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Hereditary Transthyretin Amyloidosis in African Americans: Challenges in Diagnosis, Patient Education, and Nursing Implications

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ABSTRACT

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive disease caused by mutations in the transthyretin (TTR) gene, resulting in amyloid deposition in multiple organs. African Americans are disproportionately affected, primarily due to the V122I TTR variant. Despite advances in diagnostic tools and therapies, hATTR remains underdiagnosed and frequently misdiagnosed as congestive heart failure (CHF) or diabetic neuropathy, leading to delayed treatment. This nursing-focused narrative explores the epidemiology, pathophysiology, diagnosis, treatment options, and prognosis of hATTR amyloidosis, with a focused discussion on its impact within the African American community. The critical role of nurses in reducing misdiagnosis and improving patient outcomes is also highlighted. Addressing disparities and enhancing nursing education are crucial steps toward better management of hATTR amyloidosis.

Keywords: Hereditary transthyretin amyloidosis, hATTR, African Americans, amyloidosis diagnosis, misdiagnosis, nursing practice, patient education, V122I mutation, cardiac amyloidosis, health disparities

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INTRODUCTION

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant, multisystemic disorder characterized by the extracellular deposition of misfolded transthyretin proteins as amyloid fibrils. The disease presents variably, often leading to cardiac, neurological, and gastrointestinal manifestations. Although considered a rare disease, recent research indicates that hATTR amyloidosis is more prevalent among individuals of African descent than previously recognized. Approximately 3–4% of African Americans carry the V122I mutation in the TTR gene, markedly increasing their risk for late-onset cardiomyopathy associated with amyloidosis (Damrauer et al., 2019).

Despite improvements in diagnostic technologies and therapeutic interventions, many cases remain undiagnosed or misdiagnosed, often mistaken for more common conditions such as congestive heart failure (CHF) or diabetic neuropathy. Such delays in diagnosis significantly worsen patient outcomes and survival rates. Early recognition, genetic testing, and targeted treatment are vital to improving prognoses. This nursing-focused narrative synthesizes current research on hATTR amyloidosis in African American populations, describes diagnostic and treatment approaches, highlights challenges in clinical practice, and emphasizes the role of nursing professionals in education, advocacy, and early detection efforts. By addressing these critical aspects, this work seeks to contribute to improved patient care and reduction of health disparities associated with hATTR amyloidosis.

Epidemiology and Prevalence in African Americans

Hereditary transthyretin amyloidosis (hATTR) is a global disease with significant ethnic and geographic variability. In the United States, it is estimated that approximately 3–4% of African Americans carry the V122I (valine-to-isoleucine substitution at position 122) mutation in the transthyretin (TTR) gene (Quarta et al., 2015). This mutation predominantly affects cardiac tissue and is associated with an increased risk for late-onset, restrictive cardiomyopathy.

Recent cohort studies have emphasized the clinical burden of this mutation. Damrauer et al. (2019) analyzed large genomic databases. They found that individuals carrying the V122I variant had a significantly higher risk of heart failure compared to non-carriers, independent of traditional cardiovascular risk factors, like hypertension, diabetes, and smoking. In a cohort of 9,862 non-Hispanic Black/African American women (mean age 62), among whom 333 were V122I carriers, the annualized multivariable-adjusted risk for the composite CVD endpoint (including acute heart failure, CHD, stroke, and CVD death) was 2.08% per year for carriers vs. 1.55% for non-carriers, after adjusting for demographics, lifestyle, medical history, blood pressure, BMI, and physical activity (Haring et al., 2023). That represents a relative increase of about 34% in annual CVD risk among carriers compared to non-carriers—an effect that is independent of traditional risk factors (Haring et al., 2023). Despite the relatively high carrier frequency, clinical recognition remains poor, leading to underdiagnosis and undertreatment.

The lack of awareness, coupled with overlapping clinical presentations (e.g., heart failure with preserved ejection fraction), exacerbates racial disparities in healthcare. African Americans with hATTR are often misdiagnosed, receive inappropriate heart failure therapies, and experience adverse health outcomes compared to other racial groups. The underrepresentation of African Americans in early amyloidosis clinical trials has further limited the understanding of the natural history of the disease in this population.

Addressing this disparity requires both increased genetic screening initiatives in African American communities and greater clinical vigilance among healthcare providers, particularly nurses who are often on the front lines of patient assessment and education.

Pathophysiology and Clinical Manifestations

Hereditary transthyretin amyloidosis (hATTR) arises from mutations in the TTR gene, leading to destabilization of the transthyretin tetramer. This destabilization causes misfolded monomers to aggregate into amyloid fibrils, which deposit in various tissues and impair organ function (Maurer et al., 2017). The TTR protein, primarily synthesized in the liver, functions typically to transport thyroxine and retinol-binding protein. Mutations impair its stability, shifting the protein toward an amyloidogenic pathway.

Clinical manifestations vary widely depending on the specific mutation and organs affected. In African Americans with the V122I mutation, the disease primarily manifests as a progressive infiltrative cardiomyopathy. Standard cardiac features include:

- Heart failure with preserved ejection fraction (HFpEF)
- Arrhythmias, particularly atrial fibrillation
- Conduction system disease, often requiring pacemaker placement

Neurological involvement, although less common in the V122I population, can include:

- Peripheral neuropathy, presenting as numbness, tingling, and pain in the extremities
- Autonomic neuropathy, leading to orthostatic hypotension, gastrointestinal dysfunction, and urinary retention

Non-specific symptoms, such as carpal tunnel syndrome, unexplained weight loss, and fatigue, may precede cardiac involvement by years but are often overlooked in clinical practice.

Non-Invasive Diagnostics

The diagnosis of hereditary transthyretin amyloidosis (hATTR) remains challenging due to its variable clinical presentation and symptom overlap with other diseases, such as congestive heart failure (CHF) and diabetes. Early diagnosis is critical, as it allows

for intervention that may significantly alter disease progression and improve patient's quality of life.

Genetic Testing and Screening

Genetic testing for mutations in the TTR gene is the gold standard for diagnosing hATTR. Patients with a family history of amyloidosis or those presenting with atypical heart failure, particularly when they have a high suspicion of hereditary forms of heart disease, should undergo genetic testing (Castaño et al., 2018). Testing typically involves next-generation sequencing to identify mutations such as the V122I mutation, which is prevalent in African American populations. In individuals without a clear family history but with clinical symptoms of amyloidosis, genetic counseling is recommended. Screening for the V122I mutation can help identify carriers who may not yet exhibit symptoms but are at increased risk.

Imaging and Biopsy Techniques

Cardiac imaging plays a pivotal role in the diagnostic work-up for amyloidosis. Echocardiography often reveals left ventricular hypertrophy (LVH) with preserved ejection fraction (EF), a hallmark of cardiac involvement in hATTR. However, to distinguish amyloidosis from other causes of heart failure, cardiac MRI and technetium pyrophosphate (99mTc-PYP) scintigraphy are increasingly used for non-invasive diagnosis. These imaging techniques can detect amyloid deposition in the heart, which is particularly useful in cases where genetic testing results are inconclusive.

Endomyocardial biopsy remains the most definitive method for diagnosing cardiac amyloidosis, although it is an invasive procedure that may be reserved for cases where non-invasive tests are inconclusive. Biopsy tissue, typically obtained from the heart or abdominal fat, is examined using congo red staining, which highlights the presence of amyloid deposits under polarized light.

Therapeutic Treatments

While there is no cure for hereditary transthyretin amyloidosis (hATTR), advances in pharmacologic and supportive therapies have significantly improved outcomes for patients. Treatment goals focus on reducing amyloid production, managing symptoms, and improving quality of life. Various drugs are used such as patisiran and inotersen. However, this article will be discussed one in particular as the first approved therapy for hATTR.

Tafamidis: The First FDA-Approved Treatment

The FDA's approval of tafamidis (Vyndaqel) marked a significant milestone in the treatment of hATTR. Tafamidis is a transthyretin stabilizer that binds to the TTR protein and prevents it from dissociating into misfolded monomers, which are responsible for amyloid fibril formation. By stabilizing the TTR tetramer, tafamidis

halts the progression of amyloid deposition and reduces organ damage, particularly in the heart.

Clinical trials have shown that tafamidis significantly improves both functional capacity and survival rates in patients with hATTR, especially those with cardiac involvement. In a pivotal study by Coelho et al. (2018), tafamidis was associated with a reduction in mortality and hospitalization due to heart failure compared to the placebo.

Mortality, Prognosis, and Misdiagnosis in hATTR

The prognosis of hereditary transthyretin amyloidosis (hATTR) depends on the mutation type, the extent of organ involvement, age at onset, and the timing of diagnosis and treatment. Without timely intervention, hATTR is progressive and often fatal.

Why Mortality Occurs in hATTR

Mortality is primarily driven by end-organ failure, most commonly:

- **Cardiac disease:** The leading cause of death, especially in patients with the V122I mutation, which is prevalent in African American populations. Amyloid deposition in the myocardium produces restrictive cardiomyopathy, diastolic dysfunction, arrhythmias, and heart failure, which may progress to sudden cardiac death.
- **Neurological complications:** Seen more commonly with variants such as V30M, where severe peripheral and autonomic neuropathy can lead to gastrointestinal dysfunction, malnutrition, and increased morbidity.
- **Renal and hepatic involvement:** Less common but may contribute to mortality in advanced cases.

Cardiac Involvement and Survival

Cardiac amyloidosis—particularly in those with the V122I variant—is associated with a poor prognosis when untreated. Restrictive cardiomyopathy results in HFpEF, leading to progressive heart failure. Median survival for untreated cardiac hATTR is 2–3 years after heart failure symptom onset (Dungu et al., 2019).

Early treatment markedly improves outcomes. Tafamidis, a TTR stabilizer, has been shown to:

- Reduce all-cause mortality by ~30%
- Lower heart-failure hospitalizations
- Improve 5-year survival to 65–70%, compared to significantly lower rates in untreated patients (Coelho et al., 2018).

Challenges and Misdiagnosis

hATTR is frequently misdiagnosed because its symptoms overlap with more common conditions and because general awareness is low, particularly in African American communities. Misdiagnosis leads to treatment delays, ongoing organ damage, and poorer overall survival.

Cardiac hATTR commonly presents as HFpEF, with symptoms such as dyspnea, edema, and fatigue—making it clinically indistinguishable from traditional CHF (Sabbah et al., 2019). Because ejection fraction remains preserved, providers may not suspect amyloidosis. This results in treatment directed at CHF rather than at amyloid deposition, delaying disease-modifying interventions.

Neuropathic symptoms are often mistaken for diabetic neuropathy, idiopathic neuropathy, or autonomic disorders such as Parkinsonian syndromes. Early hATTR neuropathy closely resembles diabetic peripheral neuropathy, further contributing to diagnostic delays.

The Role of Nurses in Reducing Misdiagnosis

Nurses are central to improving early detection and reducing misdiagnosis of hereditary transthyretin amyloidosis (hATTR), particularly among African American patients who experience disproportionately high rates of delayed diagnosis. As frontline clinicians, nurses frequently encounter patients presenting with nonspecific symptoms—such as unexplained weight loss, peripheral neuropathy, early autonomic dysfunction, gastrointestinal disturbances, or heart-failure symptoms that do not align with typical CHF profiles. Emerging literature highlights the need for multidisciplinary awareness and nurse-driven screening to narrow this diagnostic gap (Adams et al., 2024). Evidence-based nursing practice requires a heightened index of suspicion when symptoms are atypical, progressive, or refractory to standard therapies.

Evidence-Based Nursing Interventions

1. Early Screening and Assessment Protocols

Nurses can implement structured screening approaches for high-risk groups—such as African American adults over age 60 with HFpEF, resistant neuropathy without diabetes, bilateral carpal tunnel syndrome, or a family history of "heart problems" or early heart failure. Nursing assessment should routinely include:

- Red-flag symptom screening (e.g., orthostatic hypotension, early satiety, unintentional weight loss, paresthesia, bilateral carpal tunnel history, low-voltage EKG with LV thickening on imaging).
- Use of validated tools such as the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Neuropathy Impairment Score (NIS), and the COMPASS-31 autonomic symptom scale.
- Recognition of symptoms unresponsive to typical CHF or neuropathy treatments, prompting timely referral for genetic testing or cardiology/neurology evaluation. These nurse-led detection strategies significantly support early referral pathways (Waddington et al., 2025).

2. Culturally Tailored Education and Communication

African American patients frequently face barriers including mistrust of the healthcare system, limited disease awareness, and under-recognition of genetic disorders in primary care. Nurses can reduce these disparities through:

- Culturally responsive communication that validates patient concerns and addresses historical mistrust directly.
- Education that frames hATTR not as a "rare" disease, but as a relatively common hereditary condition in African American communities due to the prevalence of the V122I variant.
- Use of plain-language teaching tools, community-based education, family-centered sessions, and culturally relevant metaphors to reinforce understanding of hereditary risk.

Research demonstrates that culturally matched and community-centered education strategies help overcome health disparities and improve engagement in genetic screening among African American patients (Kittles et al., 2024).

3. Nursing-Led Follow-Up and Care Coordination

Nurses play a crucial role in ensuring continuity of care by:

- Conducting follow-up calls to monitor symptom progression, medication adherence, and treatment side effects (e.g., tafamidis or RNA-silencing therapies).
- Coordinating genetic counseling appointments and ensuring family members are aware of testing options.
- Establishing nurse-driven pathways that flag patients who require cardiology, neurology, or amyloidosis-center referrals.

Nursing-led care models, particularly those that integrate cardiology and neurology follow-up, have been shown to reduce diagnostic delays and improve overall outcomes in patients with hereditary amyloidosis (Waddington et al., 2025).

Addressing Health Disparities and Barriers to Diagnosis

African American patients frequently experience delayed diagnosis due to systemic issues such as diagnostic overshadowing, implicit bias, under-referral for genetic testing, and limited awareness of hereditary conditions among primary providers. Nurses can help close these gaps by:

- Advocating for equitable diagnostic evaluation when symptoms do not match common chronic conditions.
- Ensuring genetic counseling resources are accessible, affordable, and culturally appropriate.
- Building trust through ongoing communication, transparency about genetic testing, and shared decision-making strategies.
- Identifying social determinants of health—transportation barriers, caregiver strain, insurance challenges—that may prevent follow-up care.

Scholars emphasize that these systemic disparities are major drivers of late-stage diagnosis among African American patients with hereditary diseases, underscoring the essential role of nursing advocacy (Kittles et al., 2024).

By integrating evidence-based assessment, culturally informed education, and nurse-led coordination, nurses significantly enhance the likelihood of early

diagnosis and timely treatment, ultimately improving patient outcomes (Adams et al., 2024; Waddington et al., 2025).

Patient Education Strategies

Patient education remains a cornerstone of effective hATTR management. Nurses help patients understand disease progression, recognize worsening symptoms, adhere to pharmacologic treatments, and engage in routine monitoring. For African American patients, who may be unfamiliar with hereditary amyloidosis, tailored education improves disease literacy and encourages participation in genetic testing and clinical trials. Empowered patients are more likely to seek timely care, adhere to therapy, and participate in screening that may benefit affected family members.

Genetic Education and Counseling

One of the most important aspects of patient education in hATTR is genetic counseling. Many individuals with hATTR have a family history of the disease, and genetic testing plays a vital role in confirming the diagnosis. Nurses can guide patients through the process of genetic screening and counseling, helping them understand the implications of a positive result. Education should focus on the following:

- **Inheritance patterns**: hATTR is inherited in an autosomal dominant pattern, meaning that each child of an affected parent has a 50% chance of inheriting the mutation. Educating patients on the genetic nature of the disease allows them to make informed decisions about family planning and whether to pursue genetic testing for their children or other family members.
- **Impact of genetic results**: It is essential to explain the emotional and psychological impact that receiving a positive genetic diagnosis can have on patients and their families. Support services, such as counseling and support groups, should be recommended to help patients navigate the complexities of a hereditary disease diagnosis.

Support Networks and Resources

Connecting patients with support groups and community resources is a vital component of patient education. Support groups offer emotional support, practical advice, and the opportunity to share experiences with others living with hATTR. Nurses can help patients find these resources and encourage their participation in clinical trials, which offer access to cutting-edge treatments and contribute to the broader understanding of the disease.

Treatment Adherence and Lifestyle Management

Treatment adherence and lifestyle management are essential components of effective hATTR care, and nurses play a pivotal role in supporting both. Helping patients understand how disease-modifying therapies such as tafamidis slow progression and protect organ function can improve medication adherence. Nurses also reinforce the

importance of regular monitoring, including blood tests, cardiac assessments, and neurological evaluations to track treatment response and detect complications early. In addition to pharmacologic therapy, nurses guide patients in lifestyle modifications that enhance well-being, such as adopting low-sodium diets for cardiac symptoms, adjusting nutrition to support neuropathy management, and engaging in low-impact exercise to improve strength and reduce fatigue. They also assist with symptom control by offering pain management strategies, discussing physical therapy options, and recommending assistive devices to support mobility and daily functioning.

CONCLUSION

Hereditary transthyretin amyloidosis (hATTR) has long been underrecognized and underdiagnosed; increasing awareness and advances in genetic testing, diagnostic imaging, and pharmacological treatments have significantly improved patient outcomes. However, the challenges associated with misdiagnosis, particularly the tendency to mistake hATTR for more common conditions such as congestive heart failure (CHF) or diabetic neuropathy, remain significant barriers to early detection and intervention.

This condition has a profound impact on African American populations, particularly due to the V122I mutation, which is prevalent among this group. As such, it is imperative to tailor care strategies to recognize and address the specific genetic and clinical features that may present in this population. Early diagnosis and treatment are key to improving prognosis and minimizing organ damage, particularly when therapies such as tafamidis are employed.

Incorporating patient education into routine care for hATTR is essential to improve treatment adherence and empowering patients to take an active role in managing their condition. Nurses are particularly well-positioned to educate patients on the importance of genetic testing, symptom recognition, lifestyle changes, and medication adherence. Furthermore, they play a critical role in advocating for early diagnosis and coordinating care with other healthcare providers to ensure the best possible outcomes for individuals living with hATTR.

As ongoing research continues to shed light on the genetics, pathophysiology, and treatment of hATTR, the nursing profession will be integral in translating these findings into improved clinical practice. With early detection, targeted therapies, and patient education, the outlook for individuals diagnosed with hATTR has the potential to improve dramatically, offering hope to many in the African American community and beyond.

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