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Review Article

A comprehensive review on lipoid proteinosis with emphasis on ECM1 gene mutation

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ABSTRACT

The lipoid proteinosis (LP) is a rare autosomal recessive disorder, caused by mutations of extracellular matrix protein 1 gene (ECM1). The ECM1 helps in angiogenesis and connective tissue matrix generation, especially in bone and skin. The ECM1 helps in development of skin and its maintenance whereas in LP auto antibodies are raised against ECM1. Old LP patients revealed with turgid skin infiltration and thickening of general skin with a waxy and yellow colored appearance. With minor injury or stress develops excessive scarring with scars at the sites. Most often cases revealed with typical beaded papules at the eyelids and in certain cases, calcification of the temporal lobes have been observed. Also, laryngeal manifestations occur where hyaline-like material deposited in the mucous membranes of the vocal cords results with a faint or hoarse cry. Herein, we focused on LP and reviewed its epidemiology, clinical presentations, different kinds of treatment options and the progressive understanding of clinical manifestation and its histopathological characters. We have also scientifically elaborated on the various LP cases on ECM1 mutation. LP can be cured by early detection with open novel diagnosis with developing basic and clinical research approaches.

1. Introduction

The lipoid proteinosis (LP) is an autosomal recessive disorder and it is due to abnormal deposits of glycoprotein in tissues of skin, mucous membrane, brain, larynx and other internal organs.[1–5] LP is also named as Urbach–Weith disease and hyalinosis cutis et mucosae or lipoidosis cutis et mucosae.[2] LP also manifests to striated muscles, lymph nodes, lungs and central nervous system in rare cases.[4–7] But in normally the symptoms such as hoarse voice or a weak cry, unusual growths on the skin, damage to the hippocampus or temporal lobes of the brain, waxy, yellow, bead-like bumps along the upper and lower edges of the eyelids was seen.[8–10] LP is a hereditary disease and it is equally affected to both males and females. From literature, one forth was reported from African population of South Africa. But few more cases are progressively being reported throughout world including India.[11–16] LP

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has a stable/slowly progressive course. LP in children may have learning and behavioral difficulties. Sometimes obstruction in the throat may require a tracheostomy.[8] The morbidity and mortality rates in children and adults are increased due to laryngeal obstructions and respiratory tract infections.[9] In treatments oral steroid drugs and oral dimethyl sulphoxide (DMSO) and carbon dioxide laser surgery positively healed in thickened of vocal cords and eyelid bumps.[10] Once diagnosed, LP carries clinical manifestations and it there is no effective results in adults.[9] Herein, we reviewed LP with epidemiology, clinical presentations, cutaneous associations, available treatment options, and the progressive understanding of its histopathological features. We have also thoroughly elaborated on the various studies on mutation of ECM1 and an update of ECM1 gene mutation database.

2. Method of literature search

Articles regarding LP were identified through a multi stage systematic approach. First, we conducted an online search of the Medline database, Scopus and pubmed database with the word lipoid proteinosis and ECM1. Then, we systematically analyzed and reviewed all literatures. There is a limited work on ECM1 gene as compared to the present LP scenario.

3. Demographic data

In literature, the detail demographic data of LP are rarely described. LP is common among population having consanguineous marriages, which may explain high prevalance in the Saudi population.[13] LP occurs worldwide but is more common in certain geographical locations such as the Northern Cape Province of South Africa.[7] More than 300 cases of LP have been reported in the world medical literature.[8] Among them certain case reports and their clinical manifestations are described (Table 1). Pathogenic genetic mutations have been seen in the extracellular matrix protein 1 gene (*ECM1*). ECM1 is a glycoprotein, expressed in skin and other body tissues.[9,10] The ECM1 protein has vital physiological and biological implications in epidermal differentiation, binding of dermal collagens and proteoglycans, and of angiogenesis.[10] More than forty pathogenic genetic mutations have been documented in this gene including missense, nonsense, frame shift or splice site mutations where most of occurring in exons 6 and 77. Molecular genetic studies of LP linked to the chromosome 1q21.1.[11] The responsible gene for LP was identified as ECM1, which express the glycoprotein called as extracellular matrix protein 1. Till date, several mutations in the ECM1 gene have been documented in inherited LP families from different geographical areas.[12] The high incidence of LP among South African people due to the founder effect after the introduction of the mutation into the country by a German settler.[2]

4. Clinical diagnosis of LP

LP occurs due to mutations in ECM1, a glycoprotein expressed in several tissues, including the skin. This glycoprotein consists of two alternatively spliced isoforms, ECM1a and ECM1b, where ECM1b lack exon 7 of the 10-exon gene. The genetic mutations map onto chromosome 1q21. Exons 6 and 7 are the commonest sites for ECM1 mutations in LP. Clinically, the genetic mutations outside exon 7 are often associated with a slightly severe mucocutaneous LP phenotype. Neurological presentations do not show any specific genotype–phenotype correlation.[14] Clinical features of LP in the newborn child include a hoarse cry and skin manifestations, which occur in sequential but overlapping phases and include vesicles, pustules, bullae and hemorrhagic crusted eruptions over the face and limbs that are more over areas of trauma. Skin manifestations usually heal by pox-like acneiform atrophic scarring and extra-cutaneous manifestations from the incursion of hyaline-like material in the skin, larynx and the clinical features of LP vary substantially, not just among population groups, but also within population groups. This makes a definitive diagnosis, which is very difficult to perform. This also makes comparative clinical studies very difficult to perform. When a large group of patients are identified, it is a reasonable expectation that there will be significant age differences between the LP patients. This complicates comparative clinical LP studies, as the clinical features of LP are presumed to progress along with the age, the symptoms becoming more detectable and pronounced with time of progress. However there is a plethora of case documentations on LP patients in the medical literature, and from these sources, it is possible to extract the most common clinical symptoms of LP. A clinical diagnosis should be thought when a LP patient presents with a hoarseness of voice that has been present since birth or early childhood time, generally thickened and scarred skin, beaded eyelid papules and a thickened sub-lingual frenulum. Other confirmatory clinical symptoms are infiltrated warty skin papules especially on the elbows and extensor aspects of the forearms and oval bilateral, symmetrical calcifications of the anteriomedial aspect of the temporal lobes of brain. The systemic clinical manifestations of LP are learning and behavioral changes, seizures, dysphagia, and dyspnea. Generalized muscle dystonia and intestinal bleeding are rarely reported in medical literature. The patients are usually of short stature. Many authors have reported that the short stature of patients in LP could be due to defective osteoblasts.[14] Oral manifestations of LP include papules over the tongue, frenulum, and lips. These papules can cause pebbling of the oral cavity mucosa and a woody tongue that is unable to protrude fully outside, causing impaired speech and gestation and ulceration of the lips and tongue. Other clinical features may include hyperplasia or aplasia of the teeth, as well as recurrent infections of the parotid and submandibular glands. Usually a pathognomonic finding of LP is bilateral, intracranial, bean-shaped calcifications in the hippocampal area of the temporal lobes of the brain.[15] LP is a differential diagnosis of erythropoieticprotoporphyria (EPP), a condition where skin involvement confined to sun-exposure areas of body and associated with photosensitivity.[16] In EPP, there is deposition of PAS positive material which is less dense around the blood vessels. LP should also be histopathologically differentiated from amyloidosis and xanthomas, which often associated with the deposition of glycoproteins in the eyelids. In adults, the differential diagnosis includes lichenmyxoedema

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