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Review article

The development of the Mexican Familial Hypercholesterolemia (FH) National Registry

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ABSTRACT

Background and aims: In Mexico, familial hypercholesterolemia (FH) is, as in other parts of the world, largely underdiagnosed and undertreated, and represents a significant burden to the healthcare system. However, there is not enough information to design public policies against the disease. Genetic studies have shown that *LDLR* mutations are the most common cause, but in a large percentage of the cases, no mutation has been identified in the FH genes.
Methods: In accordance with the procedures of the European Atherosclerosis Society (EAS) FH registries network, the Mexican FH registry (www.fhmexico.org.mx) was launched in December 2017 to address the gaps in knowledge regarding this disease. Reference centres and the main nationwide public health providers have been invited to participate.
Results: To date, 142 cases have been registered. The mean age at diagnosis of probands is 36.42 ± 19.9 years (adults and children). Tendon xanthomas or premature corneal arcus were present in 40% and 17.6%, respectively. Molecular analysis was present in 70%, with over 95% of alterations located on the LDL receptor gene. The median untreated LDL-C is 6.5 (5.6–8.4) mmol/l and the median on treatment LDL-C level is 4.3 ± 1.7 mmol/l.
Conclusions: The Mexican FH registry aims to obtain real world information regarding the management of patients in this country. By participating in this global call to action, we hope to improve both short and long term outcomes for all FH patients in Mexico.

1. Introduction

Familial hypercholesterolemia (FH) is an inherited disorder characterised by defective clearance of low density lipoproteins (LDL-C), resulting in patients with a lifelong exposure to high LDL-C levels and increased cardiovascular risk [1]. The overall prevalence estimates suggest a figure of 1 in 200 adults, signifying a global number of cases of between 13 and 34 million persons [3]. Autosomal dominant FH is attributed to mutations in 3 different genes: low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*). Mutations in the *LDLR* account for the majority of cases. However, around 10–50% of patients may be mutation negative, especially in populations without "founder" effects and with significant non-Caucasian ancestry [1]. FH diagnosis is based on clinical phenotype ± mutational analysis, utilizing instruments such as the Dutch Lipid Clinics Network (DLCN), Simon Broome Registry, and US MEDPED (Make Early Diagnosis To Prevent Early Death) criteria [4–6]. Once an FH proband is identified, systematic cascade screening of first-degree relatives should be performed to permit opportune diagnosis and treatment of other affected individuals: this is a cost effective method to identify new FH cases. Despite

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remarkable advances in its treatment, cardiovascular mortality is still significantly higher in FH patients as compared with the general population [2]. Lifelong high intensity statin therapy, with or without ezetimibe is required. In homozygous cases, lipid apheresis is needed. Because early diagnosis and treatment increase life expectancy in this population, awareness campaigns and quality of care programs are needed in every nation [7–9].

2. Rationale for FH registries

A health care registry can be considered as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical, or policy purpose(s)" [10]. Hence, a patient registry can be a powerful instrument to observe the natural history of a disease; to record treatment and outcomes; to examine factors that influence prognosis and quality of life; to describe care patterns, including appropriateness of care and disparities in the delivery of care; to assess effectiveness of management in preventing outcomes; to monitor safety; and to measure quality of care and aid in quality improvement [11]. Registries are needed for conditions with a prevalence below 6% of the target population; regional or nation-wide studies did not have the power to identify a number of cases large enough. Institutional or regional FH registries have existed for decades, but their ability to provide evidence for the creation of public policies is inadequate due to their limited external validity. In 2015, the European Atherosclerosis Society published a "call to action" to integrate efforts across the world to tackle the health burden and gaps in the care of FH [7–9]. One of the key actions was the acquisition of large scale reliable data through the creation FH national registries. Several national FH registries have been successfully implemented, particularly in the United Kingdom, Norway, the Netherlands, the United States, Canada, Spain and the Middle East and North Africa [13–21]. Recent additions to this list include Greece, Turkey, Saudi Arabia and France [22–25]. A recent review affirms that "familial hypercholesterolemia registries are tools for clinical research and improving healthcare planning and patient care" [12].

3. What have we have learnt so far from such initiatives?

Registries have provided evidence to fill out several gaps in knowledge regarding FH management. For example, the UK Paediatric Registry has shown that the use of lipid lowering therapies is not limited by adverse events (i.e. decreased growth rate or elevations in liver enzymes or creatinine phosphokinase) [26]. The Norwegian FH registry has shown that in 1093 women with heterozygous FH, the rates of preterm delivery (<37 weeks of gestation), low birth weight (<2500 g), and congenital malformations were similar to those in the general population [27]. Mortality and morbidity data have also been collected by several registries [28]. The Norwegian registry reported that the most common cause of death was cardiovascular disease, mean age being 64.5 years. For those aged 20–39 years, the risk of cardiovascular death occurring out of hospital was increased 12-fold [29]. They also mentioned that the majority of death certificates did not record FH as a contributing factor, despite the fact that patients had a known FH mutation. The diagnosis of FH is often late and treatment targets are not universally obtained despite lipid lowering medication. In the CASCADE-FH registry, the median age of diagnosis was 47 years and the median age for initiating lipid lowering medication was 39 years [30]. Only 25% of patients had an LDL-C <100 mg/dL and 41% had a 50% reduction in their LDL-C. The prevalence of coronary artery disease in this population was 36%. More than half the population (61%) had at least 1 additional cardiovascular risk factor. Both diabetes mellitus and arterial hypertension were significantly associated with cardiovascular disease. Gender differences were also explored: the authors reported that women were less likely to receive statin therapy and achieve treatment targets compared to men [31]. Likewise, ethnic differences were found, with Asians and Blacks less likely to achieve LDL-C goals (LDL-C <100 mg/dL or a 50% reduction), suggesting under-treatment in these groups. The authors speculate that this finding can be explained by variable access to specialty lipid clinics, differences in socioeconomic status, perceptions regarding LDL-C lowering goals, ethnic variations in tolerability of statins or differences in patients' comorbidities.

The drawbacks of current diagnostic criteria have also been explored using registry data. The diagnosis of FH has been based on variables such as cholesterol levels, physical examination (i.e., tendon xanthomas, corneal arcus), personal/family history of premature atherosclerotic disease, and mutational analysis if available. It is now recognized that the classical presentation of FH is often not present due to changes in secular trends and improvements in therapy [32]. In the SAFEHEART study, in genetically confirmed patients, only 13.7% had tendon xanthomas [19,33]. As a consequence, the 2015 American Heart Association scientific statement on FH as well as the Canadian guidelines have removed this criteria from their heterozygous FH screening definition [34,35]. Another problem faced by the current diagnostic criteria is the reliance on family history of atherosclerotic disease. Kindt et al. point out that statins have been available for more than 30 years, increasing the likelihood that parents of probands have been exposed to lipid lowering treatment, and therefore may not have had any events [32]. In addition, family history is often unreliable or unavailable. The final observation is that population LDL-C levels have decreased due to diets containing less saturated fat intake and the universal use of statins.

In addition, registry data has highlighted the importance of understanding the relationship between the genetics and the clinical presentation of FH. Khera et al. found that in patients with an LDL-C $\geq$190 mg/dL, those who had no FH mutation had a six-fold increase in atherosclerotic disease risk compared to the control group with LDL $\leq$130 mg/dL. In contrast, those with an FH mutation (only <2% of patients with an LDL-C $\geq$190 mg/dL) had a 22-fold increase in risk compared to the same control group [36]. This suggests that the simple diagnostic criteria that we use now may not adequately distinguish FH from polygenic hypercholesterolemia. These authors also confirmed that the clinical severity of FH differs based on the type of mutation (i.e., loss of function *vs.* missense mutation) and affected gene. Mutations on the ApoB and PCSK9 genes generally present with a less severe clinical phenotype. In the future, Kindt et al. speculate that if genetic information is coupled with registry data, we will be able to more fully understand the genotype-phenotype relationship in FH [32].

Finally, FH registries provide us with a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness [11]. The main disadvantage is common to all observational studies, namely the possibility of bias and confounding factors. Wong et al. mention that although registries are a convenient source for assessing cardiovascular risk, one must acknowledge the potential for patient selection and ascertainment bias [29]. Quality control measures, with respect to data collection and input, should also be implemented. Such limitations are even greater in developing countries. For example, the percentage of undiagnosed cases cannot be estimated in these nations, as can be done in countries with a consolidated primary care system and universal coverage. In addition, heterogeneity of the population and quality of care is remarkably greater, increasing the possibility of biased conclusions if only reference centres participate in the survey. Despite the