Ensuring timely genetic diagnosis in adults

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Adults with undiagnosed genetic disorders wait an average of 19 years to receive an explanation for their symptoms and to receive targeted care.[1] Recently, this problem was highlighted in 3 *CMAJ* case reports of rare genetic diseases, namely acute intermittent porphyria,[2] hereditary angioedema[3] and familial Mediterranean fever.[4] These case reports highlight 5 key clinical situations that should trigger clinicians to start a genetic work-up.

A genetic diagnosis should be suspected in a patient with any of the following: multiple hospital visits and investigations without a unifying pathology, atypical response to conventional treatment, multiple diagnoses that are seemingly unrelated on personal or family history, an illness in a patient of a different demographic than is typical, or a patient lacking the expected risk factors for their presentation.

In all 3 related cases, the patients presented multiple times to the emergency department and other care environments without any unifying pathology.[2–4] In 2 of the cases, the patients required hospital admission,[3,4] 1 of them for more than 2 months.[4] All of the patients had a suboptimal response to conventional treatment and continued to be symptomatic until the correct diagnosis was made.[2–4] Although it may be challenging to differentiate a genetic disorder from a functional disorder, for which investigations may be similarly inconclusive, the presence of persistent abnormal clinical findings — such as abnormal vital signs, unexplained clinical markers and continued objective signs on physical examination — can help distinguish between them.[2–4]

Suspicion of an underlying genetic diagnosis should be increased for adults with a history of seemingly unrelated diagnoses in multiple systems, particularly when the patient is in a different demographic than is typical for a particular condition or if they lack the expected risk factors.[1–4] In one of the related cases, the patient's previous incorrect diagnoses of appendicitis, pancreatitis and cholecystitis appeared to have been made in the absence of risk factors.[4] Atypical imaging or laboratory findings and lack of expected pathology further supported the possibility of a unifying genetic diagnosis. Furthermore, with the preexisting diagnosis of hypermobile Ehlers–Danlos syndrome,[4] it would have been reasonable to initiate a full genetic assessment, given the patient's atypical recurrent fevers.

Key points

- Genetic diagnoses in adult patients are often delayed, sometimes by a decade or more.
- A genetic diagnosis should be suspected in a patient with any of the following: multiple hospital visits and investigations without a unifying pathology, atypical response to conventional treatment, multiple diagnoses that are seemingly unrelated on personal or family history, an illness in a patient of a different demographic than is typical or a patient lacking the expected risk factors for their presentation.
- Diagnosing genetic disease is now more feasible with the increased availability of publicly funded genetic tests and with front-line clinicians ordering targeted tests, with the support of guidelines or genetic care providers.
- The growing availability of targeted management and therapies has added a degree of urgency to create a sustainable framework of genetic services that better serves patients with undiagnosed genetic diseases in Canada and can help fulfill the promise of personalized medicine.

Although a family history may not always be informative, identifying family members with similar clinical problems may not only point toward a genetic diagnosis, but can enable screening of other at-risk family members. Family history was not strongly emphasized in the case reports of hereditary angioedema[3] or familial Mediterranean fever,[4] although these are autosomal dominant conditions, but was key in the case of acute intermittent porphyria, where the patient had a grandparent with distinctive urinary changes.[2] For families with known or highly suspected genetic diagnoses, GeneReviews (https://genereviews.org/) offers expert summaries of a wide variety of genetic conditions, including information on diagnosis and management.

Uncovering the genetic cause of all 3 of the related cases improved management, reduced health care use and provided the immeasurable benefit of a confirmed diagnosis for the patients. Diagnosing genetic disease in adult patients is now more feasible with the increased availability of publicly funded genetic tests. Front-line clinicians can often order targeted tests

such as gene panels, with widened eligibility. Genome-wide testing options (e.g., whole exome, whole genome sequencing) are increasingly available for patients with complex presentations,[5] although eligibility criteria vary by province. Determination of the appropriate type of genetic test (i.e., targeted or genome-wide testing) is dependent on the patient's presentation. When a patient meets clinical criteria for a genetic diagnosis or when presenting features form the pattern of a recognizable syndrome (e.g., hypertrophic cardiomyopathy, short stature and learning disability suggesting Noonan syndrome), targeted genetic testing is most appropriate. In situations without a recognizable syndrome or for which targeted testing has failed to yield a diagnosis, genome-wide genetic testing is preferred.[6]

With the expansion of genome-based testing in Canada, the skill sets of genetic care providers — including both medical geneticists and genetic counsellors — have evolved to focus on interpretation of complex results and management.[6] Front-line providers are increasingly arranging targeted genetic testing with genetic counsellor support or by applying appropriate guidelines for breast, ovarian, prostate, pancreatic and colon cancer or investigation of developmental delay.[7,8] This allows for higher volumes of patients to be given diagnoses and enables geneticists to focus on complex case management.

Genetic causes should be actively considered for adult patients who present with any of the key clinical situations outlined here, and should result in a consultation with a genetic care provider regarding appropriate next steps, either formally or by e-consultation.[9] If uncertain, providers can use the Online Mendelian Inheritance of Man (https://omim.org/) to search for potential genetic diagnoses based on imaging and clinical findings to support consultation. Other online resources, such as Genetics Education Canada - Knowledge Organization (https://geneticseducation.ca/), offer information on common genetic conditions and a comprehensive list of genetics clinics in Canada where referrals can be made.

Proactive genomic sequencing would have led to a definitive diagnosis in all of the related cases. However, making such an approach routine would require reimagining models of care and increased investment in genetic infrastructure to integrate testing, measure test performance and increase genetic literacy across disciplines.[10] The growing availability of targeted management and therapies has added a degree of urgency to create a sustainable framework of genetic services that better serves patients with undiagnosed genetic conditions in Canada and makes fulfilling the promise of personalized medicine a more attainable reality.

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