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From HDL Deficiency to Neuropathy: Insights into Tangier Disease

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ABSTRACT

Introduction: This review aims to provide a comprehensive examination of Tangier disease, focusing on its clinical manifestations, pathophysiology, and diagnostic methods. The article also delves into the available management strategies, the challenges in treating this rare condition, and the ongoing research into potential therapeutic interventions.

Materials and Methods: A comprehensive review of the literature was conducted using the PubMed and Google Scholar databases with the following keywords: "Tangier disease", "HDL deficiency", "ABCA1", "neuropathy", "high-density lipoprotein ", "HDL", "apoA-I", "CETP", "atherosclerosis", "splenomegaly".

Summary: Tangier disease is a rare autosomal recessive genetic disorder caused by mutations in the ABCA1 gene, which impairs cholesterol transport and results in low levels of HDL. This leads to the accumulation of cholesterol esters in various tissues, including the tonsils, spleen, lymph nodes, and nerves. The disease is characterized by orange-colored, enlarged tonsils, splenomegaly, peripheral neuropathy, and a heightened risk for atherosclerotic cardiovascular disease. Diagnosis is confirmed through low HDL and apoA-I levels, along with genetic testing for ABCA1 mutations. While no cure exists, treatment focuses on symptom management, controlling cardiovascular risks, and improving HDL function through lifestyle and dietary changes.

Conclusions: Tangier disease, a rare genetic disorder caused by mutations in the ABCA1 gene, leads to severe lipid imbalances and various systemic complications. Although there is no cure, managing symptoms, controlling cardiovascular risks, and adopting lifestyle changes are essential for improving outcomes. Ongoing research into gene therapies and new treatments offers hope for future breakthroughs.

Keywords: Tangier disease, HDL deficiency, ABCA1, neuropathy, high-density lipoprotein , HDL, apoA-I, CETP, atherosclerosis, splenomegaly.

Introduction

Tangier disease is characterized by a complete absence or significant deficiency of normal high-density lipoproteins (HDL) in the blood. This leads to the accumulation of cholesteryl esters in various tissues, including the tonsils, spleen, lymph nodes, thymus, intestinal mucosa, nerves, and cornea. Key clinical features include enlarged, hyperplastic orange-colored tonsils, splenomegaly, and recurrent neuropathy. Cholesterol levels are generally observed to be low, whereas triglyceride levels can vary, ranging from within the normal limits to elevated concentrations [1]. The condition results from a pathogenic mutation in the ATP-binding cassette transporter A1 (ABCA1) gene, which is essential for the biogenesis of high-density lipoprotein (HDL) particles through the transport of cellular cholesterol and phospholipids. It follows an autosomal recessive mode of inheritance. The disease exhibits a prevalence rate of one case per one million individuals [2]. Up to 2021, 35 cases have been reported in Japan and 109 cases have been identified in other countries [3]. Tangier disease is a genetic disorder that was initially identified in two brothers from Tangier Island, Virginia, located in the Chesapeake Bay and it was named after the island [2]. In 1960, Frederickson and colleagues found a 5-year-old boy with large yellow-orange tonsils. His sister had the same condition. Their tonsils were filled with cholesteryl esters, and their blood lacked HDL. These siblings were the first known cases of Tangier disease, a rare genetic HDL deficiency. The gene causing the disease was identified 39 years later [4].

Pathophysiology

Tangier disease follows an autosomal recessive inheritance pattern, with most parents being heterozygous carriers of pathogenic variants in the ABCA1 gene. A heterozygous carrier usually does not show any symptoms but typically exhibits an approximate 50% reduction in plasma HDL-cholesterol levels. There is a 25% chance that an individual will inherit pathogenic variants on both alleles, resulting in disease manifestation [5]. Following three decades of extensive research into Tangier disease, mutations were identified in the cell membrane protein ABCA1 [6]. In particular, alterations in the 9q31 region of chromosome 9 lead to a lipid transport molecule that is both structurally and functionally impaired [7]. Mutations in ABCA1 result in impaired cellular cholesterol efflux and subsequent accumulation of cholesterol esters in various tissues throughout the body [8]. ABCA1 is an essential lipid transporter that plays a

key role in the formation of HDL and the regulation of cholesterol balance. It promotes the transfer of phospholipids and free cholesterol from the plasma membrane of cells to apoA-I, the main protein component of HDL particles circulating in the bloodstream, thereby facilitating the generation of nascent HDL. By moving phospholipids to the outer leaflet of the membrane, ABCA1 creates lipid-rich domains that enhance the binding and stabilization of apoA-I. Thanks to its structural characteristics, apoA-I is able to solubilize these lipids, leading to the production of various discoidal HDL particles [9]. Generally speaking, HDL plays a crucial role in cardiovascular health by regulating cholesterol metabolism and protecting blood vessels from damage. HDL primarily facilitates the reverse transport of cholesterol from peripheral tissues to the liver, thereby maintaining lipid homeostasis within the body. HDL is extensively recognized for its atheroprotective and anti-inflammatory properties, as it promotes the efflux of cholesterol from foam cells accumulated in atherosclerotic plaques and mediates its delivery to the liver for excretion or reutilization [10].

Clinical manifestations

Tangier disease causes neuropathy in half of the affected individuals. Additional symptoms may include enlargement of the liver and spleen, ischemic heart disease or stroke, anemia, low platelet count, corneal clouding, low cholesterol levels, or it may be discovered without symptoms during family screening. Ectropion and partial eyelid closure can occur before corneal clouding and should be identified as potential indicators of Tangier disease [11]. The primary neurological manifestation of Tangier disease is neuropathy, presenting as mononeuropathy, polyneuropathy, or a syringomyelia-like neuropathy. The clinical course may be relapsing-remitting in certain cases and can clinically and electrophysiologically mimic immune-mediated neuropathies [12]. Metin Mercan's investigation in 2008 identified 54 patients diagnosed with TD accompanied by peripheral neuropathy. The syringomyelia-like neuropathy subtype was the most prevalent, accounting for 52.4% of cases, followed by multifocal sensory and motor neuropathy (26.2%), focal neuropathy (19.1%), and distal symmetric polyneuropathy (2.4%). Clinically, splenomegaly represented the most frequent manifestation, observed in 40.7% of patients. Electrodiagnostic findings demonstrated that demyelinating abnormalities were predominantly localized in the upper extremities relative to the lower extremities. Furthermore, motor nerve conduction velocity reduction was more pronounced within intermediate nerve segments compared to distal segments. The sural-sparing pattern was identified in 34.6% of subjects, whereas conduction block was present in 11.5% [13]. Disruption in HDL formation hampers cholesterol removal from cells, causing lipid

buildup. A characteristic sign of this condition is the presence of orange-toned tonsils. The tonsils in affected individuals appear enlarged and lobulated, with a vivid orange or yellowish-gray surface. According to reports, cardiovascular disease was present in 12 of 35 patients (34.3%) in Japan and in 34 of 109 patients (31.2%) from other countries, indicating that atherogenesis may be accelerated in individuals with Tangier disease. An earlier case study utilizing intravascular ultrasound (IVUS) showed widespread calcified lesions in the coronary arteries, which may have been influenced by low HDL levels and impaired glucose metabolism [3]. Although Tangier disease is known to cause early onset atherosclerotic cardiovascular disease (ASCVD), recent findings indicate that individuals carrying heterozygous variants of the ABCA1 gene also face a higher risk [14]. In the context of Tangier disease, a variety of additional clinical signs may be observed beyond the characteristic lipid abnormalities. These can include abdominal pain of unclear origin, chronic noninfectious lymphadenopathy, and dermatologic findings such as xerosis (dry skin) and nail dystrophy [2]. Less commonly, neurological symptoms may present as bilateral facial weakness (facial diplegia) [12].

Diagnosis

The diagnosis of Tangier disease relies on a comprehensive approach encompassing clinical assessment, biochemical analyses, and molecular genetic testing [15]. Tangier disease is diagnosed in an individual who has very low or undetectable levels of HDL cholesterol and apo A-I, along with pathogenic mutations in both copies of the ABCA1 gene confirmed through genetic testing [5]. This condition is characterized biochemically by plasma HDL levels at a low level, reduced total plasma cholesterol (less than 150 mg/dL), and plasma triglyceride levels that are either normal or elevated [16]. First, mandatory laboratory criteria must be met: the patient must have a plasma HDL-cholesterol concentration of less than 25 mg/dL and an apoA-I concentration in plasma of less than 20 mg/dL. In addition to these laboratory abnormalities, the patient must exhibit at least one clinical feature, such as orange-colored tonsillar enlargement, hepatomegaly and/or splenomegaly, corneal opacity, peripheral neuropathy, or cardiovascular disease. Before confirming the diagnosis, it is essential to rule out other possible causes of similar findings, including LCAT deficiency, apoA-I deficiency, and secondary forms of hypo-HDL-cholesterolemia [3]. When Tangier disease is suspected based on clinical and laboratory evidence, molecular diagnostics may employ either targeted single-gene testing or a broader multigene panel. Initial testing of the ABCA1 gene typically involves sequencing to detect subtle genetic alterations such as small insertions, deletions, or point mutations. Testing may also be conducted using a multigene panel that covers ABCA1

and other relevant genes. Incorporating both sequencing and deletion/duplication analysis, these panels aim to increase the chances of detecting the genetic cause while limiting the identification of unrelated or ambiguous variants. The specific genes included and the diagnostic performance of such panels differ between laboratories and are frequently revised [17]. Imaging techniques including ultrasound and MRI, are utilized to assess hepatic and splenic size and morphology, alongside the identification of potential atherosclerotic pathology [15]. Doppler ultrasonography of the carotid arteries is used to measure intima-media thickness (cIMT) and detect atherosclerotic plaque formation. Echocardiographic imaging is also applied to assess coronary atherosclerosis severity [18]. Biopsy specimens can be obtained from various anatomical sites, including the bone marrow, liver, jejunum, and rectum. Histopathological analysis may demonstrate prominent aggregates of macrophages engorged with cholesterol [19]. Nerve biopsy results may reveal extensive axonal loss, lipid accumulation within Schwann cells, and increased collagen in the endoneurium. The axonal loss corresponds to primary degeneration, with no signs of demyelination [20]. Peripheral neuropathy can be identified using electrophysiological tests that measure nerve conduction velocity [18].

Management

To date, there is no definitive curative treatment available for the condition, and therapies such as gene therapy targeting the ABCA1 gene have not yet been developed or established for clinical use [3]. Both older and newly developed drugs that raise HDL levels have proven ineffective in patients with Tangier disease. A more viable treatment approach would focus on selectively increasing the levels of mature HDL to restore proper cholesterol efflux. In the meantime, recently developed therapies - such as cholesteryl ester transfer protein (CETP) inhibitors like dalcetrapib and anacetrapib, as well as reconstituted HDL - could be explored as interim options until gene therapy becomes available [21]. The current therapeutic approaches for Tangier disease are mainly centered on alleviating the symptoms and addressing the various complications that arise from the disorder. Management typically involves supportive care aimed at improving quality of life and preventing progression of associated health issues [15]. Given that a significantly elevated risk of atherosclerotic diseases constitutes the primary clinical concern, effective management of modifiable risk factors is essential. This includes rigorous control of hypertension, smoking cessation, and optimal management of diabetes mellitus [3]. Various dietary factors can raise HDL cholesterol levels, including replacing carbohydrates with fats, omega-3 fatty acids, and the Mediterranean diet [22]. The Mediterranean diet, characterized by high consumption of extra virgin olive oil, vegetables,

nuts, fish, and moderate intake of red wine, has been shown to confer significant cardiovascular benefits. Studies demonstrate that this dietary pattern enhances HDL functionality by improving cholesterol efflux capacity and antioxidant properties, largely attributed to the polyphenols present in olive oil. Additionally, the intake of tomatoes rich in lycopene and omega-3 fatty acid rich fish particularly eicosapentaenoic acid EPA further supports HDL function and contributes to a reduced risk of cardiovascular disease [23]. While nutritional factors are fundamental in enhancing reverse cholesterol transport, evidence demonstrates that the most effective therapeutic outcomes are achieved when dietary modifications are combined with consistent physical exercise. This combined approach is primarily attributed to the favorable influence of exercise on HDL cholesterol concentrations. Indeed, studies have shown that physical activity can increase HDL levels to an extent comparable to, or exceeding, that achieved through dietary intervention alone [24]. Treatment is guided by the severity and location of clinical symptoms. When tonsillar hypertrophy results in airway compromise or mass effect, tonsillectomy may be necessary to alleviate obstruction. In patients with advanced corneal opacities leading to visual dysfunction, corneal transplantation can be considered to restore ocular clarity and visual acuity [2].

Conclusion

Tangier disease is a rare genetic disorder inherited in an autosomal recessive manner, caused by pathogenic mutations in the ABCA1 gene. These mutations impair the function of the ABCA1 protein, a crucial transporter responsible for cellular cholesterol and phospholipid efflux, which is essential for the formation of high-density lipoprotein (HDL) particles. The deficiency or absence of HDL leads to the pathological accumulation of cholesteryl esters in various tissues, including the tonsils, spleen, lymph nodes, peripheral nerves, and cornea. Clinically, the disease presents with hallmark features such as enlarged, orange-colored tonsils, splenomegaly, peripheral neuropathy, and an increased predisposition to atherosclerotic cardiovascular disease. Neuropathy, often syringomyelia-like, is observed in about half of affected individuals, and cardiovascular complications have been reported in a significant portion of patients worldwide. Diagnosis of Tangier disease relies on a multidisciplinary approach combining clinical examination, biochemical analyses showing extremely low HDL and apoA-I levels, and molecular genetic testing confirming biallelic mutations in the ABCA1 gene. Imaging and biopsy studies support diagnosis by demonstrating characteristic tissue lipid accumulation and nerve damage. Despite advances in understanding the molecular mechanisms underlying the disorder, there is currently no curative treatment available. Therapeutic

strategies focus on symptomatic relief, prevention of cardiovascular complications, and lifestyle interventions aimed at managing modifiable risk factors such as hypertension, smoking, and diabetes. Nutritional approaches, including omega-3 fatty acid supplementation and the Mediterranean diet, combined with regular physical exercise, are recommended to enhance HDL levels and improve cholesterol metabolism. Investigational therapies, including cholesteryl ester transfer protein (CETP) inhibitors and reconstituted HDL, show potential but require further clinical validation. In conclusion, Tangier disease underscores the vital role of ABCA1-mediated cholesterol transport and HDL in maintaining lipid homeostasis and cardiovascular health. Early recognition and comprehensive management are essential to mitigate disease progression and associated complications. Ongoing research into gene therapy and novel pharmacological agents holds promise for future curative treatments, offering hope for improved outcomes in individuals affected by this rare but impactful genetic disorder.

Disclosure

Author's contribution

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