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Hidden in Plain Sight: Cardiac Amyloidosis as a Cause of Heart Failure
Dr. Rahul Deo is the chief data scientist at One Brave Idea, an associate physician at Brigham and Women's Hospital, and a faculty member in the Department of Medicine at Harvard Medical School. In his recently published webinar “Hidden in Plain Sight: Cardiac Amyloidosis as a Cause of Heart Failure,” hosted collaboratively by the American Medical Group Association (AMGA) and its Chairman Circle Member Pfizer Inc., Dr. Deo suggests that education and technology can combine to be a valuable strategy in identifying patients with rare diseases who may otherwise go undetected in America's healthcare systems.

Dr. Deo explained that for the last decade or so, his clinical practice has been focused on treating rare forms of heart failure. Characterized by inadequate pumping of the heart where blood simply isn’t getting to the rest of the body, heart failure (HF) affects approximately 6.5 million Americans, a number that is expected to rise by 46% by 2030.1,2,† In addition to the human cost of the disease, the financial cost of HF in the United States is estimated at $30.7 billion,1,2,† over half of which is spent on hospitalizations.1-3 Troubling still is that approximately 23% of Medicare patients with a diagnosis of HF are readmitted within 30 days.4

**Redefining Classification**

Dr. Deo reviewed the many causes and contributors to heart failure and said, “as you might guess, given the sort of vagueness with which the term heart failure is described, in many patients, there could be a lot of different contributing factors. It’s almost impossible to pinpoint exactly which one is responsible, and that’s in part because a lot of these predisposing factors are quite common. These contributing factors lead to small amounts of damage over decades and decades

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**Hidden in Plain Sight: Cardiac Amyloidosis as a Cause of Heart Failure**

*Brigham and Women’s Physicians Organization*

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“**We don’t really know exactly how much of this disease is really out there, and part of the problem is you don’t have a very clear and consistent system to be able to identify all patients.”**

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**Heart failure remains the second highest cause of hospital admissions in patients over the age of 65, after septicemia.**

- **6.5 million people** are living with heart failure in the United States
- The annual cost of heart failure is estimated at **$30.7 billion**
- Approximately **23% of Medicare patients** with a diagnosis of heart failure were readmitted within 30 days
Dr. Deo pointed out that heart failure is currently classified in a “somewhat crude way” on the pumping function of the heart itself, measured by ejection fraction. Commonly, patients with heart failure present with a reduced ejection fraction, also referred to as HFrEF. However, there is an increasing number of heart failure patients who present with preserved ejection fraction, or HFpEF (approximately half of heart failure hospitalizations). Increasingly, HFpEF is being attributed to specific causes of cardiomyopathy.

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that occurs due to extracellular deposition of misfolded proteins, known as amyloid fibrils. CA is a rare, fatal, and underdiagnosed group of diseases that can lead to HF. CA typically presents as HFpEF, eventually progressing to HFrEF.

### Raising Suspicion and Evaluating

CA can be broken down into specific subtypes, including light-chain amyloidosis (AL) and transthyretin amyloid cardiomyopathy (ATTR-CM), which account for approximately 95% of all CA diagnoses. Among patients with suspected cardiac amyloidosis, it is imperative to rule out AL as it is considered a hematologic urgency and requires... The suspicion is that we’re probably only detecting low single digits in terms of percentage of this disease.

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### Main Types of CA

- **Cardiac Amyloidosis**
  - Light Chain Amyloidosis (AL)
  - Transthyretin Amyloid Cardiomyopathy (ATTR-CM)
  - Others Include: Serum Amyloid A, Apolipoprotein A1, Immunoglobulin Heavy Chain, Atrial Natriuretic Peptide (ANP)

  **Subtypes of ATTR-CM**
  - Wild-type ATTR (ATTRwt)
  - Hereditary ATTR (hATTR)

AL and ATTR-CM account for ~95% of all CA diagnoses.
“Rather than get bogged down by the algorithm, it’s much more important to think about, at the end of the day, the fact that you have input data, you have some examples, and you want to learn how to distinguish one disease from the other.”

immediate follow-up. ATTR-CM presents as either wild-type or hereditary. For those with hereditary ATTR-CM, genetic counseling and testing of the family is important to aid in patient management.13-15

Dr. Deo pointed out that there are many reasons that ATTR-CM patients may go undiagnosed. Missed, delayed, and incorrect diagnosis may lead to an inefficient use of resources and negative patient outcomes.16

Commonly, the point of entry into the healthcare system for ATTR-CM patients is through primary care. However, given the infrequency of presentation, primary care clinicians may lack the clinical experience with ATTR-CM to suspect it or the testing capabilities for proper diagnosis.17

To help clinicians better identify ATTR-CM, Dr. Deo reviewed a case study to illustrate how a patient with ATTR-CM might present. He also highlighted the red flags that may help to identify these patients, making the point that not all patients with ATTR-CM will have all the symptoms. “None of these symptoms by themselves seem to be that exciting, but they are all affecting the same patient. If you look at when these things occur, the cardiac symptoms don’t necessarily happen first. It’s generally a constellation of things to put all together,” Dr. Deo said.

Fortunately, nowadays, when ATTR-CM is suspected, there is a clear pathway to diagnosis and treatment options are available.13,21

Education to providers about CA and ATTR-CM may not be sufficient due to the rareness of the disease and the myriad symptoms with which patients may present. One way to support providers as they seek to identify patients’ underlying cause of HF is to enable technology to support the diagnosis of rare diseases, like ATTR-CM.

Artificial Intelligence (AI)22-24

Parallel to his own clinical work, Dr. Deo’s research over the years has steered him toward the utilization of AI in medicine. He leads a large machine learning implementation and human translation biology program at One Brave Idea. Dr. Deo is optimistic that AI may support the identification of patients suffering from rare diseases such as ATTR-CM.
Dr. Deo shared from his experience that AI algorithms can take broadly available EHR inputs (diagnostic codes, images, etc) and estimate probabilities of disease often with high accuracy. The clinical data that serves as inputs to AI varies in availability and information content, but Dr. Deo and others have shown that healthcare systems can leverage these signals to detect diseases such as cardiac amyloidosis. With this new set of information at hand, educated decisions can be made regarding more focused follow-up diagnostic testing and risk assessment.

The potential upside with these types of systems is large, but there are challenges to validating and implementing any novel diagnostic approaches, especially if they disrupt existing clinical workflow. Dr. Deo reflected, "One of the things that has been recognized with a lot of automated systems is if all you do is make more work for the people, you're not going to make any friends and adoption will be low." Dr. Deo recommends thinking about whose workflow will be improved in this process, rather than just generating a flurry of pop-up windows. One key to success is being sensitive to these things, which are solvable.

Providers need to be realistic on training. As is the case for any diagnostic test, education around a specific machine learning algorithm is necessary. Providers will likely appreciate how technology can support them in the identification of patients suffering from rare diseases such as ATTR-CM.

AI, along with provider education, may help healthcare providers interact, guide, and facilitate the right person-to-person strategies and decisions downstream. The combination of education and technology may offer health care systems the best chance of identifying and managing patients with rare diseases such as ATTR-CM.

*American Heart Association (AHA) estimate.

†Cost estimates include both direct and indirect costs for treatment and care of patients with HF. Direct costs were estimated to be 68% of total HF costs.¹ Direct costs were estimated using the 2004-2008 Medical Expenditure Panel Survey (MEPS). Indirect costs were estimated based upon per capita work loss and home productivity loss costs, which were attributable to HF based upon estimates from the 2001-2008 MEPS data and a negative bimodal model for annual days of work missed and annual days in bed attributable to illness or injury as a function of HF or other comorbid conditions.²
Q: *Why do you think the diagnosis rate of ATTR-CM is so low?*

A: I think, first, there is a tendency that if there is not a treatment solution for something, someone may not look for it. Many of us trained during a time where there weren’t therapies available and our own approaches were very much tailored to “if it’s not treatable, I’m not going to go out of my way to be able to detect it.” Second, diseases that have spanned multiple systems in a somewhat nonspecific way are the hardest ones for anyone to detect because they require you to combine lots of different things together. I think those 2 things end up making diagnosis particularly challenging.

Q: *What approach would you recommend a system take in identifying rare disease patients?*

A: Ideally, you would build as many things as possible in a partially automated way, where you take what inputs are likely available in routine care and figure out a way to build a model around these and facilitate the next diagnostic steps. This helps make providers’ lives easier and reduce variability. That is the automated solution. Education can work but can be challenging as you must hit all the specialties together. Automation is the better chance to make a solution.

Q: *Can you restate when you should start to consider cardiac amyloidosis?*

A: I look at patients that have heart failure and look for other features that might be surprising (e.g., preserved ejection fraction, carpal tunnel syndrome, lumbar spinal stenosis). The combination of noncardiac and cardiac manifestations together can be quite a bit more helpful. After that, you get help from an electrocardiogram in terms of seeing some of the characteristic reduction in voltage as a disease feature but eventually you’ll want an echocardiogram. All of these things are clues that can help in getting to a point where you suspect cardiac amyloidosis. You need to make observations that merge noncardiac manifestations with manifestations of heart failure itself.
References


