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Diagnostic algorithm for familial chylomicronemia syndrome

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Abstract

Background: Familial chylomicronemia syndrome (FCS) is a rare genetic disease that leads to severe hypertriglyceridemia often associated with recurrent episodes of pancreatitis. The recognition and correct diagnosis of the disease is challenging due to its rarity, and to the lack of specificity of signs and symptoms. Lipid experts, endocrinologists, gastroenterologists, pancreatologists, and general practitioners may encounter patients who potentially have FCS. Therefore, cooperation between experts and improved knowledge of FCS is essential in improving the diagnosis. Currently, a consensus on best practice for the diagnosis of FCS is lacking.
Methods: Aiming to define a diagnostic algorithm for FCS, a board of European experts was instituted. Such an algorithm for FCS is important to guide practitioners in the diagnosis of suspected FCS and to optimize therapeutic strategies.
Results: The multidisciplinary views were merged, leading to a diagnostic algorithm, proposed here.
Conclusion: This diagnostic algorithm represents a potentially useful tool to support primary and secondary care practitioners in the recognition of signs and clinical manifestations in individuals potentially affected by FCS.

Keywords: Chylomicrons; Familial chylomicronemia syndrome; Hyperlipoproteinemia; Lipoprotein lipase deficiency; Pancreatitis

1. Introduction

1.1. Familial chylomicronemia syndrome

Familial chylomicronemia syndrome (FCS), formerly known as type 1 hyperlipoproteinemia, is a rare (one to two individuals in every million) [1] autosomal recessive monogenic disease caused by mutations in genes that encode for key molecules in the lipolytic cascade. A hallmark of the disease is the abnormal persistence of circulating chylomicrons (CM) following a fasting period of 12−14 h [2].

Mutations in the lipoprotein lipase (LPL) gene account for more than 80% of the cases of FCS reported in literature, and more than 180 mutations have been identified [3]. This specific form of FCS is defined as lipoprotein lipase deficiency (LPLD). The condition has been described in all ethnicities, but there are a few areas of the world in which it is much more common due to a founder effect [4].

The pathophysiology of FCS relies on the lack of a functional LPL protein, a key enzyme in the catabolism of triglyceride-rich lipoproteins, in particular CM and very low density lipoproteins (VLDL), after fat intake [1].

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1.2. Physiological role of lipoprotein lipase and co-factors in the lipolytic cascade

Human LPL is a 475-amino acid enzyme (448 after removal of signal peptide), which is mainly expressed in muscle and in adipose tissue [5]. The hydrolytic action of the enzyme on the triglyceride content of CM and VLDL allows internalization of free fatty acids (FFA) in heart or skeletal muscle for energy production or in adipose tissue for storage.

The maturation and functionality of the enzyme is dependent on a number of co-factors and transport proteins.

Following synthesis, LPL is secreted and is enzymatically active as a homodimer. The formation of homodimers is dependent on lipase maturation factor 1 (LMF1), a membrane protein of the endoplasmic reticulum; in absence of LMF1, LPL is unable to dimerize and is rapidly degraded intracellularly [6].

Once secreted, the enzyme must be transferred to the luminal surface of the endothelium in order to interact with its intravascular substrate [7]. Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) is fundamental in shuttling LPL across the endothelium to the capillary lumen and in keeping the lipase anchored to the endothelium [7] (Fig. 1). The enzyme can be released into the circulation by treatment with heparin [8].

In order to be fully catalytically active, LPL requires binding to a co-factor called apolipoprotein (Apo) C2. The N-terminal portion of LPL is implicated in this binding.

ApoA5 also is involved in the hydrolysis of triglyceride-rich lipoproteins by enhancing LPL activity [9], while other factors such as angiopoietin-like proteins and ApoC3 function as LPL inhibitors [10].

Each of the co-factors and maturation proteins mentioned above are fundamental for the correct function of LPL, and mutations in any of the four genes encoding LMF1, GPIHBP1, ApoC2 and ApoA5 could interfere with correct activity of LPL, leading to FCS and eventually associated clinical manifestations resembling LPLD.

Currently, full gene sequencing of LPL and the four co-factor genes is the preferred method in establishing the diagnosis in patients with suspected FCS [11].

1.3. Familial chylomicronemia syndrome, hypertriglyceridemia and associated risk of pancreatitis

Fasting chylomicronemia is characterized by a fasting plasma triglyceride level of greater than 10 mmol/L, classified as severe hypertriglyceridemia by the European Atherosclerosis Society Consensus Panel [12] (Table 1).

According to the Fredrickson classification of hyperlipidemias [13] (Table 2), disorders in which, primarily, the metabolism of CM is impaired are defined as type I hypertriglyceridemia.

The accumulation of CM is evident in blood samples of LPLD patients, which present as lactescent. To diagnose the presence of CM, the “refrigerator test” can be performed: after overnight storage in the refrigerator, CM float in the blood sample leading to appearance of a creamy supernatant [14].

The high levels of circulating CM can accumulate in specific body locations, such as the skin, producing eruptive xanthomas, or in the retinal blood vessel, a manifestation called lipemia retinalis.

The most life-threatening complication of FCS is the occurrence of severe and recurrent episodes of acute pancreatitis.

Pancreatitis is associated with overall mortality rates of 5–6%, which can rise up to 30% in subgroups with severe complications (pancreatic necrosis in association with infected abscesses or persistent multiple organ failure) [15,16].

Patients affected by chylomicronemia due to LPLD are at much greater risk of pancreatitis compared with subjects with hypertriglyceridemia caused by other conditions, suggesting a direct correlation between accumulation of CM and pancreatitis (Fig. 2).

The mechanism underlying the greater risk of pancreatitis in patients with FCS is thought to be associated with the accumulation of CM in the pancreatic capillaries, resulting in lipolysis by the pancreatic lipase. Subsequent accumulation of FFA in the acinar cells may cause direct cytotoxicity. Formation of microthrombi, ischemia and tissue necrosis are events that further contribute to trigger the acute pancreatitis [18]. The hypoxic process explains the high frequency of severe necrotic pancreatitis.

FCS is often poorly recognized in the primary-care setting, because of the rarity of the condition. Due to the heterogeneity of signs and symptoms, patients are often referred to different specialists.

Lipidologists and endocrinologists are first in line in the recognition and management of FCS patients because of severe and uncontrolled hypertriglyceridemia. Pancreatologists and gastroenterologists have the possibility to encounter patients in the event of acute pancreatitis attacks. Collaboration and cooperation between different medical specialties is essential in order to improve diagnosis. This is important since the increased understanding of the molecular basis of familial chylomicronemia has led to the development of targeted therapies.

1.4. Current and future therapeutic options

The mainstay for management of FCS is a diet severely restricted in fat content (20–25 g/day). Long-term compliance with such a diet is extremely difficult to maintain, negatively impacts on patients’ quality of life and does not mitigate the high risk of pancreatitis in all subjects [17,19]. Traditional lipid-lowering agents such as fibrates and omega-3 are usually only marginally effective in these patients [16].

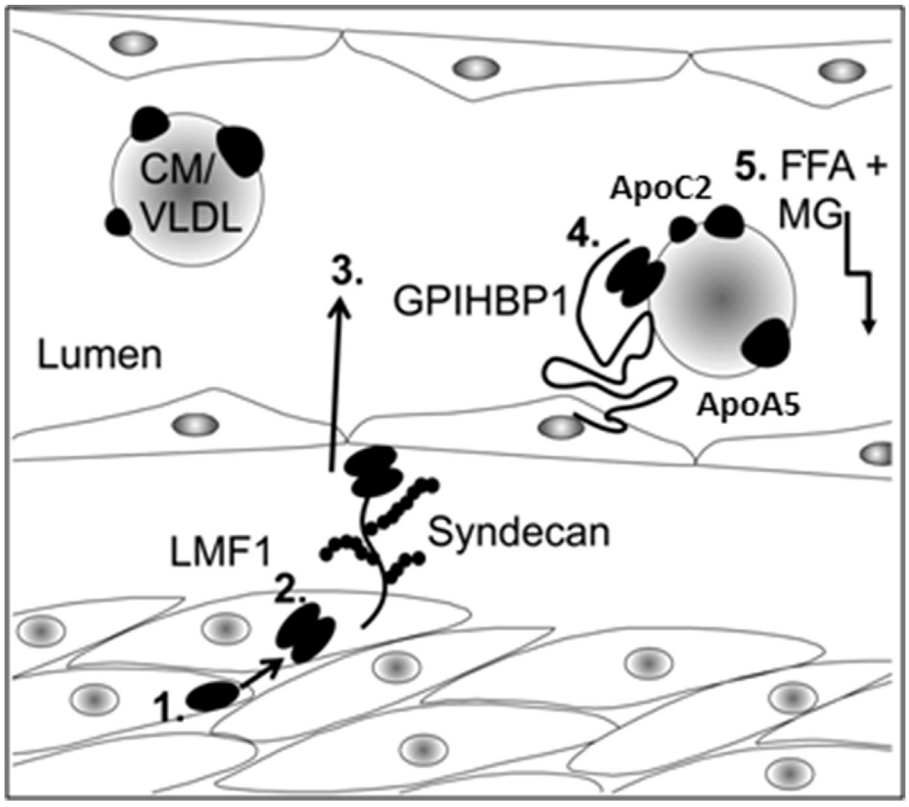

Fig. 1. Lipoprotein lipase (LPL) is synthesized in the intracellular environment of adipose and muscle cells (1); lipase maturation factor 1 (LMF) guarantees correct homodimerization of LPL (2); glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) is involved in the shuttling of LPL in the lumen of the capillaries (3); LPL is anchored to the capillary endothelium where it hydrolyzes the triglyceride content of chylomicrons (CM) and very low density lipoproteins (VLDL) (4); hydrolyzed free fatty acids (FFA) and monoglycerides (MG) are able to be transported inside myocytes or adipocytes where they are used for energy production or lipid storage (5).

In 2012, the European Medicines Agency approved alipogene tiparvovec (AAV1-LPLS447X gene therapy), the first gene therapy medicinal product in the Western world, for treatment of adult LPLD patients with severe or recurrent pancreatitis [20,21].

Several other pharmacological agents (ie, microsomal triglyceride transfer protein (MTTP) and diacylglycerol acyltransferase 1 (DGAT1) inhibitors, antisense oligonucleotides directed against APOC3 and ANGPTL3 mRNAs) currently in development may also contribute to the successful treatment of FCS in the near future [2].

A first step towards an improvement in FCS diagnosis is the implementation of a diagnostic algorithm.

Such an algorithm proposes how to diagnose a patient with suspected FCS. Following the return of a positive result with the algorithm, the patient should be referred for genetic screening in order to confirm the molecular diagnosis.

A proposed diagnostic algorithm is shown in Fig. 3.

Table 1
Classification of hypertriglyceridemia. Adapted from Hegele et al. [12].

	Plasma triglyceride concentration (mmol/L)
Normal	<1.7
Hypertriglyceridemia	1.7–9.9
Severe hypertriglyceridemia	≥10

2. Patient presentation

LPLD subjects can present with a variety of symptoms such as eruptive xanthomas, lipemia retinalis, hepatosplenomegaly and acute or recurrent episodes of abdominal pain or pancreatitis [1]. Symptom onset, as typically seen in monogenic disorders, is usually during

Table 2
Fredrickson classification [13].

Fredrickson phenotypes		
Phenotype	Elevated lipoprotein	Elevated lipid
I	CM	TG and TC
V	CM and VLDL	TG and TC
IV	VLDL	TG and normal-moderate increases in TC
III	Floating β-lipoproteins	TG and TC
IIb	LDL and VLDL	TG and TC
IIa	LDL	TC

CM, chylomicrons; *LDL*, low density lipoprotein; *TC*, total cholesterol; *TG*, triglyceride; *VLDL*, very low density lipoprotein.

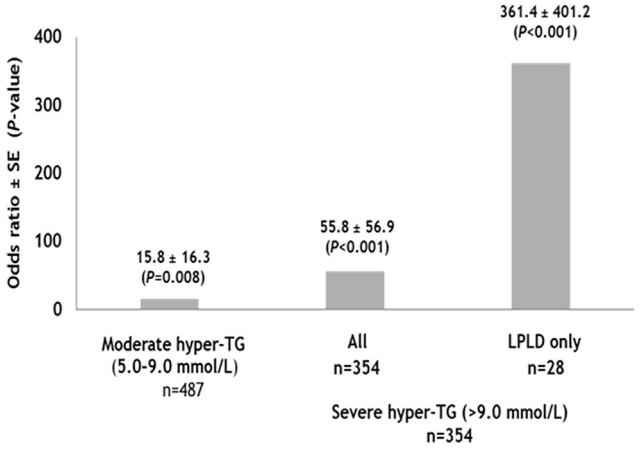

Fig. 2. Risk of pancreatitis in the lipoprotein lipase deficient population. Adapted from Gaudet et al. [16]. LPLD = lipoprotein lipase deficiency; TG = triglyceridemia.

childhood or adolescence [12]. Eruptive xanthomas, generally present on buttocks, shoulders and extensor surfaces of extremities, represent an inflammatory response to the accumulation of lipids in tissues and are noted in about one-third of all LPLD patients. In lipemia retinalis, retinal vessels appear whitened on fundoscopy, but vision is not impaired. Hepatosplenomegaly is due to the infiltration of macrophages in response to CM deposition [22]. Although acute pancreatitis is the most serious clinical manifestation of LPLD, it is known that not all patients suffer from pancreatitis events; indeed, it has been estimated that pancreatitis rates in this patient population range from 50 to 80% [3]. Absence of a history of pancreatitis should not exclude the suspicion of LPLD, if other signs or symptoms are indicative.

From a biochemical point of view, LPLD patients can be readily identified. Fasting blood samples from patients with chylomicronemia have a lactescence appearance, presenting with a white CM layer that floats above the other plasma components after chilling overnight. Subjects are affected by severe hypertriglyceridemia (above 10 mmol/L in the fasting state).

Because the etiology is genetic, fasting triglyceride levels remain extremely elevated at different timepoints; finding of severe hypertriglyceridemia in three consecutive samplings should raise the suspicion of a genetic disease.

A ratio of total triglycerides to total cholesterol (TG/TC) above 2.2 (if measured in mmol/L) or above 5 (in mg/dL) clearly indicates a high level of circulating CM and VLDL; the ratio depends on the VLDL proportion and on the size of circulating CM. Differential diagnosis of other conditions known to increase triglyceride levels, such as polygenic combined hyperlipidemia (pCH), needs to be considered. Patients affected by pCH present with high levels of triglycerides and LDL-cholesterol, related to increased plasma levels of apolipoprotein B 100 (apoB) [23]. Determination of apoB is one of the best diagnostic and prognostic factors for pCH [23–25]. pCH subjects present with apoB levels above 120 mg/dL, while subjects affected by familial chylomicronemia have low to normal levels of the apolipoprotein (<100 mg/dL). Therefore, measurement of apoB represents a relevant and simple biochemical parameter for determining a differential diagnosis between these two metabolic disorders. The ApoB app, currently available for free on Google Play, allows doctors to identify which particles are elevated by assigning total cholesterol, triglyceride and apoB levels. This allows reliable distinction between VLDL particles, remnant particles (dysbeta) and CM (LPLD).

Many different secondary factors can contribute to high levels of circulating triglycerides; in the process of assessing a metabolic genetic disorder, it is important to exclude all concomitant agents and activities that may contribute to hypertriglyceridemia, such as alcohol abuse and obesity.

During pregnancy, triglyceride levels may rise in healthy subjects, but pregnancy is not a condition that should exclude further investigation to find the root cause of hypertriglyceridemia as LPLD patients are often first suspected during pregnancy [26], especially during the last trimester.

LPLD patients show very poor or absent response to therapy with traditional lipid-lowering agents. A three-month trial of fibrates and omega-3 is a pragmatic method to confirm the suspicion of a genetic disorder.

2.1. Hypertriglyceridemia-related pancreatitis

LPLD subjects suffering from acute pancreatitis can also be identified in the emergency setting.

The most frequent causes of acute pancreatitis are alcohol abuse and gall stone disease, which account for 80% of the total events [18]. Severe hypertriglyceridemia is a well-established cause of acute pancreatitis, alleged to account for 10% of pancreatitis episodes [16]. It has been assessed that in these rare cases, the high concentration of circulating CM triggers the acute pancreatitis event [27].

Diagnosis of acute pancreatitis can be established where there is an increase of more than three times the upper limit of normal in serum lipase activity with associated pancreatic pain.

Imaging techniques, in particular computerized tomography (CT) scanning, are needed in confirming the diagnosis and assessing the severity of the event. If the patient is admitted a few days after pain onset, serum lipase could return to basal levels, in which case the CT scan is essential in confirming the diagnosis.

An attack of acute pancreatitis should be considered severe if it is associated with failure of at least one organ or if tissue necrosis is present, in accordance with the revised Atlanta classification [28] and based on the CT severity index score as reported by Balthazar et al. [29] (Balthazar score >4). Presence of 10–20% necrosis is suggestive of a severe attack.

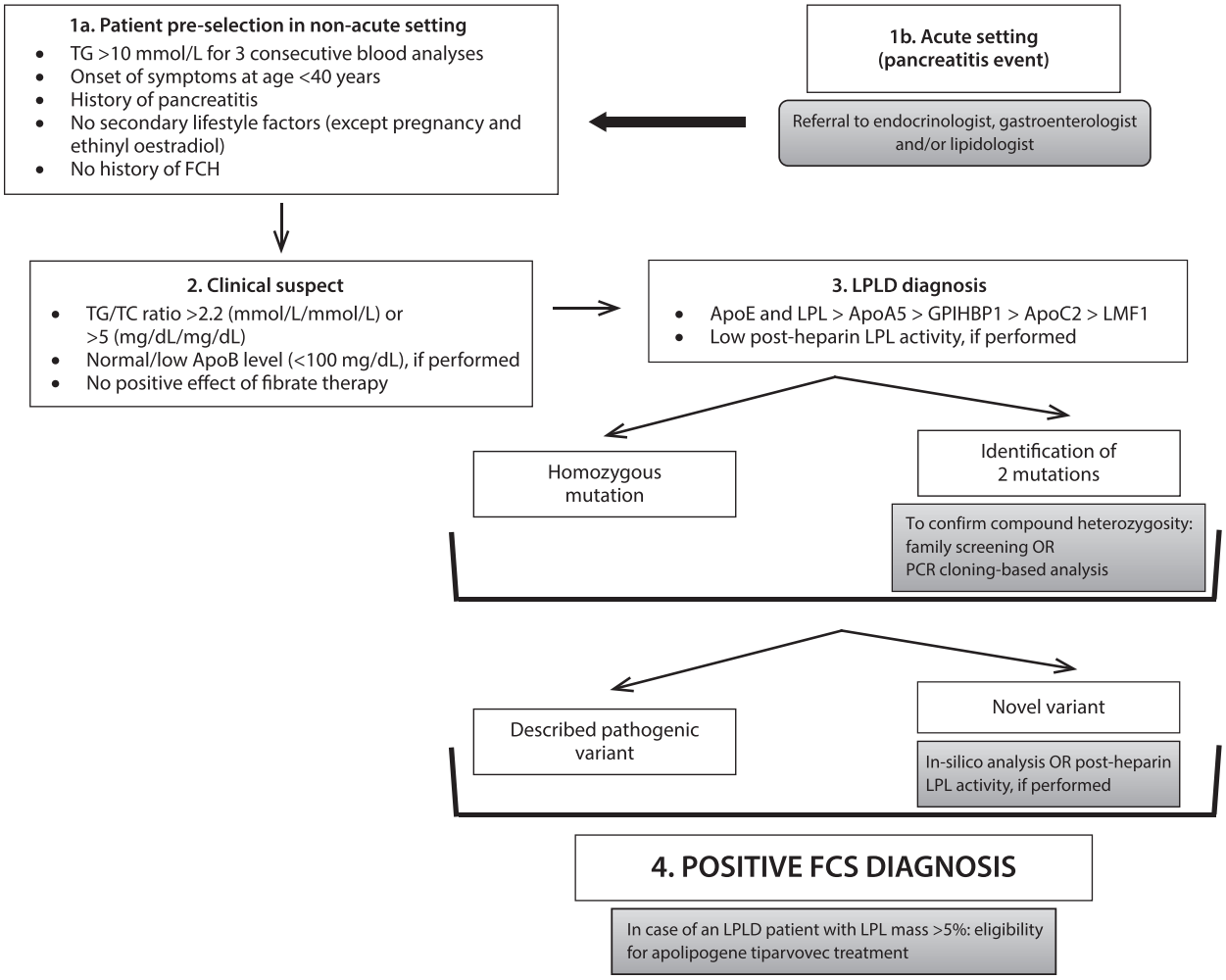

Fig. 3. Algorithm for diagnosis of familial chylomicronemia syndrome.

The task of a pancreatologist treating patients admitted to the emergency room is management of the acute event; once the event is resolved, the cause of the attack should be investigated. FCS diagnosis in the acute setting is difficult to establish. Confounding factors such as alcohol consumption and diabetes may overlap with FCS suspicion.

Exclusion of alcohol abuse and biliary diseases, and the presence of high fasting triglyceride levels are suggestive elements of a metabolic disorder.

If an acute attack of hypertriglyceridemic pancreatitis is confirmed and is not associated with secondary factors, it is important to refer the patient to a lipids expert for further assessment. In the acute phase, it is advised to consider plasmapheresis to acutely lower triglyceride and CM levels, although randomized trials showing improved outcome following plasmapheresis are lacking [30]. In two to three sessions, triglyceride levels can usually be reduced to below 10 mmol/L. In view of the absence of triglyceride-lipolysis, the fasting state should be maintained during the acute phase in order to avoid additional triglyceride elevation.

Referral to a lipids expert, once the event of pancreatitis has resolved, will allow the clinician to investigate the patient's clinical and biochemical presentation according to the mentioned criteria, as long as plasma triglyceride has been measured in the acute phase.

3. Confirmation of LPLD diagnosis

Once the patient is considered possibly affected by LPLD, a fundamental step to establish a correct diagnosis is genetic analysis.

LPLD is the most common cause of familial chylomicronemia; other causes include the deficit of ApoA5, GPIHBP1, ApoC2 and LMF1 [3]. These four proteins are important co-factors of LPL; if any are mutated and dysfunctional, the lipolytic cascade of triglyceride-rich lipoproteins could be compromised, leading to chylomicronemia [31], and disease manifestation undistinguishable from that seen in LPLD.

Full gene sequencing of LPL and of the four additional genes is advised and represents the gold standard to precisely

determine which mutated protein forms the basis of the metabolic disorder. To exclude transitory decompensation of dysbetalipoproteinemia, which may also present with severe hypertriglyceridemia, ApoE sequencing can be considered. In contrast to LPLD, dysbetalipoproteinemia usually only manifests itself later in life. Furthermore, precipitating factors (such as decompensated diabetes, weight gain, new medications, etc) are usually detectable.

In the case of more than one mutation in one of the candidate genes being present, a family screening or a PCR-cloning based analysis is necessary in order to assess simple or compound heterozygosity.

In the case of mutations in the LPL gene, two studies are available to support clinicians and geneticists in assessing pathogenicity of the identified variants: details of mutations along with a mutation map of the causative genes are described in the Western Database of Lipid Variants [32] and a second classification is available based on screening performed with a microarray LPL chip [11].

Novel LPL mutations are continuously being discovered, and the test of LPL activity can be useful to assess pathogenicity of previously undescribed variants. Here, post-heparin patient plasma is exposed to a VLDL substrate prepared using normolipidemic human serum, avoiding the requirement for sonication, radioactive or fluorescent substrates. The liberated free fatty acids are then assayed and LPL activity is expressed as micromoles of fatty acids released per minute per liter (μmol/l/min) of plasma [33]. Carriers of pathogenic mutations either in LPL or in its co-factors will show severely reduced or undetectable LPL activity.

Additionally, in-silico analysis, which allows computer simulation of the mutated protein, is a general approach supportive of pathogenicity determination in the five genes.

4. Conclusion

LPLD is an extremely rare and under-recognized metabolic disorder characterized by hyperchylomicronemia which is associated with an increased risk of clinical complications [26]. The most debilitating clinical manifestation of the disease is recurrent, potentially life-threatening acute pancreatitis. Pancreatitis correlates with significant morbidity and mortality in up to 20−30% of patients, impacting on health-related quality of life and placing a significant economic burden on healthcare systems [16].

Due to the heterogeneity of symptoms and comorbidities that may affect FCS patients, different medical specialists may encounter these patients. For this reason it is important to improve collaboration and referral among different clinical departments.

The diagnostic algorithm proposed here represents a potentially useful tool to support primary and secondary care practitioners in the recognition of signs and clinical manifestations in individuals potentially affected by FCS.

Conflict of interest

MA has received honoraria from Amgen, Chiesi, Astra Zeneca, MSD, Sanofi, Mediolanum and Alexion for consulting in advisory boards.

J-ML has received honoraria from Mylan/Abbott for lecturing and from Chiesi for participating in the advisory board mentioned in this manuscript.

PM has received honoraria from Chiesi/UniQure, paid to his university for participating in the advisory board mentioned in this manuscript. He has received honoraria for presentations, advisory board activities and/or research support by Aegerion, Amgen, MSD, Novartis, Regeneron, Sanofi. KGP has received honoraria for presentations, advisory board activities, data monitoring committee activities and/or research support by Aegerion, Amgen, Berlin-Chemie, Chiesi, Fresenius, Genzyme, Isis, Kaneka, Kowa, MSD, Novartis, Pfizer, Regeneron, Roche and Sanofi.

VR has received honoraria from Chiesi for participating in the advisory board mentioned in this manuscript.

ES has received (non-significant) honoraria from Amgen, Sanofi, Merck and Chiesi for lecturing.

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