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Challenges in familial chylomicronemia syndrome diagnosis and management across Latin American countries: An expert panel discussion

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Abstract: Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by extremely high triglyceride levels due to impaired clearance of chylomicrons from plasma. This paper is the result of a panel discussion with Latin American specialists who raised the main issues on diagnosis and management of FCS in their countries. Overall FCS is diagnosed late on the course of the disease, is characterized by heterogeneity on the occurrence of pancreatitis, and remains a long time in care of different specialists until reaching a lipidologist. Pancreatitis and secondary diabetes are frequently seen,

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often due to late diagnosis and inadequate care. Molecular diagnosis is unusual; however, loss of function variants on the lipoprotein lipase gene are apparently the most frequent etiology. A founder effect of the glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 gene has been described in the northeast of Brazil. Low awareness of the disease amongst health professionals contributes to inadequate care and an inadequate patient journey.
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Introduction

Chylomicronemia syndrome (CS) is a term used to describe individuals presenting severe hypertriglyceridemia (HTG) due to accumulation of chylomicrons in the fasting state.[1] This syndrome most often results from a cluster of minor genetic variants that causes polygenic hypertriglyceridemia, which may be exacerbated by conditions or medications that increase triglyceride levels beyond the saturation point of the triglyceride removal system. Such cases are termed multifactorial chylomicronemia syndrome (MCS).[2] Another condition that also presents very high triglyceride levels is familial chylomicronemia syndrome (FCS). FCS is a rare autosomal recessive disorder characterized by impaired clearance of chylomicrons from plasma due to defects on triglyceride lipolysis. FCS is usually caused by loss of function variants in both alleles of the lipoprotein lipase (*LPL*) gene, leading to non-function or very low LPL activity. Less frequently, the phenotype is caused by monogenic variants in the genes that modulate LPL function that include but are not limited to apolipoprotein C2 (*APOC2),* apolipoprotein A5 *(APOA5),* glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (*GPIHBP1)* and lipase maturation factor 1 (*LMF1).*[1,3] Accumulation of chylomicrons in plasma leads to hypertriglyceridemia that may reach values of several thousands of mg/dL and may cause episodes of eruptive xanthomata and acute pancreatitis.[2–4]

FCS has an estimated population frequency of 1 person per 700,000 to one million (1) and frequently goes underdiagnosed.[1–3] However, as FCS can lead to critical conditions including death from acute hemorrhagic pancreatitis,[4] the timely and correct differential diagnosis is of paramount importance. The adequate diagnosis of these syndromes has important management and prognostic implications since FCS is refractory to standard pharmacological lipid lowering therapies and responds only to severe dietary fat restriction.

To discuss this important clinical condition, a group of Latin American experts from Argentina, Brazil, Chile, Colombia, and Ecuador, gathered on a virtual meeting on September 17, 2020, to discuss the challenges of FCS diagnosis and management in the region. The main points raised by the experts are summarized in this paper.

Dr. Santos (Chairman, Brazil): FCS diagnosis usually occurs late in life due to the heterogeneity of its clinical phenotype presentation, making it difficult to accurately diagnose the condition. In this sense, what is your experience and perception about patients with persistent unresponsive hypertriglyceridemia already been seen by different clinicians, some of them experiencing several episodes of pancreatitis before being referred to your site?

Dr. Nogueira (Argentina): In my experience, patients are diagnosed around the age of 30 or 40, sometimes at age 20. Common features amongst them are cutaneous lesions, neurological and cognitive impairment, and poor quality of life. Pancreatitis is not necessarily always present though it is a serious complication.

Dr. Aimone (Argentina): I can confirm that before reaching our center, patients have already been seen by several doctors and are only referred after non-responsiveness to various treatments. Some have triglyceride (TG) levels of 800–900 mg/dL, present cutaneous lesions, highly lipemic serum, or long-term complaints of abdominal pain but have not had a more serious event yet. I have seen two siblings with the same TG level, one that already had several episodes of pancreatitis and a sister with no manifestations at all. However, she carries a different genetic variant from her brother.

Dr. Santos (Brazil): High TG levels non-responsive to current therapies are always the "entrance door". Cutaneous lesions are also very usual in these patients.

Dr. Lorenzatti (Argentina): I have a patient that had several episodes of pancreatitis, actually, more than 15, and very poor quality of life who was referred to my clinic due to unresponsiveness to therapy, and this is a key point. Her sister, 10 years younger than her, had TG levels of 1000–1500 mg/dL but never had a pancreatitis episode. Another patient of mine, a medical student, was referred by an endocrinologist after attending a lecture on FCS. This case stresses the need to raise awareness among clinicians. Being a rare disease, patients are not correctly and early diagnosed because the possibility of FCS is simply not suspected.

Dr. Izar (Brazil): I receive different types of patients, from newborns whose serum has been found to be lipemic - and this is the most severe clinical presentation - to patients with multiple pancreatitis episodes and no eruptive xanthoma, and adults with TG levels of 8000 mg/dl. We have treated a pair of siblings that, despite highly elevated TG levels, have never had a pancreatitis episode, although pancreas atrophy has been demonstrated by magnetic resonance imaging. He has prediabetes, while his sister has developed type 2 diabetes. It's worthwhile to mention that their parents are cousins. In general, patients are diagnosed at 20–25 years of age and are only referred after been seen by different primary care physicians. These two patients had confirmation of homozygosity for *LPL* loss of function variant (c.644G > *A*, leading to a substitution of a glycine-to-glutamate in codon 215

[p.Gly215Glu]), predicted as pathogenic by in silico analysis.

Dr. Santos (Brazil): Indeed, the disease is highly heterogeneous in its clinical presentation, and pancreatitis has uncertain correlation with TG levels which makes FCS a complex disease.

Dr. Lima (Brazil): I have data from families with specific types of variants, 17 patients with TG levels > 1000 mg/dL, mean age 42 years, 64% female, 50% with type 2 diabetes, mean TG level of 1058 mg/dL and very low HDL-cholesterol levels, as expected. From those 17:

- 8 with confirmed variant for *LPL*;
- 1 has *LPL* variant but heterozygote;
- 2 with *GPIHBP1* variants;
- Almost 50% have had pancreatitis, one patient presented more than 30 episodes (currently TG levels of 800–900 mg/dL).

Other colleagues that also have patients with *GPIHBP1* variants and I have found a novel homozygous mutation in intron 2 of the *GPIHBP1* gene not previously described in the literature.[6] The population consists of:

- 12 patients (9 women);
- Mean age 21 years: the youngest patient was a baby diagnosed at 6 months of age and the oldest one at age 48;
- Most of the patients are from the northeastern region of Brazil;
- 50% have a history of consanguinity, that increases the chance of homozygous variants;
- 30% have already had pancreatitis episodes;
- 30% present eruptive xanthoma;
- Median TG levels: 2669 mg/dL but some with levels as high as 40,141 mg/dL;
- Very low levels of HDL-cholesterol: mean 17.5 mg/dL (3.8–41 mg/dl);
- Mean total cholesterol: 396 mg/dL (200–1763 mg/dL);
- Body mass index: 22.7 ± 3.3 kg/m2.

According to the recommendations of the Human Genome Variation Society the new variant was named c.182–1G > *T* and this novel *GPIHBP1* pathogenic intronic mutation suggests the occurrence of a founder effect.[6]

Dr. Santos (Brazil): Do these patients have insulin-dependent type 2 diabetes mellitus (T2DM) due to pancreas involvement? It's common to see T2DM and chylomicronemia and sometimes it's difficult to know what comes first.

Dr. Lima (Brazil): Diabetes is usually secondary to pancreatitis. I tried to establish a correlation to see if diabetes patients had higher TG levels than non-diabetic ones, but my sample was too small to demonstrate a statistically significant difference. Also we could not associate diabetes with pancreatitis or cutaneous xanthomas.

Patients also have pancreatic exocrine insufficiency, and this characteristic correlates with pancreatitis episodes: the more episodes, higher the chance of developing exocrine insufficiency. I estimate that percentage of patients is < 50%.

Dr. Lourenço (Brazil): As a geneticist, all my patients have been diagnosed at a young age, usually before 1 year old. My oldest patient is currently 9 years old. All of them have *LPL* variants. The major difficulty is to achieve metabolic control in children.

Dr. Santos (Brazil): How about Colombia and Chile?

Dr. Alonso (Chile): In my experience, I have seen 3 patients with FCS (2 women and 1 man), all of them between 20 and 30 years old by the time of the diagnosis. Two women were from outside the country, and the man had been recently diagnosed in Santiago. All cases with severe hypertriglyceridemia and recurrent pancreatitis, and poor quality of life due to restrictions in diet. Genetic diagnosis was positive in the 3 cases. None of them developed diabetes mellitus. I remember another interesting case of a young girl who debuted with hyperchylomicronemia, but the functional study did not show *LPL* deficiency. She developed antibodies in the context of systemic lupus erythematosus. In general, FCS is not suspected by doctors and genetic diagnosis is not performed in the country.

Dr. Ruiz (Colombia): In my opinion, the disease may not be that rare. And I think the problem is unawareness of the disease and late referral. I can recall a young man, 28 years old, completely asymptomatic, normal physical examination but TG of 1800 mg/dL. His only complaint was abdominal pain since he was a child but that never bothered him enough to make him see a doctor. Genetic test showed an *LPL* variant. The other case is a 14-year-old boy referred due to xanthomata and abdominal pain with TG of 3000 mg/dL, who developed pancreatitis subsequently. In my opinion, increasing awareness is of utmost importance so clinicians will at least raise the hypothesis of FCS when seeing a patient with hypertriglyceridemia.

Dr. Colón (Colombia): I completely agree that there is a lack of awareness of the disease. Disease spectrum is wide, and doctors do not suspect it, even in patients with recurrent pancreatitis. I have a patient who developed symptoms at 40 years but was correctly diagnosed only at 60 years. No one suspected it could be FCS despite recurrent episodes of pancreatitis. I also have two patients referred to me because of diabetes, but they were FCS patients as genetic tests confirmed *LPL* variants. Even though one of them suffered 14 episodes of pancreatitis in one year, no doctor considered the hypothesis of being FCS. Even specialists don't recognize the disease despite patients matching all scores for FCS. But personally, I do not think that scores are helpful in diagnosing the condition.

Dr. Vargas (Colombia): I have 4 cases, 3 men and 1 woman. All presented initially with severe pancreatitis, none with T2DM. One reached TG levels of 8700 mg/dL. Unfortunately, I have no possibility to perform genetic tests because they are not available in my region.

Dr. Garay (Ecuador): A 37-year-old patient was referred for liver transplantation due to hepatosplenomegaly, thrombocytopenia, TG of 1700 mg/dL, abdominal pain and had a genetically confirmed *LPL* variant. His-sister (35 years old) had died of pancreatitis 2 years ago. The patient himself had

suffered 14 pancreatitis episodes and no one suspected FCS. Despite being an ultra-orphan disease, it is also undervalued.

Dr. Santos (Brazil): We think that frequency of FCS is 1 in 1 million people, but in fact it may be more frequent bearing in mind that frequency of severe HTG is higher than FCS obviously. The paper by Hegele et al.[5] shows that approximately 30% of people have high TG but only 0.1% have severe HTG. When severe HTG is present there is a possibility of being a monogenic autosomal recessive heritage. Another situation is heterozygote with a high polygenic score associated with an inadequate lifestyle.

Dr. Santos (Brazil): Regarding the genetic profile, what kind of patients do you see more often?

Dr. Izar (Brazil): I have patients with heterozygous variants (*GPIHBP1* gene), but the clinical picture is of the monogenic form, with very high TG levels, 2000 mg/dL and even 4000 mg/dL, associated with diabetes mellitus, not its severe form, and under insulin therapy. I have many other patients with these characteristics, not all of them genetically tested. Of those who have been tested, we found variants in heterozygosis in *LMNA*, another in *CAV1* characterizing partial lipodystrophies; one with 2 variants in the gene that causes cystic fibrosis (*CFTR*) and one homozygous for *AGPAT2* (1-acyl-sn-glycerol-3-phosphate acyltransferase beta), characterizing the Berardinelli-Seip Syndrome. Therefore, genetic testing is crucial for ruling out other causes of chylomicronemia.

Dr. Lourenço (Brazil): There are cases of heterozygosis that are not heterozygotes - this occurs because there are deeper intronic variants or variants that modify the transcription or some intragenic variants. I've reviewed all published cases within the last 5 years, and so far, there are no known cases of intragenic deletion though we know they exist. Another possibility is uniparental disomy when the patient carries an allele in duplicate and appears as heterozygote. Other alterations are possible, but within the last 5 years, only one gene has been discovered, and I expect that with NGS (New Generation Sequencing), we'll discover more genes in other areas. For example, comparing chylomicronemia with genetic epilepsy with intellectual deficiency and other genetic diseases, no new genes have been discovered as in those other areas. This means it might be possible that there are no new genes left to be discovered. We've been performing exome sequencing in patients with intellectual disability, with genetic syndromes still not diagnosed and I'm really astonished with the number of patients that are heterozygotes for familial hypercholesterolemia (FH). Tests were not performed aiming to diagnose FH but we found this alteration in epilepsy, and patients are also heterozygotes for *LPL* and have mild TG increase.

Dr. Corral (Argentina): When you perform exome sequencing, many variants will appear making you suspect they are the cause of the phenotype.

Dr. Santos (Brazil): Which definition of severe and extremely severe hypertriglyceridemia is adopted in your country?

Dr. Garay (Ecuador): According to the Endocrine Society, a biochemical value greater than 1000 mg/dL would be classified as severe HTG. The European Atherosclerosis Society considers values greater than 880 mg/dL (10 mmol/L). And in my country, both values serve as a definition of severe hypertriglyceridemia. And for very severe, the value to be considered is greater than 2000 mg/dL.

Dr. Izar (Brazil): Severe HTG $>$ 500 mg/dL and extremely severe $>$ 1000 mg/dL.

Dr. Alonso (Chile): in Chile, severe HTG is defined as $>$ 500 mg/dL.

Dr. Santos (Brazil): Considering the genes involved in FCS etiology - *LPL*, *APOA5*, *APOC2*, *LMF1*, *GPIHBP1* - what kind of variant is most common in your countries?

Dr. Lourenço (Brazil): Literature describes many variants (nonsense, frameshift, duplication/deletion), but in Brazil some of them predominate. In small children, the 3 commonest variants are all missense. Nonsense variants causes a premature interruption of protein production; frameshift variant modifies protein reading; insertion/deletion do the same. The most complex variant is missense variant with VUS (variant of uncertain significance). It is necessary to prove segregation, to look at regions genetically preserved and use programs to predict pathogenicity.

Dr. Santos (Brazil): There's a Roundtable discussion by Drs Brown, Hegele and Gaudet published in the Journal of Clinical Lipidology[7] describing that in 147 subjects with FCS due to null variants on *LPL,* 45% of the relatives that were heterozygotes for the same defect presented with a Type IV phenotype. This suggests that in half of these heterozygous patients LPL is rate-limiting for triglyceride clearance.

Dr. Izar (Brazil): If there is a variant of susceptibility associated to the defect in a heterozygote, this magnifies the clinical condition.

Dr. Lourenço (Brazil): Parents of our missense variant patients do not exhibit a significant increase in TG, but parents of the heterozygotes for nonsense or with frameshift variants do have increased TG levels. It is possible to say that heterozygotes with only missense variants show $>$ 40–50% of enzyme function; however, for heterozygotes with nonsense or frameshift variant, enzyme functionality is lower, around 20–30% only.

Dr. Colón (Colombia): My patients have missense variants.

Dr. Lima (Brazil): I have a patient with an intronic variant in *GPIHBP1* between exon 2 and 3 in the receptive part of the splice, which is not common, exhibiting a severe phenotype.

Dr. Santos (Brazil): How is FCS managed in your country?

We all agree that a hallmark of FCS is non-responsiveness to fibrates. Nonetheless, most of us prescribe this class of drugs and argue that the rationale is to establish a differential diagnosis with MCS. Plasmapheresis is controversial, its effect persists only for a few days, and there is no published data comparing it to fasting. Currently the only effective approach in patients with FCS is a very restrictive low-

fat diet (< 15% of total calories) and supplementation with fat-soluble vitamins.

Dr. Lottenberg (Brazil): Which is very hard to follow as a long-term treatment. Patients' adherence to a very low-fat diet (< 10% of total caloric intake) is a challenging issue. And just to clarify, medium chain triglycerides (MCT) are used only to supplement calories, and bear in mind that coconut oil is not MCT. MCT is formed only with caproic (C6), caprylic (C8) and capric (C10) fatty acids, that are not transported in the chylomicron particle. Patients are also advised not to consume sugar and alcoholic beverages. The intake of fat-soluble vitamins and essential fatty acids (omega-6 and omega-3) should be monitored.

The experts concluded that FCS is a disease of significant heterogeneity in symptoms and evolution, the most prevalent feature being extremely high levels of TG, leading to abdominal pain and recurrent pancreatitis episodes, as well as cutaneous xanthomatosis and neurological/cognitive symptoms. The age of diagnosis in Latin American patients is widely variable. Patients are most commonly diagnosed in adulthood after being evaluated by many doctors, meaning that there might be a large number of undiagnosed patients yet.

Major challenges in all LA countries include creating awareness of the disease amongst primary care physicians who first see these patients, early referral to sites that can proceed with genetic tests to confirm the diagnosis, difficulty in following a very restricted fat diet, and hopefully the introduction of an effective pharmacological therapy in the near future.

Declaration of Competing Interest

RDS received honoraria related to speaker activities, consulting or research from Abbott, Aché, AstraZeneca, Amgen, EMS, Esperion Therapeutics, Getz Pharma, Kowa, Merck & Co, MSD, Novo Nordisk, Novartis, Pfizer, PTC Therapeutics and Sanofi-Aventis.

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PC received honoraria related to consulting activities from Amgen, Sanofi, PTC Therapeutics and Boehringer Ingelheim.

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