or in university hospitals.

The results of this survey show that an educational program is important in order to improve the treatment of hypertriglyceridemia in patients with AP; an Italian National Registry is important both for improving knowledge regarding this disease and for identifying the causal factors.

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