The Burden of Illness in Patients with Familial Chylomicronemia Syndrome (FCS) in the United Kingdom

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Abstract

Background: Familial chylomicronemia syndrome (FCS) is a rare genetic disorder associated with a deficiency in lipoprotein lipase activity, which is characterized by severe hypertriglyceridemia, recurrent abdominal pain and episodes of acute pancreatitis. Investigation of Findings and Observations Captured in Burden of Illness Survey in FCS Patients (IN-FOCUS) assessed the impact of FCS on patient quality of life (QoL) and quantified the burden of illness attributable to FCS for 166 patients in 10 countries. Given the lack of data to support value-based treatment of FCS in the United Kingdom (UK), a prespecified sub analysis of respondents from the UK was performed to evaluate country-specific experiences for patients with FCS and any associated outcomes. **Methods:** A web-based survey captured information on diagnostic experience, symptoms, comorbidities, disease management, and impact on multiple life dimensions from adults living with FCS. **Results:** Twenty respondents from the UK completed the survey. Three-quarters indicated that FCS limits their life and significant time and energy is required to manage their FCS. Respondents reported moderate physical symptoms 1–3 times every 2 weeks, all respondents reported worrying about their FCS getting worse with age and 85% worrying about the long-term impact of FCS on their health. Only 3 respondents (15%) reported working full-time, 53% of respondents reported that their diminished employment was largely or entirely due to FCS. Furthermore, 90% of respondents reported restricting their dietary fat consumption to an extreme degree and 75% reported using fasting to help manage the symptoms of FCS, suggesting a level of overcompensation. Only one of five women reported a pregnancy. The UK data was largely consistent with the overall study, except for an increased prevalence of worry and differences in disease management. **Conclusions:** FCS is associated with an ongoing physical and emotional burden that negatively impacts QoL for patients in the UK. Attempts to self-manage FCS may increase the burden of disease. Results from the UK sub analysis are consistent with the overall cohort of IN-FOCUS in suggesting that increased disease awareness and improved management strategies for FCS are required.

Background

Familial chylomicronemia syndrome (FCS) is a serious, rare, genetic disease that results in severely elevated (>10 mmol/L) plasma triglycerides (TG) that are carried primarily in chylomicrons (Brahm and Hegele 2015). Plasma TG accumulate in chylomicrons, causing chylomicronemia, due to a functional deficiency in lipoprotein lipase (LPL), the enzyme that mediates lipolysis of plasma TG and other TG-Rich lipoproteins (Brahm and Hegele, 2015). FCS is caused by mutations in either the gene encoding the LPL enzyme or mutations in genes that encode for other proteins necessary for LPL to function properly (Surendran et al. 2012).

The physical manifestations of FCS include mild to incapacitating recurrent abdominal pain, eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly (Burnett et al. 2017). The most severe clinical outcome for patients with FCS is recurrent, acute pancreatitis that can become chronic. No approved treatment currently exists for FCS and standard treatments (fibrates, fish oils, niacin, statins) to lower plasma TGs are largely ineffective because their effectiveness depends, at least in part, on a functional LPL enzyme, which is deficient in patients with FCS (Brahm and Hegele, 2015). The only management strategy currently available is an extremely restrictive low-fat diet that limits fat intake to 15% of total daily calories, strict avoidance of alcohol and medication known to increase triglyceride levels such as oral contraceptives (Gaudet et al. 2014; Burnett et al. 2017). Eighty (Gelrud et al. 2017) to over 90% (Davidson et al. 2018) of patients with FCS report this diet is extremely difficult to follow and maintain and 90% (Gelrud et al. 2017) report episodes of abdominal pain and recurrent pancreatitis despite strict dietary adherence.

In addition to the clinical symptoms of FCS, patients with FCS report cognitive, emotional and psychosocial manifestations of their disease, which were recently reported in the analysis of an online survey of 166 patients with FCS, known as the Investigation of Findings and Observations Captured in Burden of Illness Survey in FCS Patients (IN-FOCUS) (Davidson et al. 2018). The most common cognitive symptoms experienced were difficulty concentrating (18%), brain fog (17%), forgetfulness (10%), impaired judgement (8%) and memory (8%). The emotional symptoms most commonly reported were constant worry about having pain or acute pancreatitis (34%), anxiety/fear/worry about their health (26%) and meal planning (20%), embarrassment due to always thinking about and planning food (20%) and feeling sad/down/blue/depressed (18%). Psychosocial symptoms reported were anxiety/fear/worry in social situations – food related (17%) and feelings of social withdrawal or isolation (13%). All these factors contribute to the decreased quality of life (QoL) reported by these (Davidson et al. 2018) and other studies (Gelrud et al. 2017; Davidson et al. 2018) of patients with FCS.

Reports of social isolation are common among people with rare diseases (Bogart and Irvin, 2017) and concerning because people without social connections potentially have both a lower QoL (Tehrani et al. 2011) and a higher rate of mortality than people with a social network (House et al. 1988). Connecting patients with FCS to FCS support groups and resources improved the QoL of FCS patients and their caregivers (Salvatore et al. 2018).

The IN-FOCUS study was the first study of 166 patients with FCS across 10 countries designed to quantify the impact of FCS on patient QoL. Past QoL studies among patients with rare conditions have highlighted the potential for distinct country-specific outcomes (Forestier-Zhang et al. 2016; Lopez-Bastida et al. 2016). Because the United Kingdom (UK) has made managing rare disorders a priority (Health DO, 2012), we conducted this pre-specified sub-analysis of IN-FOCUS to provide UK-specific data on the impact of FCS on QoL to inform future treatments for FCS patients in the UK.

Methods

Study design

A comprehensive description of the study methods has been previously published (Davidson et al. 2017) and are briefly described here. IN-FOCUS was a global, web-based survey used to gather demographic information about the self-reported experiences of patients with FCS using established assessment methodologies. Data were collected between 24 June 2016 and 24 February 2017. A pre-specified sub-analysis was completed to ascertain symptom presentation, disease progression and corresponding effects on the lives of patients with FCS in the UK.

Patients

Patients with FCS were recruited using flyers, word of mouth (physician referral and patient support group postings), and social media as described previously (Davidson et al. 2017). Upon initial login to the web-based questionnaire, respondents completed a series of screening questions to confirm their eligibility to participate as per the following four inclusion criteria previously reported (Davidson et al. 2017): 1) patients were age ≥ 18 years; 2) diagnosed with FCS, Fredrickson type I hyperlipoproteinemia, lipoprotein lipase deficiency, or high TG combined with a history of pancreatitis or high TG with a history of severe abdominal pain requiring hospitalization; 3) fasting TGs ≥ 8.4 mmol/L (750 mg/dL) in the most recent fasting TG test or fasting TG < 8.4 mmol/L in the most recent fasting TG test with self-reported diet management to minimize fat content, and 4) no participation in a clinical trial for investigational FCS treatment(s) in the previous 6 months. Additionally, respondents had to satisfy one of the following: 1) a history of TG-induced acute pancreatitis or recurrent abdominal pain requiring emergency department

visit/hospitalization due to high TG levels, in the absence of another cause; 3) a family history compatible with FCS or Fredrickson type I hyperlipoproteinemia, in the absence of another known cause; or 4) genetic diagnosis consistent with FCS.

Ethical approval was provided by National Health Services (NHS) Research Ethics Committee for respondents in the UK.

Data analysis and presentation

Continuous variables, including rating scales, were analyzed descriptively and are presented either as means with standard deviations, or medians with ranges. Comparisons were made between UK patients and the overall IN-FOCUS survey population. Categorical variables were analyzed as frequencies and percentage of occurrence for each category. IBM SPSS statistics 22 (Armonk, NY) was used to conduct all analyses.

Results

Respondent demographics

Twenty respondents from the UK completed the survey. UK participants were predominately male (75%) with a median age of 32 years (range: 19–53 years) (Table 1). Patients reported the median age of FCS diagnosis was 8 years (range: 2–17 years) and 80% of respondents were diagnosed with FCS prior to age 10 years (Table 1). In agreement with the young age of diagnosis, respondents reported beginning to utilize dietary management strategies in adolescence. All but one respondent reported TG values greater than 8.4 mmol/L at the time of diagnosis and 35% had TG levels above this value at their most recent test, despite multiple management strategies.

Experience with health care professionals (HCPs)

Participants reported seeing a mean of four HCPs regarding their symptoms prior to receiving a diagnosis of FCS (Table 1). Of the 12 respondents who could recall their diagnosing physician, pediatricians were the most common diagnosing HCP (Fig 1a), followed by endocrinologists (n=3), and lipid specialists (n=2). Four respondents (20%) reported that their symptoms were initially misdiagnosed as either acute pancreatitis (n=2), stomach pain (n=1) or mental retardation (n=1). These misdiagnoses were by primary care physicians (n=2) and an ER doctor (n=1); the fourth patient could not recall this information.

Eighty-five percent of respondents (n=13) reported their FCS is currently managed by a pancreas specialist (30%), endocrinologist (35%), or lipid specialist (20%) (Figure 1b). Seventy percent of patients reported they were satisfied with current HCP management of their FCS (Figure 1c). Obtaining a knowledgeable and dependable HCP to manage their FCS is critical for these patients because 86% of patients reportedly receive information regarding FCS from their managing HCP.

Symptoms of FCS

Participants reported experiencing a median of four symptoms of FCS at any one time, regardless of the severity of their symptoms at the time (Table 2). Physical symptoms of moderate severity, 1–3 times every 2 weeks, were reported as typical and included generalized abdominal pain, indigestion, fatigue and lack of appetite (Table 2). Emotional symptoms of FCS related to anxiety, fear and/or worry were reported by the respondents as typically occurring with moderate severity once or twice weekly, while other emotional symptoms may present once or twice

monthly (Table 2). The most pervasive emotional symptom was constant uncertainty regarding an attack of pain/acute pancreatitis at any time which was reported by five (25%) respondents each. Cognitive symptoms most frequently reported in both severe and typical periods was impaired judgment (n=3, 15%). During severe periods, patients reported similar symptoms to those experienced during typical periods, but slightly less frequent and of much greater severity (Table 2).

Comorbidities and Acute Pancreatitis

All respondents had been diagnosed with at least one FCS-related comorbidities (Figure 2a,b), including nine respondents (45%) who had experienced FCS-related acute pancreatitis. Respondents reported an average of one episode of acute pancreatitis in the preceding 12 months and 13 episodes during their lifetime. All respondents who reported acute pancreatitis required hospitalization for at least one of their episodes and one patient was readmitted within 30 days of being discharged for acute pancreatitis. Amongst the nine patients hospitalized for acute pancreatitis, the mean length of stay was 4 nights, with one patient staying 8 nights. The second most reported comorbidity (n=6, 30%) was a physician diagnosed eating disorder and FCS-related diabetes was also reported by three (15%) respondents.

Management of FCS

Respondents reported that they employ a median of five strategies for managing symptoms of FCS (Figure 3). Ninety percent (n=18) of respondents reported following an extremely low-fat diet, adhering to a maximum reported daily fat intake of 25g (mean = 22g). However, only 55% of respondents reported also reducing their consumption of carbohydrates and 50% completely abstain from consuming alcohol. Fifteen (75%) respondents reported using fasting to help manage the symptoms of FCS, seven of whom reported fasting routinely. Use of TG-lowering medications was reported by 40% of respondents. The strategies for managing FCS can be extremely challenging to maintain and may not alleviate symptoms. Three-quarters of respondents (n=15) reported that significant time and energy is required to manage their FCS and despite strict compliance to this rigid management strategy, 40% of respondents continue to experience symptoms (Figure 4). Anxiety, fear, or worry due to health concerns and food preparation and management were also reported by 20% of respondents in varying degrees of severity (Table 2).

Impact on Employment Status and Career Selection

FCS impacted respondents' employment status, career selection, and work place productivity. Thirteen (65%) respondents reported being employed, but only three had a full-time position (15%) (Figure 5a). Of the 14 UK respondents who were unemployed, or employed part time, at least 50% reported it was largely due to their FCS and only 2 respondents reported that FCS had no impact on their employment status (Figure 5b).

Eighteen (90%) respondents believe that FCS has impacted their career choices (Figure 5c). Respondents reported they cannot pursue a career that involves travel (83%) or that their ideal career is prohibitive to adhering to their strict diet (78%). Twelve (67%) of these respondents indicated they can only do their job effectively on "good days" and a feeling of forced under employment due to FCS was reported by seven out of the 13 (62%) respondents in paid employment. Nine out of 13 respondents (69%) in paid employment also reported requiring a mean 15 days off work in the preceding 12 months due to FCS-related issues.

Impact on Outlook and Social Engagement

The extremely restrictive nature of the management strategies makes it difficult to interact socially with friends, colleagues, and family. Respondents reported that their current management strategy impacts their ability to entertain at their home, be spontaneous, or travel. Additionally, the unique nature of FCS and its management strategies causes stress for respondents' families and is challenging to explain to social and professional acquaintances. (Figure 6).

FCS had a negative impact on the emotional and mental well-being of many respondents. FCS was considered to be a major stressor by 70% of respondents (Figure 7). Sixty five percent of respondents also reported that FCS has significant impact on their feeling of self-worth (Figure 7). Combined, these factors severely detract from the mental well-being of patients with FCS as reported by 55% of respondents (Figure 7).

Respondents in the UK had a higher prevalence of concern about the progression of their FCS with age, compared to the global study. All respondents reported worrying about their FCS getting worse with age and 85% worry about the long-term ramifications of FCS on their health (Figure 8). FCS also had an impact on the decision to have children, or how many to have, with 10 respondents reporting the decision was influenced by their FCS. One of the five female respondents reported a pregnancy and even though she was diagnosed at the age of 2 was unaware of the complications associated with FCS.

Discussion

The UK subanalysis of the IN-FOCUS study was consistent with the findings of the global IN-FOCUS study analyses (Davidson et al. 2018), showing that patients with FCS face a vast array of physical, emotional and cognitive symptoms that impact healthcare resource utilization, while also uncovering unique, country-specific experiences and outcomes for patients in the UK. For example, respondents from the UK consulted a mean of four HCPs before obtaining a diagnosis of FCS and at a slightly lower age (median = 8 years) than reported in the overall study outcome, in which individuals reported an average of five physicians being consulted before diagnosis at a median age of 9 years (Davidson et al, 2018). UK respondents were also all diagnosed prior to the age of 18, while the global sample age of diagnosis ranged from 1 to 57. However, 90% of the global respondents were diagnosed prior to age of 18 as well. Pediatricians diagnosed a third of the cases of FCS in UK respondents, which corresponds to the young age of diagnosis, but is a much greater portion than the global analysis (10%) which may be due to differences in the pathway of care or healthcare systems. The frequent requirement for patients to be examined by multiple HCPs, from a variety of specialties, before a definitive diagnosis is offered emphasizes the critical need for increased education and awareness regarding FCS. Enhanced communication between specialists and primary care physicians is also necessary to facilitate early diagnosis and appropriate initiation of treatment. Likewise, while the proportion of patients prescribed TG-lowering medication in the UK is lower than the overall IN-FOCUS population (40% vs 60%), given the lack of efficacy of these medications in patients with FCS, the need for additional education on FCS is reinforced. The importance of optimizing patient care pathways by reducing delays in diagnosis and offering value-based treatment for patients with rare diseases was highlighted by the United Kingdom Plan For Rare Diseases, released by the Department of Health.(Health 2012) This plan noted the need for HCP education on rare disorders and the need for a cross disciplinary approach when diagnosing and treating patients with rare diseases.

Acute pancreatitis, the most severe clinical characteristic of FCS, was reported as a comorbidity due to FCS by 45% of UK respondents, which was slightly higher than the global analysis (40%). Respondents from both analyses experienced a mean of 10 events over their lifetime so far and they all required hospitalization for some of the events. Acute pancreatitis induced by high triglycerides, that patients the FCS experience, may have a more severe course (Nawaz et al. 2015), while also representing a substantial healthcare expense. Cost and outcome modeling has predicted that a 50% reduction in TGs could have substantial lowering effect on acute pancreatitis events, corresponding to a significant reduction in medical expenses while simultaneously contributing to improved patient QoL.(Lin F 8-12 November 2014)

The effect of FCS experienced by patients extended far beyond symptom profiles. Notably, FCS is associated with a significant emotional burden related to anxiety, fear and worrying, which appears to translate into an increased burden relating to attempts to self-manage the condition and avoid symptoms. Notably, the prevalence of extreme dietary measures beyond those recommended in guidelines, such as fasting, amongst respondents in the UK, highlights the need for additional patient education surrounding the optimal management of FCS. Fasting, in particular, may carry a risk of this behavior becoming habitual and transitioning into an eating disorder (Stice et al. 2018), as well as potentially affecting the nutritional status of the patient. The percentage of UK respondents that reported utilizing fasting as a management strategy was higher than the global population and emphasized the importance of a collaborative approach between health care professionals to treat patients with FCS. Specifically, registered dietitians are critical as the diet is challenging to adhere to and each patient requires an individualized strategy to optimally manage their FCS (Williams et al, 2018). Despite, a potentially more efficient pathway to diagnosis and appropriate treating specialist for UK respondents, all of them still reported concern about their condition getting worse with age and 85% reported being worried about the long-term health consequence of their FCS. While these concerns were also expressed by many in the global analysis, 87% and 86% respectively, the near unanimous agreement on worry regarding long-term ramifications of FCS in UK respondents highlights the need for effective treatment options.

While more UK respondents reported being employed compared to the global study (60% vs 65%), only 15% of UK respondents were employed full time while 23% of the global study respondents reported full time employment. Additionally, 90% of respondents in both analyses reported that FCS impacted their ability to fulfill responsibilities at work and their career choice was influenced by their FCS. Professional time off taken due to FCS was reported in both analyses, with 69% of UK respondents reporting a mean of 15 days off and 60% of global respondents reporting 24 days. All of these factors, combined with the median age of UK respondents (32), demonstrate that FCS potentially has a devastating impact on patients' lifetime earning potential.

Pregnancy is also an innately challenging prospect for women with FCS patients because is it accompanied by a natural increase in plasma TG levels and can trigger an episode of acute pancreatitis.(Luo L 2017) Interestingly, the one UK respondent who became pregnant indicated that she was unaware of the potential implications of pregnancy for patients with FCS. While the history of the four other female respondents who had not become pregnant was not investigated (two-thirds of respondents to questions about FCS and child-bearing indicated that their FCS influenced decisions around pregnancy and children) suggesting that while education about FCS and pregnancy may have occurred, it may not currently be universal amongst patients with FCS in the UK.

The IN-FOCUS study was a substantial effort to quantitatively examine the breadth of impact on QoL in patients with FCS and is well-aligned with narratives presented in patient studies and perspectives (Gelrud, Williams et al. 2017, Neelamekam S. 2017). While IN-FOCUS, and the associated UK subanalysis, provide additional insight and

granularity to the burden of illness of FCS and its impact on patient QoL, several key limitations should be noted. The recruitment strategy for the study was largely due to word-of-mouth through patient organizations and social media outlets, indicating this could be a subset of the FCS population that is actively connected to these organizations. The act of being connected and involved in these organizations potentially alters perceptions of QoL as recently explored in the CONNECT study (Salvatore et al. 2018). As a self-reported survey, stated responses could not be independently verified. For example, the retrospective nature of some questions relating to events that potentially occurred several decades ago, such as diagnosis, may not be reflective of the current practice in diagnosing new cases of FCS, subject to recall bias and also limited by the high proportion of respondents who were unable to provide a definitive answer. The small sample size of the UK analysis also makes drawing definitive conclusions challenging but provides insight into country-specific differences in disease presentation and management. Additional analyses are planned to gain further knowledge about these potential differences.

Conclusions

The IN-FOCUS study highlights the continued need for specialized QoL assessments in rare diseases to adequately capture patients' experience and provide detailed insight into the specific challenges faced by patients living with FCS in the UK. (Cohen JS. 2010)(Havermans T. 2008) The UK subanalysis demonstrates that although FCS has characteristic symptoms, which are germane to all patients, country-specific differences exist with regard to the diagnosis and management of FCS, and its subsequent impact on QoL and healthcare resource utilization. This data will help inform efforts to offer value-based care for patients with FCS by providing a benchmark for patient QoL.

List Of Abbreviations

FCS – Familial chylomicronemia syndrome

HCP – Health Care Professional

LPL – Lipoprotein Lipase

QoL – Quality of life

TGs – Triglyceride

UK – United Kingdom

Declarations

Ethics and Consent to participate

Ethical approval was provided by National Health Services (NHS) research ethics committee for respondents in the UK. Written consent was provided by participants.

Consent for publication

Not Applicable

Availability of data and material

All datasets used and/or analyzed during the IN-FOCUS study are available from the corresponding author on reasonable request.

Author Contributions:

Study conception: MS

Study design: HS, MS, RJ

Data analysis: HS, MS, BH, RJ, BI

Data interpretation: HS, MS, BH, RJ, BI

Writing—original draft: BH, RJ

Writing-reviewing and editing: HS, MS, BH, RJ, BI

Final approval: HS, MS, BH, RJ, BI

Competing interests

HS has received research grants from Alexion, Amgen, Chiesi, MSD and AKCEA, and speaker honoraria, personal fees for consultancy and educational grants from Aegerion, AKCEA, Alexion, AstraZeneca, Amgen, Janssen Cilag Limited, Lilly, MSD, Pfizer and Sanofi.

MS, BH, and RJ are employees of Akcea Therapeutics Inc.

BI reported no relevant disclosures.

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Tables

Table 1: Respondent demographics and clinical characteristics

Demographics	Overall sample (N = 166)	UK sample (n = 20)
males, n (% of total)	116 (70)	15 (75)
Current age, median (range)	33 (18 - 59)	32 (19 - 53)
Age of FCS diagnosis, median (range)	12 (1 - 57)	8 (2 - 17)
Physicians seen before diagnosis, median (range)	5 (1 - 30)	4 (1 - 6)
Family history of FCS, n (% of total)	119 (72)	16 (80)

Table 2: Five most commonly experienced symptoms for each category during typical periods

Category	Symptom	Typical period, % (N=20)	Severe episode, % (N=20)
Physical (21 symptoms)	Generalized abdominal pain	40	40
	Indigestion	30	35
	Fatigue	30	25
	Lack of appetite	30	35
	Bloating	20	25
Emotional (13 symptoms)	Constant uncertainty about having an attack of pain or acute pancreatitis at any time	25	25
	Anxiety/fear/worry about health due to FCS	20	15
	Anxiety/fear/worry in social situation (food-related)	20	20
	Embarrassment about always thinking about and planning for my food	20	20
	Feeling out of control/powerless because of my FCS	20	–
	Anxiety/fear/worry about having to plan what or how much to eat	–	15
Cognitive (7 symptoms)	Difficulty concentrating	15	15
	Impaired judgement	10	5
	Difficulty understanding what others are saying	5	5
	Brain fog	5	5
	Forgetfulness	5	5

Figures

Figure 1

Interaction and Satisfaction with Physicians. Respondents reported the specialty of their diagnosing physician (a) and main FCS treater (b) and also their satisfaction with current healthcare professional on a 7-point Likert like scale (c).

Figure 2

Comorbidities reported by respondents with FCS – Respondents reported the comorbidities that have been diagnosed by a physician due to FCS (a). Respondents predominately had one comorbidity, but some had as many as 3 (b).

Figure 3

Strategies used by respondents to manage their FCS: Respondents reported the strategies they utilize to manage their FCS. Respondents could indicate more than one strategy, so percentages are for each strategy and will total more than 100.

Figure 4

Impact of managing FCS on quality of life. Respondents reported the impact managing FCS has on their quality of life by rating their agreement with provided statements using a 7-point Likert like scale.

Figure 5

Impact of FCS on respondents' employment. Respondents reported their current employment status (a) and the impact FCS had on that status (b). Respondents also reported the overall influence of FCS on their career choice using a 7-point Likert like scale.

Figure 6

Impact of FCS on social interaction – Respondents reported the impact of FCS on their social interactions by rating their agreement with provided statements using a 7-point Likert like scale.

Figure 7

Impact of FCS on mental and emotional well-being – Respondents reported the degree that FCS interfered with different areas of their mental and emotional well-being using a 7-point Likert like scale.

Figure 8

Impact of FCS on Future Outlook – Respondents reported the impact of FCS on their long term