DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLEMIA IN THE CLINICAL PRACTICE: PERFORMANCE OF THE DUTCH LIPID CLINIC NETWORK SCORE

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BACKGROUND

Familial hypercholesterolemia (FH) is an inherited disorder characterized by high levels of blood cholesterol from birth and premature coronary heart disease (CHD). Thus, the early identification of FH patients is crucial to prevent the onset of cardiovascular events. Despite the availability of clinical tools (e.g. Dutch Lipid Clinic Network [DLCN] score) supporting physicians in identifying FH patients, a significant proportion of patients remains without a diagnosis due to lack of information.

RESULTS

Overall, only 56.6% of patients had all the data required to calculate the DLCN score through the 8 criteria besides LDL-C, and about 10.0% had 4 or more missing data. In particular, among subjects with a DLCN score of 5 (9.2%), just below the threshold of the possible diagnosis, about 46.0% had at least one missing criteria.

Number of missing criteria	Frequency	Percentage
0	779	56.57
1	209	15.18
2	185	13.44
3	67	4.87
≥4	137	9.95

Compared with subjects without missing data, the lack of information related to the family clinical history did not modify the rate of patient identified as FH; in contrast, the lack of information concerning the physical signs typical of FH or the personal history of cardio/cerebrovascular events strongly reduced the percentage of subjects with a probable/definite FH diagnosis.

AIM and METHODS

To test the performance of the DLCN score based on completeness of required data, an analysis was carried out in all mutation-positive patients (as established by genetic test performed by different laboratories) enrolled in the LIPIGEN study, aged 18 years or more, who underwent clinical evaluation and had information on pre-treatment LDL-cholesterol (LDL-C) levels available. The DLCN performance was evaluated as a function of the number and type of missing criteria. In addition, a stepwise logistic regression analysis (odds ratios [OR] and 95% CI) was carried out in order to identify which factors among DLCN criteria and other additional covariates (i.e. non-HDL-C, Lp(a), LDL-C >180 mg/dL since age <18 years) had a greater impact in predicting the probability of having monogenic FH.

As the pre-treatment LDL-C levels were not available for many FH subjects, we evaluated whether the use of estimated pre-treatment LDL-C based on statin type and dose might affect the DLCN score. Overall, 39.6% of subjects without known pre-treatment LDL-C values had estimated LDL-C levels >325 mg/dL, leading to an overestimation of patients classified as probable/definite FH.

LDL-C levels	FH population (N= 1.377)	Not on statin (768)	On treatment, with <u>known</u> pre-treatment LDL-C levels (397)	On treatment, with <u>estimated</u> pre-treatment LDL-C levels (212)
<155 mg/dL	2.47%	2.60%	1.26%	4.25%
155-190 mg/dL	6.46%	7.42%	6.30%	3.30%
191-250 mg/dL	28.40%	28.91%	31.74%	20.28%
251-325 mg/dL	36.75%	39.06%	34.51%	32.55%
>325 mg/dL	25.93%	22.01%	26.20%	39.62%
DLCN score > 8	37.91%	33.46%	37.53%	54.72%

For this analysis, 1650 adults with a clinical FH diagnosis (78.2% with genetically-confirmed FH) were enrolled. Among the 9 items evaluated for the DLCN score calculation, **the presence of tendon xanthoma and very high LDL-C levels**, in the patient and/or in first degree relatives, showed the strongest association with the probability of having monogenic FH. Regarding the additional factors, the only one included in the final model was the **detection of LDL-C>180 mg/dL before 18 years old** (OR 1.83 [1.26-2.66]). This factor could be considered together with DLCN criteria for the clinical diagnosis of FH .

	OR	95% CI
Tendon xanthoma	2.47	1.41 4.32
Premature CHD	1.24	0.79 1.94
LDL-C >180 mg/dL since age <18 years	1.83	1.26 2.66
First-degree relative with known LDL-C >95th percentile by age and gender for country	2.33	1.49 3.64
First-degree relative with tendon xanthoma and/or corneal arcus	5.51	2.28 13.31
Child(ren) <18 years with LDL-C >95th percentile by age and gender for country	1.82	1.21 2.74
155 ≤ LDL-C ≤ 190 mg/dL	1.24	0.62 2.48
191 ≤ LDL-C ≤ 250 mg/dL	1.39	0.75 2.58
251 ≤ LDL-C ≤ 325 mg/dL	3.84	2.03 7.25
LDL-C >325 mg/dL	15.5	7.12 33.75

CONCLUSIONS

In this analysis, the DLCN score failed to identify a third of subjects with genetically-confirmed FH, leading to suggest the need of its update and validation. Although the DLCN score is a useful tool for physicians in the diagnosis of FH, it may be limited by the difficulty to retrieve all the essential data, suggesting a crucial role of the clinical judgement in the identification of FH subjects.