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Report of Visiting Fellowship at Boston Children's Hospital Department of Cardiology, Preventive Cardiology Program

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Spending 12 weeks at the Preventive Cardiology Program of Dr. Sarah di Ferranti for me was a very valuable combination of observing in outpatient clinic and focusing on research related to childhood cardiovascular risk factors.

Clinical part

As planned, I spent 2 days per week in outpatient clinic, made up of 9 weeks observing in preventive cardiology clinic and 3 weeks in the obesity clinic, run by the endocrinology department. I gained exposure to obesity and lifestyle related risk factors, including dyslipidemias and hypertension. This is particularly important since this is an area less well explored at my home institution and the clinical work in Boston nicely complemented my experience with familial hypercholesterolemia (FH) in Dutch children and adolescents. I have also shared my own experiences with my colleagues in Boston. This demonstrated some key learning points including my exposure to a wide range of patients with dyslipidemia other than FH (high TG, obesity related dyslipidemia, sitosterolemia), the "Boston" practice with regard to the diagnosis and treatment of children with (lifestyle related) hypertension, as well as the management of patients with cardiovascular risk factors: cancer survivors, ex-premature born patients, nephrotic syndrome, type 1 diabetes, etc.. I have learned some important principles and practical points about nutrition counseling for abnormal TG, HDL, LDL, blood pressure. I was very much inspired by the patient approach, which is generally 'focus on health, not weight; focus on fitness, not fatness'.

Research part

The remaining 3 days per week were spent focusing on pediatric preventive cardiology research, focusing on several projects:

Comparing guidelines / differences in treatment due to genetic testing

To identify individuals with FH and initiate primary prevention efforts at a young age, lipid screening during childhood and adolescence has been recommended by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, the American Heart Association, and the National Lipid Association. Children with LDL-C levels ≥ 190 mg/dL on more than one occasion should be considered as having FH, whereas 2 consecutive

LDL-C levels ≥ 160 mg/dL in combination with a family history of hypercholesterolemia or premature CVD are highly suggestive of FH (Wiegman EHJ 2015).
Yet family history cannot be relied upon to identify FH due to lack of access to relevant family history (single parent), a familial culture that avoids discussing medical issues, or balancing genes that counteract the effects of an adverse LDL receptor defect. Furthermore, the utility of family history as a predictive factor may be lessening; parents and extended family members of children with FH may already be aggressively treated with statins, thereby preventing the premature CVD event that may otherwise have occurred. This is a key consideration as the presence or absence of a family history for CVD is an important criterion in the treatment algorithm from current US guidelines.
For example, a child ≥ 10 years of age with an elevated LDL-C in the absence of a family history of CVD or other risk factors, statin treatment is only recommended when LDL-C is consistently > 190 mg/dL; whereas, statin therapy would be recommended for that same child at a lower LDL-C threshold if there was a family history of premature CVD. In the Netherlands, all children with a suspicion of FH are genetically tested. With a proven molecular diagnosis, statin treatment is recommended in children ≥ 8 years of age with an LDL-C of ≥ 160 mg/dL, and in children ≥ 10 years of age with an LDL-C of ≥ 130 mg/dL, independent of the family history of premature cardiovascular disease according to the Dutch treatment guideline.
So, children with FH are treated differently in different parts of the world. We hypothesizes that some of the children with moderately elevated LDL-C levels might be undertreated, due to the fact that one of the criteria to initiate lipid lowering therapy include a positive family history of early CVD events, which is no longer a valid marker of cardiovascular risk in the era of lipid lowering therapy.
We have analyzed data from my home institution (Pediatric Lipid Clinic, Amsterdam UMC), where all children are genetically tested for FH, together with the data from the lipid clinic in Boston, where the diagnosis is clinically made. We explored how family history has changed over the past decades and how it influences clinical decision making, especially when genetic testing is not available. In addition, tried to make an assumption of the underestimation of the risk of children with highly probable FH, who have a negative family history of premature CVD.
The manuscript of this study is in preparation.

Comparing different methods of estimating LDL-C
LDL-C is an important causal modifiable factor in the development of coronary heart disease. For decades, LDL-C has been of clinical and research interest and a key target in clinical practice guidelines for both adults and children. Despite the extensive research focus, there remains debate in regards to the best approach to measure LDL-C for clinical practice. Novel approaches have been proposed but none have been evaluated in children.
The most common approach to determining LDL-C in the clinical laboratory is the Friedewald calculation, obviating need for ultracentrifugation. It estimates LDL-C from measurements of total cholesterol, triglycerides (TGs), and HDL-C. Although convenient, the Friedewald calculation suffers from several well-established limitations. Recent studies have shown that the Friedewald method underestimates LDL-C especially at lower levels, which could result in misclassification or undertreatment of patients. This was most pronounced in lower LDL-C levels (especially LDL-C < 70mg/dL), particularly in combination with high triglyceride levels (>100 mg/dL). A novel method (Martin/Hopkins) using a patient-specific conversion factor provides more accurate LDL-C levels. It was shown that in patients achieving very low LDL-C levels with PCSK9 inhibition, the Martin/Hopkins method more closely approximates LDL-C from 'gold standard' assays (ABC method) as compared with the Friedewald approach to LDL-C estimation. It was therefore

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suggested that Martin/Hopkins estimation should be the preferred method to estimate LDL-C levels in specific patient groups. In the U.S., XYZ labs is reporting LDL-C results using the Martin/Hopkins methods.
In children, LDL-C levels with regard to reference values and treatment thresholds and targets, are generally lower as compared to adults. For example, an LDL-C level of < 110 mg /dL is considered normal in children and adolescents, whereas LDL-C ≥ 110 and < 130 mg/dL is borderline high, and LDL-C ≥ 130 mg/dL is elevated. Consequences of the two different methods to calculate LDL-C in terms of modifying risk classification or treatment recommendations has not been studied in children. The objectives of this study were to: 1) evaluate disconcordant risk classification and treatment recommendations that would occur if the Martin/Hopkins method was utilized instead of the Friedewald equation, and 2) compare the Martin/Hopkins method to the Friedewald equation in relation to a 'gold standard' assay, ABC assay in a large pediatric hospital-based laboratory.
We are still working on the analysis and the manuscript of this study is in preparation.

Factors contributing to carotid intima-media thickness in obese children
I have made substantial progress on the analysis comparing vascular measures in children with FH, obesity, and healthy children supported in part by discussions that were fostered with Dr. Elaine Urbina, a friend and colleague of dr. de Ferranti with important expertise in vascular testing in childhood. I presented these data in abstract form at the International Atherosclerosis Society in Toronto in June, 2018, just prior to starting my fellowship in Boston, and then spent time writing the full manuscript.
The manuscript is submitted for publication.

Other
I collaborated on a grant proposal to explore compliance to LDL apheresis in homozygous FH patients, which, while not successfully funded, allowed us to better understand relevant issues to patient care and formed the basis for new projects on this topic.

To conclude
I think my time with dr. de Ferranti at the Boston's Children Hospital was spent very fruitfully. Though these clinical experiences, research projects, and my regular attendance at weekly lab meetings and clinical care review conferences, I solidified my ambition to continue my academic work and our future scientific collaboration. Although research in cardiovascular risk factors in children is very important and needed, it is a relatively unexplored research field. In my home institution, studies in this area were limited to children with familial hypercholesterolemia and in Boston I had the opportunity to expand this importantly.
I am currently working both as a pediatrician in the field of childhood obesity and dyslipidemia, and as a post-doc in the research field of cardiovascular risk in children, in which I can use my experiences from Boston every single day.

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