Paediatric familial hypercholesterolaemia reverse cascade screening: A proactive approach to early recognition and treatment

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INTRODUCTION

Familial hypercholesterolaemia (FH) is a hereditary disorder characterised by elevated LDL-cholesterol levels from birth, posing a significant risk of atherosclerotic cardiovascular disease (ASCVD). FH is inherited in an autosomal dominant pattern, meaning that individuals with one affected parent have a 50% chance of inheriting the condition. Without proper management, FH can lead to early onset of ASCVD, emphasising the importance of early diagnosis and lifelong treatment to reduce the risk of complications [1]. Even though FH is a rather frequent disease with an estimated prevalence of 1 in 250, disease awareness in developed countries continues to be poor, and <10% of patients are diagnosed and appropriately treated [2].

In recent years, the importance of early detection and intervention for FH, especially in paediatric populations, has gained recognition. One promising strategy that has attracted substantial attention is paediatric FH reverse cascadescreening. This is a proactive approach which has the potential to revolutionise the identification and management of FH at an early age, decreasing the risk ofASCVD, improving long-term health outcomes, and ultimately saving lives.

Traditionally, efforts to detect individuals with FH were augmented with the use of the so-called cascade screening. This involves identifying and testing relatives of an index case diagnosed with FH. However, reverse cascade screening flips the conventional approach on its head by initiating the screening process in children. Rather than waiting for an adult with FH to be identified, this method aims to detect FH in children first and subsequently screen their parents and extended family members.

Paediatric Reverse Cascade Screening is considered most beneficial, and its implementation would certainly affect:

1. *Early Intervention*: One of the primary advantages of paediatric reverse cascade screening is the ability to intervene early. Identifying FH in children allows for timely medical intervention and the implementation of lifestyle modifications, which can significantly reduce the risk of cardiovascular events later in life. By intervening during childhood, we could break the vicious cycle of heart disease that often plagues families affected by FH.

Early studies have shown the effectiveness of early intervention in FH. It has been shown that early treatment of FH patients with statin therapy starting in

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childhood is associated with a significantly lower risk of cardiovascular events compared to those who started treatment later in life. These findings highlight the importance of early intervention in improving long-term outcomes for individuals with FH [3].

2. *Enhanced Family Detection*: By focusing on children, reverse cascade screening increases the chances of identifying undiagnosed FH cases within families. Since FH is an inherited condition, there is a high probability that parents or siblings of affected children may also carry the gene mutation. Identifying and treating these cases promptly can prevent the progression of the disease and its potentially devastating consequences. Moreover, the identification of FH in children can motivate and raise awareness among their extended family members, leading to improved detection rates across generations.

Indeed, screening FH in the youth provides the potential for the identification of previously undiagnosed FH cases in parents and siblings. This approach is reportedly associated with a higher detection rate and facilitated early intervention in family members, reducing the overall burden of ASCVD within the family [4].

3. *Cost-Effectiveness*: Despite initial concerns about the cost of implementing such screening programs, reverse cascade screening has the potential to be a cost-effective strategy in the long run. Detecting FH in childhood reduces the need for expensive interventions later in life, such as coronary artery bypass grafting (CABG) surgery and/or lifelong medication. By investing in early screening and preventive measures, the economic burden of ASCVD can be significantly reduced, ultimately reducing healthcare costs. In addition, for reverse cascade screening based on biochemical rather than genetic testing, childhood is the most cost-effective period for FH screening since LDL-C levels are more reliable, reflecting predominantly the genetic predisposition and not anydietary or hormonal influences, as is the case in adulthood.

A cost-effectiveness analysis demonstrated that paediatric reverse cascade screening is a cost-effective strategy especially if it starts in children aged 1-2 years at the time of immunisation. This strategy appeared acceptable to parents and was highly cost-effective as a detection strategy for families at risk of FH [5].

4. *Public Health Impact:* Implementing paediatric reverse cascade screeningfor FH aligns with the broader public health objective of preventing ASCVD. By identifying individuals at risk and intervening early, we can reduce the overall disease burden, improve the quality of life, and potentially save lives. Moreover, as the identified individuals receive appropriate treatment and disease awareness increases, their contribution to the transmission of FH within the population diminishes, offering long-term benefits to society and future generations.

Challenges and Future Directions:

While the concept of paediatric FH reverse cascade screening holds immense potential, there are several challenges that need to be addressed to ensure itssuccessful implementation and long-term effectiveness:

1. *Access to Screening*: Ensuring equitable access to screening tests is crucial. Screening programs should be accessible to children from all socioeconomic backgrounds and geographic locations. Efforts should bemade to remove barriers such as cost, limited healthcare infrastructure,and geographical distance, to ensure that no child is left undiagnosed and untreated.
2. *Public Awareness and Education*: Raising awareness among healthcare professionals and the public about the importance of paediatric reverse cascade screening is essential. Healthcare providers should be educated about the identification and management of FH in children, and guidelines should be developed to assist them in implementing screening programs effectively. Additionally, public education campaigns can help parents and caregivers understand the significance of early disease detection in their children and themselves and encourage them to participate in screening programs.
3. *Genetic Counseling and Psychological Support*: Genetic counseling plays a vital role in FH screening programs. It provides families with valuable information about the inheritance patterns, potential risks, and available treatment options. Genetic counselors can also help individuals and families cope with the emotional and psychological aspects of living with FH, offering support and guidance throughout the screening and treatment process.
4. *Long-Term Monitoring and Follow-Up*: Continuous monitoring and follow-up are crucial for individuals identified with FH during childhood. Regular cholesterol level checks, cardiovascular risk assessment, and adherence to treatment and lifestyle modifications should be ensured. Long-term studies are needed

to assess the effectiveness and sustainability of early interventions in preventing cardiovascular events and mortality.

5. *Integration into Routine Paediatric Care*: To maximise the impact of paediatric reverse cascade screening, it should be integrated into routine paediatric care. Incorporating FH screening as part of well-child visits or school health programs can increase the reach and effectiveness of the screening programs. Collaboration between paediatricians, primary care providers, and specialists is necessary to ensure seamless implementation and follow-up care.

In this respect, EPIRUS-FH registry is a model program of reverse cascade screening for FH in children and adolescents in Northwest Greece that aims to increase public and physician awareness, strengthen the national registry of familial hypercholesterolaemia (HELLAS-FH) and constitute the core for a national FH registry in children and adolescents in Greece (NCT05825612).

CONCLUDING REMARKS

Paediatric FH reverse cascade screening holds great promise for the early identification and management of FH, potentially preventing the devastating consequences of ASCVD. By focusing on children, this proactive approach offers the potential to break the cycle of FH within families, improve long-term health outcomes, and reduce the burden on healthcare systems. However, several challenges must be addressed to ensure equitable access, raise awareness, provide necessary support, and integrate screening into routine paediatric care. By overcoming these challenges and investing in the implementation and ongoing evaluation of paediatric reverse cascade screening programs, we can take significant strides towards a future with reduced cardiovascular disease burden and improved public health outcomes.

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