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The Draupadi of dyslipidemia: Familial hypercholesterolemia

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Modern medicine is often criticized for disease mongering and noun piling. Menopause and andropause, for example, are criticized by skeptics, who highlight the lack of need for such diagnostic labels.[1] Paradoxically, however, modern endocrinology may overlook relatively less common disorders which fall within its ambit. Type 1 diabetes, for instance, is a condition which has to fight for its place under the sun, distinct from the shadow of its ubiquitous cousin, Type 2 diabetes.[2]

A similar situation holds true in lipid metabolism. Familial hypercholesterolemia (FH),[3] a well-known genetic disease with well-characterized lipo-phenotypes, is often buried under the Himalayan burden of mixed dyslipidemia. This is especially true in Asian nations, where limited diagnostic and therapeutic facilities, coupled with the lack of awareness, lead to under-recognition, misdiagnosis, inadequate treatment, and suboptimal outcomes in FH. This forms the noesis of our editorial.

FH is a distinct genetic condition, found to be more common than thought earlier.[4] Recent data suggest that it may occur in up to 0.73% of the Danish population.[5] In Australia, 1 out of 267 adolescents is reported to have FH.[6] This makes FH much more common than other genetic disease such as Down's syndrome or Turner's syndrome.

Commonly, an autosomal co-dominant disease caused by mutation in the low-density lipoprotein (LDL) receptor gene, it may also be caused by mutation in proprotein convertase subtilisin/kexin Type 9 (PCSK9), apolipoprotein B (Apo B), or hypercholesterolemia adaptor protein (HAP) genes. Both homozygous (HoFH) and heterozygous (heFH) variants are known. HAP is characterized by extremely high LDL cholesterol, cutaneous and tendinous xanthomas, valvular and supravalvular stenosis, and premature onset of atherosclerosis and cardiovascular disease (CVD).

Various clinical criteria have been developed to aid in the diagnosis of FH and are accepted as an inexpensive, low technology, yet feasible, sensitive means of screening. Multiple international guidelines describe procedures for the screening, diagnosis, and management of FH.[7,8,9,10,11,12,13] In spite of this, however, <1% of the population with FH is estimated to have been diagnosed properly, even in developed nations.[14,15]

Late (or no) diagnosis and inadequate treatment lead to uncontrolled lipid levels, and do not help arrest the natural history of FH, which culminates in premature atherosclerosis and CVD. This, in no small way, contributes to be pandemic of metabolic disease and CVD that we all are uncomfortably familiar with.

Among the list of characteristics that a disease should have, in order to qualify for screening, the availability of intervention to prevent or treat it.[16] One of the reasons for the lack of interest in FH may be the lack of potent medical lipid-lowering therapy (LLT). Till recently, only high-intensity statins and apheresis were available for the management of FH. As results of medical LLT have hardly been encouraging, this may have acted as a deterrent to proactive screening.

In the past few years, three new classes of drugs have been approved by the US Food and Drug Administration for the management of HoFH. These include microsomal triglyceride transfer protein inhibitors (lomitapide), Apo B synthesis inhibitors (mipomersen), and PCSK9 inhibitors (PCSK9i) (alirocumab, evolocumab).[17] Results from Phase 2 and Phase 3 trials for PCSK9i, in particular, hold hope for better results in FH care.[18] Evolocumab is reported to be effective in lowering levels of LDL cholesterol in patients with both heterozygous and homozygous FH, with or without concomitant administration of cholesterol-lowering treatment. The maximum reductions in plasma levels of LDL cholesterol observed in patients with heterozygous disease were 59.2% (for patients treated with 140 mg evolocumab every 2 weeks) and 61.0% (for patients treated with 420 mg evolocumab monthly). Thus, PCSK9i are heralds of hope for specific target-oriented treatment of FH.

All these developments, however, have not translated into tangible benefits for the Indian FH community at large. Indian guidelines on lipid management pay fleeting attention to FH.[19] No independent risk scores or screening tools have been created for the Asian lipo-phenotype. Published data on FH from India is scarce and is limited to small case series and sporadic case reports.[20,21,22] No nationwide screening program or registry is operational, through these activities are essential if we wish to halt the endemic of premature CVD, in the country.

One explanation may be the lack of “ownership” of FH. While multiple subspecialties profess to manage dyslipidemia, few (at least in India) has advocated for the cause of FH. Internal medicine, pediatrics, cardiology, endocrinology, and neurology, all list dyslipidemia as a risk factor to be screened for, prevented, and treated. The sheer magnitude of mixed dyslipidemia that they deal with, however, perhaps prevents them from recognizing and espousing the special needs of people with FH.

The situation of FH is similar to that of Princess Draupadi, the heroine of the Mahabharata. Married to five powerful brothers, the Pandavas, she should have led a life of luxury. Yet, when she needed help, none came to her rescue. Similarly, FH seems to be neglected, even though the lobby for lipid control and CVD prevention is strong. FH needs the support of all concerned specialties, who must work together to sensitize physicians in this regard. Simple screening tools should be developed and popularized, and capacity building carried out for genetic confirmation. The approval of modern LLT, such as PCSK9i, should be fast tracked, to help reduce the burden of uncontrolled LH, accelerated atherosclerosis, and premature CVD in the country.

In the Mahabharata, it took nearly 14 years for Draupadi to get justice. We all need to act, together, to ensure that FH, the Draupadi of dyslipidemia, does not have to wait that long.

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