Development and Validation of Clinical Criteria to Identify Familial Chylomicronemia Syndrome (FCS) in North America

#117

[1]Robert A Hegele, MD; [2]Zahid Ahmad, MD; [3]Ambika Ashraf, MD; [1]Andrew Baldassarra, BA; [4]Alan Brown, MD; [5]Alan Chait, MD; [6]Steven Freedman, MD; [7]Brenda Kohn, MD; [8,9]Michael Miller, MD; [2]Nivedita Patni, MD; [9]Daniel Soffer, MD; [10]Sarah N Gibbs, MPH; [10]Irina Yermilov, MD, MPH, MS; [10]Cynthia Campos, MPH; [10]Eunice Chang, PhD; [10]Michael S Broder, MD, MSHS

[1]Western University, London, Ontario, Canada; [2]UT Southwestern, Dallas, Texas, USA; [3]University of Alabama at Birmingham, Birmingham, Alabama, USA; [4]Advocate Lutheran General Hospital, Park Ridge, Illinois, USA; [5]University of Washington, Seattle, Washington, USA; [6]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [7]New York University, New York, New York, USA; [8]Crescenz Veterans Administration Medical Center, Philadelphia, Pennsylvania, USA; [9]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [10]Partnership for Health Analytic Research (PHAR), LLC, Beverly Hills, California, USA

Background & Objective

- Familial chylomicronemia syndrome (FCS) is an ultrarare, inherited disorder caused by impaired lipolysis leading to severe hypertriglyceridemia (HTG) and systemic manifestations, the most serious of which is acute pancreatitis.[1]
- Genetic testing is the standard to confirm diagnosis but is not always feasible.
- Clinical FCS can be defined as both classical (autosomal recessive monogenic) and functional (signs/symptoms and biochemical traits of classical FCS without the classical variants or indeterminate genetic results).
- In 2017, European clinicians (Moulin et al.) developed a “FCS score” to differentiate between FCS and multifactorial chylomicronemia syndrome (MCS), a much more common condition with some overlapping features.
- **This study aimed to develop a score to facilitate diagnosis for North American clinicians based on signs/symptoms and biochemical traits of FCS, regardless of genetic testing results.**

Methods

- To develop and validate the North American Familial Chylomicronemia Syndrome (NAFCS) score, we used the RAND/UCLA modified Delphi panel process and a registry of patients with FCS and MCS at Western University, Canada.
- The panel convened physicians with experience treating patients with FCS (9 United States,1 Canadian) and 1 adult patient with FCS. The panel reviewed current evidence on FCS diagnosis and developed 248 clinical scenarios with varying characteristics. Pre- and post-meeting, panelists rated whether patients described in scenarios were likely to have classical or functional FCS or neither.
- Median post-meeting ratings were used to conduct linear regression analyses to develop the NAFCS score (**Figure 1**). Experts evaluated the score for face validity.
- We assessed the score’s validity by calculating the NAFCS score and its sensitivity/sensitivity at various score cutoffs in a group of 75 patients (11 classical FCS, 16 functional FCS, 48 MCS) from Western University’s registry of patients.

References

1. Moulin P, Dufour R, Averna M, Arca M, Cefalù AB, Noto D, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an “FCS score.” Atherosclerosis. 2018 Aug;275:265–72.

Disclosures

RAH reports grants or contracts from Ionis, Arrowhead, Novartis, Amryt; consulting fees from Arrowhead, Amgen, Ionis-Akcea, Novartis, Pfizer, HLS Therapeutics; honoraria from Amgen, Sanofi, HLS Therapeutics, and Ionis; and participation on a data safety monitoring board or advisory board for Novartis. ZA reports institutional grants or contracts from the U.S. Department of Defense, the NIH, Ionis; honorarium from Ionis. AA reports grants or contracts from Aegerion, BioMarin, and NIDDK, and honorarium from Ionis. AB (Western University) reports honorarium from Ionis. AB (Advocate Lutheran General Hospital) reports consulting fees from Pfizer, Amgen, Novartis, Ionis, Esperion, and Amarin; payment or honoraria from Amgen, Regeneron, Esperion, Amarin, Zoll/Itamar. AC reports honoraria from CME Outfitters and Ionis. SF reports honorarium from Ionis. BK reports honorarium from Ionis. MM reports consulting fees from Amarin Corporation, 89bio, Ionis. NP reports consulting fees from Amryt Pharmaceuticals Inc. for advisory board and from Ionis; honoraria from Amryt Pharmaceuticals Inc. DS reports consulting fees from Amryt, Akcea, Ionis, Novartis, Regeneron, GenInCode; participation on a data safety monitoring board of advisory board for Amgen; leadership or fiduciary role as President, National Lipid Association and Director, Philadelphia Lipid Atherosclerosis Club. SNG, IY, CC, EC, MSB are employees of PHAR, which was paid by Ionis Pharmaceuticals to conduct the research described in the poster. PHAR also discloses financial relationships with the following entities outside of the submitted work: AbbVie, Akcea,

Results

- Components of the score are illustrated in **Figure 1.**
- The score required all patients be treatment resistant (i.e., omega-3 fatty acids, high-dose fibrates), and therefore included more severely affected MCS patients.
- When tested in real-world data (**Table 1**), the NAFCS score reliably distinguished classical FCS from MCS (i.e., score ≥60 had 100% specificity [**Table 2**]), though it was less effective at distinguishing between functional FCS and MCS at various score cutoffs between ≥25-≥60 (60.4-100% specificity and 24.0-72.0% sensitivity).

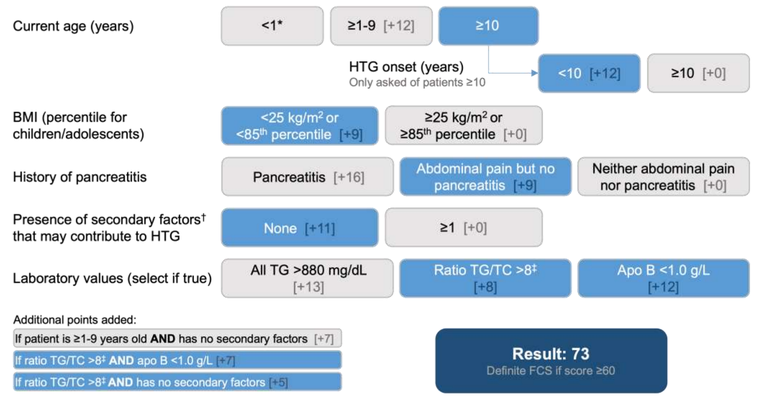
Scoring

- Experts agreed that a score of ≥60 strongly indicates “definite FCS.”
- A score of ≥45-59 indicates a patient is ”probably or very likely” to have FCS.
- A score of ≥30-44 identifies patients who may have FCS; genetic testing should be considered in these patients.

Figure 1. Illustrative Example of NAFCS Score

The following figure illustrates a static example of what we hope will eventually be an interactive calculator. The user will be instructed to answer each characteristic for their patient (e.g., patient age, BMI, clinical history), and the tool will provide the NAFCS score. For illustrative purposes, assume the user has selected items in blue. Scores in grey brackets indicate how much weight the other items are given. Add them together to calculate a patient’s NAFCS score.

When to use: This tool can be used to facilitate a diagnosis of FCS. It should only be used in patients ≥1 year old with HTG (≥440 mg/dL). It may be useful for patients who have not yet been tested genetically for FCS, or in whom genetics testing was inconclusive). Among patients ≥10 years old, the tool should only be used for patients who are not responsive to fibrates and high-dose omega-3 fatty acids even when the patient is compliant with therapy (i.e., TG do not decrease by 20% or more from these treatments and do not remain reduced).



Apo B=Apolipoprotein B100, BMI=Body mass index, FCS=Familial Chylomicronemia Syndrome, HTG=Hypertriglyceridemia, TC=Total cholesterol, TG=Triglycerides
*Patients <1 year old cannot be assigned an NAFCS score, but FCS is likely if they present with the following characteristics: HTG and no secondary factors that may contribute to HTG; or HTG, ≥1 secondary factor that may contribute to HTG, 2 TG readings >10 mmol/L, and unexplained failure to thrive.
†E.g., lifestyle, clinical conditions, medications.
‡ Ratio based on TG/TC in mg/dL.

Table 1. NAFCS Score Validation Sample in Patient Registry

	Classical FCS	Functional FCS	MCS	All patients
N (%)	11 (14.7)	16 (21.3)	48 (64.0)	75 (100.0)
Mean score (SD), Median*	67.6 (20.5), 68	24.0 (16.1), 27	20.3 (14.1), 23	26.9 (21.6), 25
Age at onset of HTG, N (%), years				
<10	6 (54.5)	0 (0)	0 (0)	6 (8.0)
10-19	0 (0)	1 (6.3)	2 (4.2)	3 (4.0)
20-39	4 (36.4)	10 (62.5)	31 (64.6)	45 (60.0)
40	1 (9.1)	5 (31.3)	14 (29.2)	20 (26.7)
Unknown	0 (0)	0 (0)	1 (2.1)	1 (1.3)
History of pancreatitis prior to diagnosis, N (%)	7 (63.6)	10 (62.5)	19 (39.6)	36 (48.0)
Closest 3 (adults) or 2 (children/infants) TG laboratory tests prior to diagnosis, with at least 1 reading >1770 mg/dL (20 mmol/L), N (%)	11 (100.0)	13 (81.3)	18 (37.5)	42 (56.0)
Closest TG/TC ratio prior to or on day of diagnosis, N (%)*				
≤8	3 (33.3)	11 (68.8)	40 (83.3)	54 (74.0)
>8	6 (66.7)	5 (31.3)	8 (16.7)	19 (26.0)
Closest apo B reading prior to or on day of diagnosis, N (%)*				
≥1.0 g/L	0 (0)	8 (50.0)	17 (35.4)	25 (34.2)
<1.0 g/L	9 (100.0)	6 (37.5)	30 (62.5)	45 (61.6)
Unknown	0 (0)	2 (12.5)	1 (2.1)	3 (4.1)

SD=standard deviation, HTG=hypertriglyceridemia, TG=triglycerides, TC=total cholesterol
*NAFCS score not calculated in infants <1 year old; 2 infants with classical FCS excluded.

Table 2. NAFCS Score Validation Metrics (Classical FCS vs. MCS)

	Sensitivity (%)	PPV (%)	Specificity (%)	NPV (%)
Score ≥25	100.0	24.3	56.3	100.0
Score ≥30	100.0	40.9	79.7	100.0
Score ≥35	88.9	38.1	79.7	98.1
Score ≥40	88.9	47.1	85.9	98.2
Score ≥45	88.9	80.0	96.9	98.4
Score ≥50	77.8	77.8	96.9	96.9
Score ≥55	77.8	87.5	98.4	96.9
Score ≥60	66.7	100.0	100.0	95.5

PPV=positive predictive value, NPV=negative predictive value

Conclusions

- We developed the first North American FCS Score using a combination of signs/symptoms and biochemical traits.
- This score may aid clinicians in diagnosing patients with FCS who might otherwise go undiagnosed or misdiagnosed. We hope it will be useful in diagnosing patients without the need for genetic testing or when genetic testing is inconclusive
- Functional FCS remains an evolving concept with no clear criteria other than a clinician’s general impression, representing a greater clinical challenge than usual patients with MCS. Due to the requirement of treatment resistance, the clinical presentation of patients with MCS in our cohort was severe and similar to that of patients with functional FCS.
- As the definition of functional FCS evolves and becomes clearer, studies should aim to refine the NAFCS score to improve its ability to distinguish patients with MCS from patients with FCS.

Poster presented at NLA Scientific Sessions, Las Vegas, NV, May 30 - June 2, 2024

This investigation was funded by Ionis Pharmaceuticals.