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Photo Vignette

Hennekam syndrome: a rare cause of primary lymphedema

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Abstract

Hennekam syndrome (HS) is an autosomal recessive disorder characterized by the association of lymphedema, intestinal lymphangiectasia, moderate mental retardation, and facial dysmorphism. We describe a 14-year-old girl affected with Hennekam syndrome.

Introduction

Hennekam syndrome is a rare autosomal recessive disorder that presents with lymphedema, intestinal lymphangiectasia, moderate mental retardation, and facial dysmorphism. Less than 40 cases have been reported in the literature. We describe a 14-year-old girl affected with Hennekam syndrome.

Case synopsis

Our patient is the third-born child of healthy, consanguineous parents (first cousins). Lymphdema of the legs was first noted at 7 years of age, increased gradually, and has persisted with recurrent secondary infections. When she came to our attention, the patient was 14 years old. She had moderate lymphedema of the lower limbs (Figure 1). Examination of the face revealed a flat face, flat and broad nasal bridge, a small mouth, hypertelorism, and low set ears (Figure 2). Lymphography revealed the absence of lymphatic flow in both lower limbs

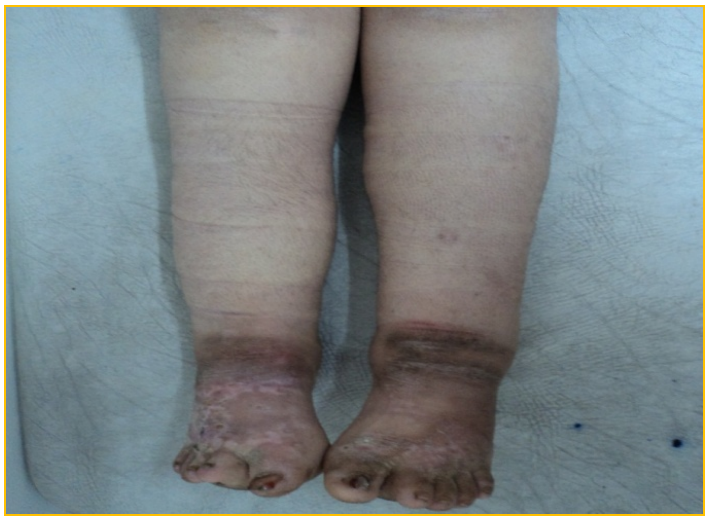

Figure 2. Hypertelorism, Flat face, flat and broad nasal bridge, and small mouth **Figure 1.** Lymphedema of lower limbs

Discussion

Hennekam syndrome, also called multiple congenital anomaly/mental retardation (MCA/MR) syndrome, was first desribed by Hennekam and coworkers in 1989 [1]. Since then, 35 cases have been reported in the literature [2]. HS is transmitted as an autosomal recessive trait. Phenotypic abnormalities relate to impaired prenatal and postnatal lymphatic flow resulting from mutations in the collagen and calcium-binding EGF-domain 1 (CCBE1) on chromosome 18q21 during lymphangiogenesis. The function of *CCBE1* is not completely understood. *CCBE1* is not expressed in endothelial cells, but is expressed along the migration routes of lymphatic endothelial cells and may be involved in lymphangioblast budding and migration. Research to identify other possible causative genes is in progress [3].

Lymphedema, resulting from generalized lymphatic maldevelopment, usually appears at birth or during early infancy. It can affect limbs, genitalia, face, and eyes. In most cases, lymphedema is present in the distal limbs and face. It can be stable or progressive. Intestinal lymphangiectasia has been present in most patients. The intestinal biopsy shows dilatation of intestinal mucosal lymphatic channels in the lamina propria, enlargement of the villi, and thinning of the lymphatic vessel walls. Lymphatic impairment can be evaluated by lymphoscintigraphy.

Intestinal lymphangiectasia may result in protein-losing enteropathy, mild growth retardation, peripheral edema, and ascites. Biological studies may reveal hypogammaglobulinemia, hypoalbuminemia, lymphopenia and increased alpha-1 antitrypsin excretion in the feces. The lymphangiectasias can also be present in the pleura, pericardium, thyroid gland, and kidney.

The facial characteristics of HS most typically include a flat face, a broad and depressed nasal bridge, and hypertelorism. Other features are epicanthal folds, a small mouth, low-set and dysplastic ears with narrow meatus, a broad forehead, smooth philtrum, gingival hypertrophy, tooth anomalies, preauricular tags, and atretic ear canals. There can be facial asymmetry [2, 4, 5].

Other manifestations include delayed puberty, seizures, glaucoma, blood vessel anomalies, narrow upper throrax, nonimmune hydrops fetalis, chylothorax, alopecia, brain cysts, and craniosynostosis [2, 4, 5]. The degree of intellectual deficit is variable.

The differential diagnosis includes other syndromes associated with congenital lymphedema such as Noonan syndrome and cholestasis-lymphedema syndrome.

Treatment is not usually necessary and depends upon symptoms [4]. Some patients may require a medium-chain triglyceride-rich and high-protein diet, albumin infusions, and vitamin and electrolyte supplements in the case of protein-losing enteropathy. Pulmonary lymphangiectasia is difficult to treat. The lymphedema may be severely handicapping and require surgical interventions. The prognosis is variable, severe manifestations can lead to early death.

In our case, the typical features of mental retardation, lymphedema, and facial dysmorphism allowed us to confirm the diagnosis.To our knowledge, this is the first Moroccan case to be reported.

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