Characterization of Children with Homozygous Familial Hypercholesterolemia from the CASCADE FH® Registry

M.P. McGowan[1], D.E. MacDougall[1], M.C. Card [1], M Cuchel [2] , P.C. Lee [3] , L.C. Hudgins[4], S. D. de Ferranti[5] , D. Staszak[6], K.A.Wilemon[1].

[1] Family Heart Foundation, Pasadena, CA, [2] University of Pennsylvania, Philadelphia, PA, [3] Washington University in St. Louis, MO, [4] The Rogosin Institute/ Weill Cornell Medical College, NY, NY [5] Harvard Medical School, Boston, MA, [6] Atomo Inc, Austin,TX

Background

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition characterized by extremely elevated levels of serum low-density lipoprotein cholesterol (LDL-C) and risk of premature atherosclerotic cardiovascular disease (ASCVD) as early as the first decade of life. Clinical diagnosis includes LDL-C levels and the presence of positive family history and/or xanthomas. The American Academy of Pediatrics (AAP) recommends lipid screening for children with a family history of ASCVD or FH at age 2 and universal screening between ages 9-11 and again between 17-21.

Methods

The current analysis includes a total of 67 HoFH patients enrolled at sites participating in the CASCADE FH® registry (Figure 1), a multi-site patient registry created in 2013 by the Family Heart Foundation that tracks the characteristics, treatment patterns and clinical events in heterozygous [HeFH] and HoFH patients in the US. Here a comparison is made between 16 HoFH patients who were children (<18 years old) and 51 who were adults at time of enrollment into the CASCADE registry.

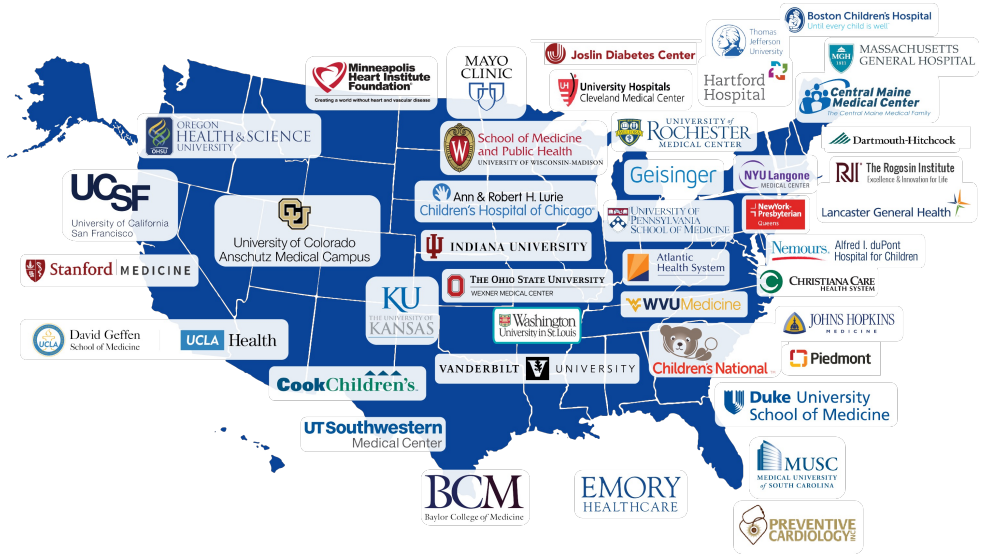

Figure 1: Family Heart Foundation CASCADE FH Registry sites – 20 of 40 contributed to HoFH data

Results

Age of diagnosis (median; IQR) was 2.0 years (2.0/3.5) in children and 12.6 years (4.1/26.5) in adults. Untreated levels of LDL-C (median; IQR) in the children were extremely elevated at 776 mg/dL (704/892) and significantly higher than untreated levels in the HoFH adults at 533 mg/dL (467/702) (p=0.001). At enrollment, 18.8% and 43.8% of the children had evidence of aortic valve stenosis (AS) and ASCVD, respectively, median age of onset for ASCVD was 8.9 years. The earliest reported ASCVD diagnosis occurred at ages 2 and 3 years in children who underwent liver transplant at 4 and 8 years respectively. Two children underwent coronary artery bypass grafting at ages 6 and 14. Five subjects underwent liver transplant prior to age 18. Despite a more severe phenotype, children had not uniformly developed tendon xanthomas or corneal arcus and had younger family members with lower rates of ASCVD (Table 1). Treatment reduced LDL-C substantially, but only 25% of children achieved LDL-C goal. Goal attainment was more likely with increased number of lipid lowering therapies prescribed.

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Table 1: Medical, Physical and Family Characteristics of Children and Adults Diagnosed with Homozygous Familial Hypercholesterolemia in the CASCADE FH Registry at time of enrollment

	Enrolled as Children		Enrolled as Adults		P-value
Cardiovascular disease	n		n		
Aortic valve stenosis, *n (%)*	16	3 (18.8)	51	13 (25.5)	0.7
CAD, *n (%)*	16	7 (43.8)	51	40 (78.4)	0.02
Age at onset, *median (IQR)*	7	8.9 (4.5/10.7)	38	30.5 (21.1/41.0)	<0.001
Untreated LDL-C					
LDL-C (mg/dL):	16	776 (704, 892)	39	533 (467, 702)	0.001
Physical findings					
Corneal arcus, *n (%)*	16	0 (0.0)	47	22 (46.8)	<0.001
Tendon xanthomas, *n (%)*	16	9 (56.3)	51	41 (80.4)	0.1
Family history					
Cardiovascular disease, *n (%)*	16	6 (37.5)	44	37 (84.1)	<0.001
FH or Hypercholesterolemia, *n (%)*	16	16 (100.0)	50	49 (98.0)	1.0

CAD, coronary artery disease; IQR, interquartile range.

Discussion and Conclusion

HoFH patients enrolled in the CASCADE FH registry as children were diagnosed earlier and had higher untreated LDL-C than their adult counterparts, raising the possibility that only children with the most severe phenotypes are diagnosed before adulthood. Neither family history of ASCVD, nor physical findings (xanthomas or corneal arcus) reliably identified children. Moreover, at enrollment over half the children had evidence of ASCVD or AS. These findings and recent improvement in lipid lowering therapies make a compelling case for rigorous compliance with AAP's guidelines for screening at age 2 in children with a family history of FH or ASCVD.[1] This should be followed by cascade family screening.[2] Unfortunately, even routine screening between ages 9-11 is not routine in the US.[3-5] A country-wide call for consistent screening is warranted. Only then, will all children with HoFH be consistently identified.

[1]. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* **128 Suppl 5**, S213-256 (2011). [2]. Lee, C., et al. New case detection by cascade testing in familial hypercholesterolemia: a systematic review of the literature. *Circ Genom Precis Med* **12**, e002723, doi:10.1161/circgen.119.002723 (2019). [3].Valle, C. W., et al. Physicians' lack of adherence to National Heart, Lung, and Blood Institute guidelines for pediatric lipid screening. *Clin Pediatr (Phila)* **54**, 1200-1205, doi:10.1177/0009922815576885 (2015). [4]. Dixon, D. B., et al. Implementation of lipid screening guidelines in children by primary pediatric providers. *J Pediatr* **164**, 572-576, doi:10.1016/j.jpeds.2013.10.027 (2014). [5]. Sleeth CM, et al. Pediatric dyslipidemia screening by pediatricians and family medicine physicians: current practices and future directions. Pediatrics (2020) 146 (1_meeting abstract); 636-637.

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