Familial hypercholesterolaemia and cascade testing in general practice

Lessons from COVID-19

Edward Garrahy, Clare Heal, Charlotte Mary Hespe, Jan Radford, Gerald F Watts, Tom Brett

THE COVID-19 PANDEMIC highlights the key role of general practice in Australian health service delivery, especially for our most vulnerable patients.[1] While terms such as 'index case' (defined as the first identified case in a group of related cases of a particular communicable or heritable disease) and 'cascade testing' (the extension of genetic testing to individuals at risk of inheriting a pathogenic variant previously identified in a biological relative) have long been associated with genetic testing for hereditary conditions among families, the recent increased public awareness of and experience with epidemiological concepts such as contact tracing offers new potential to improve detection and management of familial hypercholesterolaemia (FH) in the community.

On 1 May 2020, new Medicare Benefits Schedule (MBS) item numbers relating to genetic testing for FH were introduced in Australia,[2] offering a timely opportunity for general practice to collaborate with lipid specialists to facilitate improved detection and management. While an infectious disease such as COVID-19 cannot be directly compared with inherited conditions such as FH, lessons learned from the pandemic and developments in remote consulting can be applied to the management of FH.

Background

FH is an autosomal dominant condition characterised by marked elevation in plasma low-density lipoprotein cholesterol (LDL-C) concentration from birth, which, if untreated, accelerates premature atherosclerotic cardiovascular disease (ASCVD).[3] It has an estimated prevalence of one in 250 in the general population in Australia.[4] Currently >90% of Australia's 100,000 FH cases remain undetected despite the vast majority attending GPs at least annually.[5] The key is not simply diagnosing new index cases; rather, it is the 50% of first-degree relatives harbouring the disease who need systematic cascade testing to confirm or rule out the disease.

FH is a treatable cause of premature ASCVD, contingent on early diagnosis and appropriate therapy to minimise lifetime cholesterol burden, with primary prevention strategies potentially halving fatal coronary events.[6] Research shows cascade testing of close relatives is cost effective in preventing premature ASCVD.[7] Early diagnosis and treatment of FH has a large positive impact on public health[8] and is an exemplar of a personalised strategy in preventive medicine.[9]

Diagnosis of familial hypercholesterolaemia

A phenotypic diagnosis of FH can be made using Dutch Lipid Clinic Network (DLCN) criteria,[10] which incorporate LDL-C levels with clinical history and examination findings. However, phenotypic diagnosis has limitations: details of family history of hypercholesterolaemia and ASCVD, and clinical stigmata of FH can be unreliable markers of disease, with elevated LDL-C not discriminating sufficiently between FH and other dyslipidaemias.[4]

Pathogenic variants in three genes (low-density lipoprotein receptor, apolipoprotein B and proprotein convertase subtilisin/kexin type 9) account for 60–80% of cases with a clinical diagnosis of definite FH.[11] The identification of such defects confirms index case diagnosis and, such as in COVID-19, triggers further case finding. In the case of FH, close relatives are systematically targeted. New cases of FH found via genetic testing then become further probands for recurrent cascade cycles. The identification of the correct genotype may also guide therapy, as there is established heterogeneity of response within the FH group, as well as improve concordance with lipid-lowering therapy, predict risk and facilitate preconception and prenatal counselling.[4] Children of affected adults should also be tested, with those as young as 8–10 years of age benefiting from treatment.[12]

Lessons from the pandemic: Tracing and technology

The emergence of the COVID-19 pandemic has necessitated significant upskilling across the healthcare sector, particularly regarding the development

of national registries and in the provision of extra resources for contact tracing. Such new developments could be applied to the nationwide management of FH. While specialist support is required to authorise genetic testing for suspected FH index cases, once the disease is genetically proven, the patient's general practitioner can then arrange appropriate counselling and genetic testing for their close relatives. In the case of FH, cascade testing starts with first-degree relatives (parents, siblings and children) and can prove highly effective, given the one in two chance of inheritance and high penetrance of the gene variants. Consent from the index case is essential, with counselling for risks and benefits of early detection and treatment provided as an integral part of the process. The lack of infrastructure to facilitate cascade testing from primary care is a major handicap.[11]

Telehealth consultations have been used frequently to avoid face-to-face contact during the pandemic. They may also be turned to advantage in the sphere of inherited conditions. The care of people with FH in Australia is challenged by issues such as complex family dynamics, poor health literacy, clinician understanding of genomics, and the availability of specialists with an interest in lipidology.[13] Given that families in remote locations are less likely to avail of the care they need, video consultations may prove helpful by overcoming geographic boundaries, with the assistance of the new telehealth MBS item numbers.[1] Although telehealth does not directly assist with contact tracing, it may prove helpful in the identification of suspected index cases among patients who would not have been willing to travel for an appointment. As the nature of FH does not demand an in-office assessment for risk stratification (DLCN criteria can be applied on the basis of the history and examination obtained from a telehealth consult), those deemed at risk can then proceed to appropriate testing, contributing to the formulation of a nationwide registry.

Future directions

In the face of the COVID-19 pandemic, the Australian healthcare service has proven that it can deliver frameworks enabling swift contact tracing and testing.[1] Such frameworks could be applied in a modified format to the diagnosis of inherited conditions such as FH. Additionally, the widespread currency of telehealth consultations has democratised care and facilitated the availability of remote consults, which, used in tandem with the new MBS item numbers, can help to bring the benefits of genetic testing to the many Australians with undiagnosed FH, thereby providing a novel paradigm for personalised medicine within Australia.[14]

Authors

Edward Garrahy MB BCh BAO, Academic General Practice Registrar, Launceston Clinical School, Tasmanian School of Medicine, University of Tasmania, Tas; General Practice Registrar, Newstead Medical, Tas. edward.garrahy@utas.edu.au

Clare Heal MBChB, DRANZCOG, DipGUMed, FRACGP, MPHTM, PhD, Promotional chair, Discipline of General Practice and Rural Medicine, Mackay Clinical School, James Cook University College of Medicine and Dentistry, Qld

Charlotte Mary Hespe FRACGP, MBBS (Hons), DCH (Lon), Associate Professor, Head General Practice and Primary Care Research, School of Medicine Sydney, The University of Notre Dame, NSW; General Practitioner, Glebe Family Medical Practice, NSW

Jan Radford MBBS, MPsychMed, MEd, FRACGP, FARGP, GAID, AFANZAHPE, Churchill Fellow 2017, Associate Professor of General Practice, Launceston Clinical School, Tasmanian School of Medicine, University of Tasmania, Tas; General Practitioner, West Tamar Health, Tas; Provost, RACGP Tasmanian Faculty, Tas

Gerald F Watts DSc, PhD, MD, FRACP, FRCP, Winthrop Professor and Consultant Physician, School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, WA; Lipid Disorders Clinic, Cardiometabolic Service, Departments of Cardiology and Internal Medicine, Royal Perth Hospital, WA

Tom Brett MD, FRACGP, MRCGP, Professor and Director, General Practice and Primary Health Care Research, School of Medicine, The University of Notre Dame, WA; General Practitioner, Mosman Park Medical Centre, WA

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