Late-Onset Genetic Cholestasis: Underdiagnosis in Adults Examined

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Late-onset genetic cholestatic diseases, while rare, present a significant diagnostic challenge in adult hepatology, often mimicking more common liver conditions. The immediate takeaway from discussions at EASL 2026 is that a substantial number of these cases are likely undiagnosed, prolonging patient morbidity and delaying access to targeted therapies.

KEY TAKEAWAYS

- The Pivot: Genetic cholestatic diseases, traditionally considered pediatric, are now recognized as a significant cause of adult liver disease.
- The Data: Estimates suggest up to 10-15% of unexplained adult cholestasis may have a genetic basis, with specific gene mutations identified in a subset.
- The Action: Clinicians should consider genetic testing earlier in adults with unexplained, persistent cholestasis, particularly when common etiologies are excluded.

Genetic cholestatic diseases, such as progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC), are classically associated with pediatric onset. However, a growing body of evidence indicates that these conditions, and others like ABCB4 deficiency (formerly known as MDR3 deficiency), can manifest with a late-onset phenotype in adulthood.1 This late presentation often leads to diagnostic delays, as symptoms like pruritus, fatigue, and jaundice are non-specific and can be attributed to more prevalent conditions such as primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).2 The clinical dilemma lies in differentiating these genetic disorders from acquired cholestatic liver diseases, which have distinct management strategies.

The underdiagnosis of late-onset genetic cholestatic diseases in adults has significant implications for patient care. Without a precise genetic diagnosis, patients may undergo unnecessary invasive procedures, receive ineffective treatments, and miss opportunities for specific therapies that target the underlying genetic defect. For instance, some genetic cholestatic conditions may respond to ursodeoxycholic acid (UDCA) or require specific surgical interventions, while others might benefit from emerging gene-specific therapies.3 The lack of awareness among general practitioners and even some specialists contributes to this diagnostic gap, highlighting the need for increased education and a lower threshold for genetic testing in appropriate clinical scenarios.

Understanding the underlying molecular mechanisms is crucial for targeted therapies. PFIC types 1 and 2, for example, result from mutations in ATP8B1 and ABCB11, respectively, genes encoding for canalicular phospholipid flippase and bile salt export pump (BSEP). These defects impair bile flow at the hepatocyte level, leading to the accumulation of toxic bile acids. ABCB4 deficiency, or PFIC3, involves mutations in the ABCB4 gene, which encodes for the multidrug

resistance protein 3 (MDR3), a flippase responsible for secreting phospholipids into bile. A deficiency in MDR3 leads to bile with an altered phospholipid-to-bile salt ratio, rendering it more cytotoxic and causing cholangiocyte damage. These distinct mechanisms underscore the importance of genetic diagnosis for guiding specific therapeutic approaches, including liver transplantation in severe cases.3

The Diagnostic Challenge in Adults

Discussions at EASL 2026 underscored the complexity of diagnosing late-onset genetic cholestatic diseases. Expert consensus highlighted that the prevalence of these conditions in adults is likely underestimated. While precise epidemiological data for adult-onset genetic cholestasis are scarce, estimates suggest that genetic factors may account for 10-15% of unexplained chronic cholestasis in adults, particularly in cases where autoimmune or obstructive causes have been rigorously excluded.4 This figure represents a substantial patient population that could benefit from a definitive diagnosis.

The diagnostic pathway typically involves a comprehensive workup to rule out common causes of cholestasis. This includes liver function tests, imaging studies (ultrasound, MRI, MRCP), serological markers for autoimmune liver disease, and sometimes liver biopsy.5 When these investigations are inconclusive, or when there are atypical features, genetic testing becomes a critical next step. Specific gene panels, targeting genes such as ATP8B1 (PFIC1), ABCB11 (PFIC2), ABCB4 (PFIC3/MDR3 deficiency), and TJP2, are increasingly available.6 The interpretation of genetic variants, particularly variants of uncertain significance (VUS), remains a challenge, requiring careful correlation with clinical phenotype and family history.7

A key limitation in current practice is the infrequent consideration of genetic etiologies in adults with cholestasis. Many clinicians do not routinely include genetic testing in their diagnostic algorithms for adult patients, often due to a perceived rarity of these conditions or a lack of familiarity with their adult presentations.8 Furthermore, the cost and accessibility of comprehensive genetic panels can be barriers in some healthcare systems. Future efforts must focus on developing clear clinical guidelines for when to suspect and test for late-onset genetic cholestatic diseases in adults, potentially incorporating risk stratification tools to identify high-probability cases. This would facilitate earlier diagnosis, improve patient outcomes, and reduce the burden of undiagnosed liver disease.

Readers seeking further authoritative information on the diagnosis and management of liver and biliary system diseases, such as cholestasis, are directed to Sherlock's Diseases of the Liver and Biliary System.

> **CLINICAL IMPLICATIONS**
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> The underdiagnosis of late-onset genetic cholestatic diseases in adults is not merely an academic point; it represents a tangible failure in patient care. When a patient presents with persistent pruritus and elevated alkaline phosphatase, the default diagnostic algorithm too often stops at PBC or PSC, even when serology is negative or imaging is equivocal. This diagnostic inertia means patients endure years of symptoms, receive empiric treatments, and may even undergo liver transplantation without ever understanding the true etiology of their disease. The availability of targeted genetic panels means that clinicians no longer have an excuse for not considering these conditions. It is time to integrate genetic testing earlier into the diagnostic workup for unexplained adult cholestasis, particularly when the usual suspects are ruled out.
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> For the pharmaceutical industry, the recognition of a larger adult population with genetic cholestatic diseases

opens new avenues for drug development. While current treatments for PFIC and BRIC are often supportive or involve surgical diversion, the increasing understanding of specific gene defects creates opportunities for precision medicine. Companies like Mirum Pharmaceuticals, with their focus on ileal bile acid transporter (IBAT) inhibitors, are already demonstrating the potential of targeted therapies for specific cholestatic conditions. However, the market for these therapies will only expand if the underlying genetic diagnoses are made more consistently. This necessitates investment not only in drug development but also in diagnostic awareness campaigns and accessible genetic testing infrastructure.

Ultimately, the goal is to move beyond a 'wait and see' approach for adult cholestasis. Patients deserve a definitive diagnosis, not just a label of 'idiopathic.' The evidence presented at EASL 2026 should serve as a wake-up call for guideline bodies such as AASLD and EASL to update their recommendations, providing clearer pathways for genetic testing in adult cholestatic liver disease. Without such guidance, the current underdiagnosis will persist, leaving a significant number of patients without the benefit of a precise diagnosis and potentially effective, disease-modifying treatments.

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