Medical and Research Publications
International Open Access

Case Report

Journal of MAR Cardiology (Volume 4 Issue 4)

Hennekam Syndrome Presenting in the form of Pulmonary Lymphangiectasia and Cardiac Anomalies in a 4-Year-Old Girl; A Case Report

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Received Date: May 14, 2022

Published Date: June 01, 2022

Key Clinical Message

Classic phenotype of hennekam syndrome includes lymphangiectasia (particularly of the intestine), lymphedema, characteristic dysmorphic features, and mental disabilities.

Abstract

Our patient is a 4-year-old girl with a variation of the syndrome caused by FAT4 mutation, syndromic appearance, mental retardation, pulmonary lymphangiectasia and multiple cardiac anomalies. In children with syndromic appearance and cardiopulmonary disorders, Hennekam syndrome is a rare diagnosis to be considered, even if there is no intestinal lymphangiectasia.

Keywords: *Hennekam syndrome, lymphangiectasia, FAT4 gene*

Introduction

Hennekam syndrome is a rare autosomal recessive disorder characterized by congenital lymphedema, intestinal lymphangiectasia, mental retardation, and facial anomalies, which was first described by Hennekam et al in 1989. The patients all represent the same underlying pathogenesis of lymphatic system malfunction, with varying severity (1). There are also reports of hydrops fetalis. This lymphangiectasia–lymphedema syndrome is a genetically heterogeneous disorder which is related to mutations in CCBE1 and FAT4 in 25 and 20 percent of the cases respectively (2,3). In this paper we present a 4-year-old girl arriving at the pediatric clinic with dyspnea and facial dimorphism which had pulmonary vessels anomalies on cardiac imaging and a FAT4 mutation on genetic testing.

Case presentation

This female 4-year-old patient was born to a ? year old G?P? mother at term via a normal vaginal delivery. She was the second child of healthy unrelated parents. She presented to the clinic with the chief complaint of dyspnea. She demonstrated short stature (< 5th

percentile) and had a syndromic appearance consist of an abnormal facies, characterized by prominent forehead with shallow supraorbital ridges, hypertelorism (increased distance between the orbits), epicanthal folds, flat nasal bridge, low-set ears, and retruded mandible.

There was also camptodactyly (permanently bent fingers), and a slight clubfoot malformation (figure 1). Chest radiograph demonstrated no pulmonary parenchymal lesion, but revealed prominence of the right atrium (figure 2).

Echocardiography was performed indicating: normal IVC continuity with RA, mildly dilated hepatic veins, normal pulmonary venous return to LA, dilated C.S (persistent left superior vena cava), absent

right superior vena cava, normal levocardia, aneurysmal IAS with septum primum mal-alignment, mod size ASD (0.7 cm), no significant MR, mild TR PPG=36 mmHg, dilated RA and RV, good LVEF, Intact IVS, normally related great arteries mildly dilated MPA, no PS, mild PI, moderate PH, no AS, no Al, tricuspid aortic valve, normal coronary arteries, no PDA, no CoA, and a left aortic arch.

CT angiography was recommended to detect further possible vascular anomalies which demonstrated: atrial and visceral situs solitus, levocardia (the heart on the normal side), D-loop ventricle (normal),AV concordance, VA concordance, septum secundum, ASD (5.3 mm) with aneurysmal interatrial septum, accessory auricle in anterosuperior aspect of LA (26x10 mm), partial septum in LA, severe RA enlargement, thickened tricuspid valve, left sided aortic arch with mild narrowing in distal arch (6.6mm), dilated main pulmonary artery (18.2 mm), LSVC terminated to severely dilated coronary sinus, and partial anomalous venous return of right superior pulmonary vein to aneurysmal part of interatrial septum.

Considering the patient's syndromic appearance and the presentations compatible with pulmonary lymphangiectasia (severe RA enlargement, thickened tricuspid valve) and cardiac anomalies, genetic consultation and testing was performed which resulted in the detection of a homozygous FAT4 mutation.

Patient’s echocardioagheraphy and angiogeraphy have been shown in the figure 3 and 4

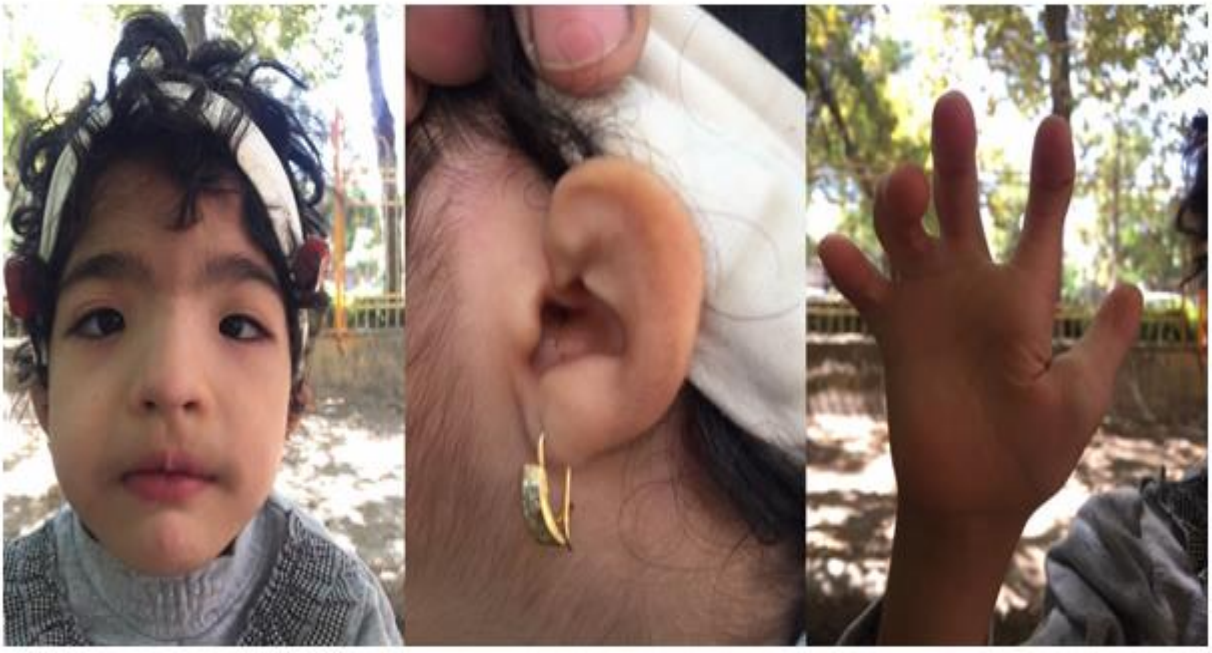

Figure 1. Syndromic appearance. Hypertelorism, epicanthal folds, flat nasal bridge, and retruded mandible (left), low set ears and camptodactyly (right)are evident.

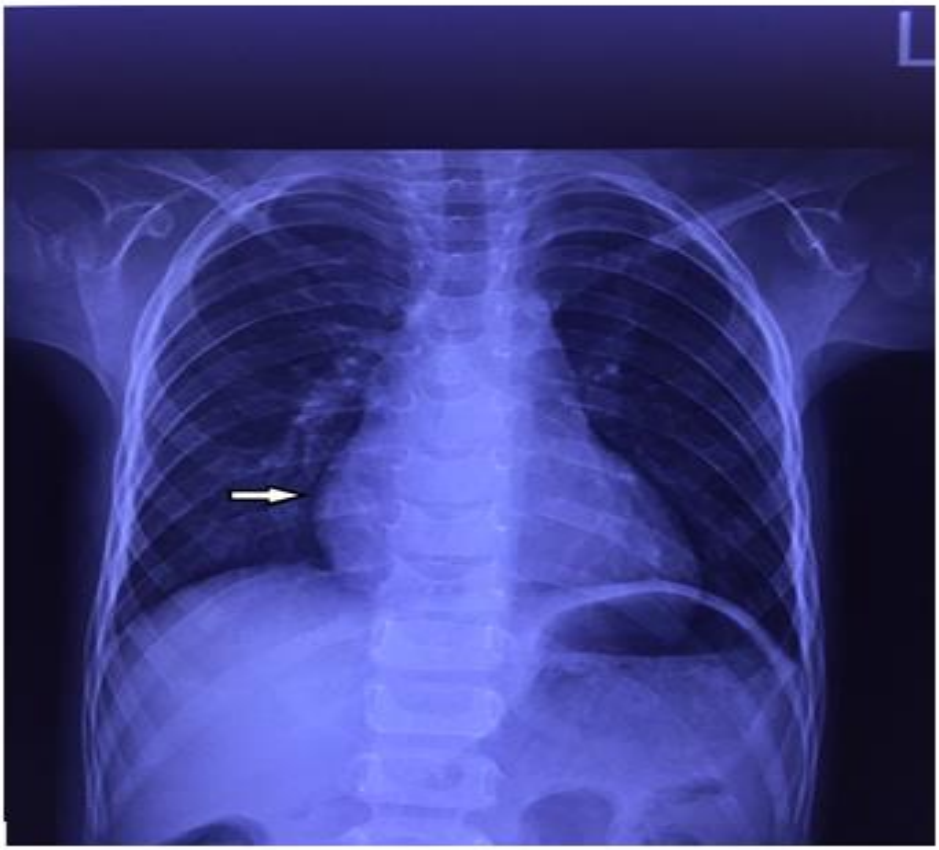

Figure2. Chest radiograph. Note the prominence of the right atrium (arrow).

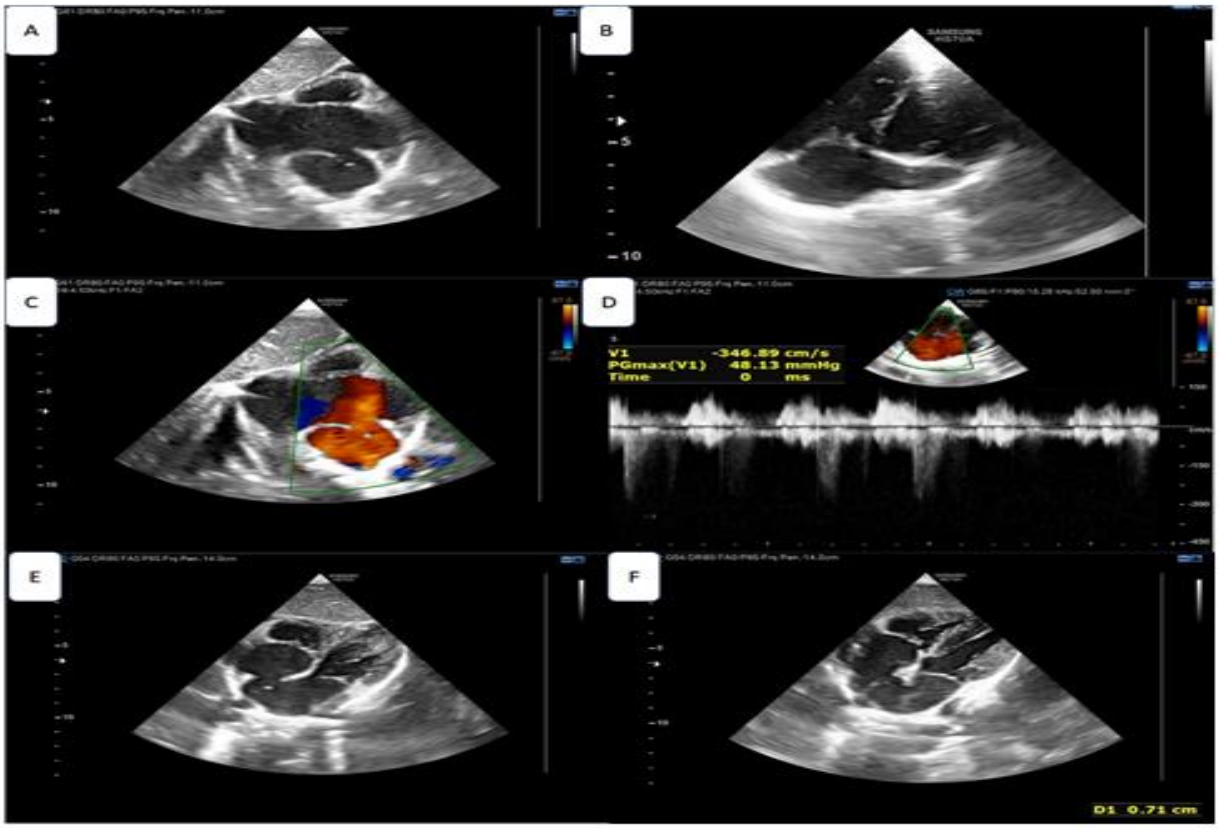

Figure3. Echocardiogheraphy of the patient. A: bicaval echo view and absent RSVC, B: Dilated coronary sinus, C: doppler echo bivaval view and absent RSVC, D: Doppler echo and TR gradiant, E: More than one ASD, F: the major ASD

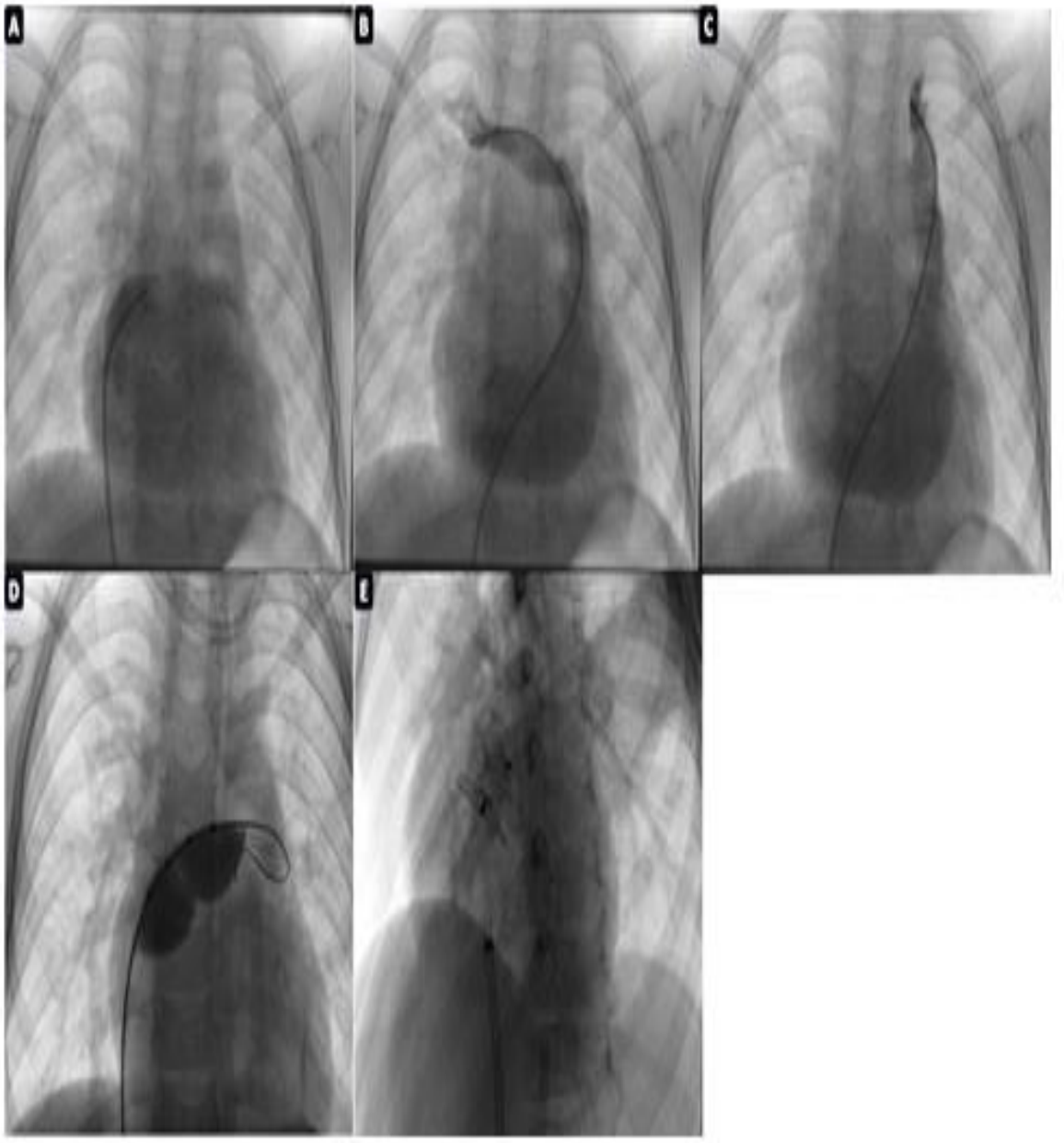

Figure 4: Angiogeraphy of the patient. A: absent RSVC, B: absent RSVC & and persistant LSVC to dilated CS, C: LSVC to CS, D: ballon sizing, E: final deploing

Discussion

Hennekam syndrome is a rare autosomal recessive disorder with an incidence rate of approximately 1:100,000. There are up to 50 cases reported in the literature, but the precise prevalence is unclear. The syndrome consists of multiple organ lymphangiectasia as a result of lymphatic vascular abnormalities caused by genetic mutations, dysmorphic appearance characterized by round flat faces, hypertelorism, epicanthal folds, puffy eyelids, large and depressed nasal bridge, small ears and tooth anomalies (4).

This syndrome is related to mutations in the CCBE1 or FAT4 genes in 45 percent of the cases. Although CCBE1 is known to be involved in the migration of nascent lymphatic endothelial cells, providing migratory signals from the extracellular matrix, the function of FAT4 in the lymphatic system is still unknown (4,5). In 2014, Alders et al reported the mutations in FAT4 as a second cause of Hennekam syndrome. They declared that mutations in FAT4 were identified in 5 out of 24 families (~20%). The mutations in this gene are also present in Van Maldergem Syndrome (VMS) which is characterized by facial dysmorphism, mental disability, periventricular heterotopia (results in epilepsy), camptodactyly, and syndactyly (fused fingers), small kidneys, osteoporosis and tracheal anomaly (might require tracheostomy). VMS is not associated with lymphatic dysfunction (2). It seems reasonable to conclude that the presence of camptodactyly in our patient is a phenotypic indicator of the mutation found to be the cause. But the presence of pulmonary lymphangiectasia is more in favor of Hennekam syndrome than VMS.

In addition to being heterogeneous in terms of genetic mutations, clinical manifestations of Hennekam syndrome reported in the literature consist of a wide range of presentations from nonimmune hydrops fetalis in neonates,to mild childhood protein losing enteropathy and facial anomaly with no mental disability(6,7); Although given that most of the features of the syndrome are perceived to be secondary to disordered lymphovascular development in the embryonic period, it seems not far from expectation that these patients all represent the same underlying pathogenesis, with varying severity in each case (3). The 2 main categories of clinical manifestations are facial anomalies and lymphovascular disorders caused by lymphangiogenesis defects. Facial features are contributed to intrauterine facial lymphedema, or are brought about by lymphatic obstruction that affects the migration of neural crest tissue. It is also hypothesised that neural crest differentiation to become face and lymphatic vessels, is developed aberrantly in early gestation and results in the two main characteristics of the disease. Mental development varies widely, even within a single family, from almost normal psychomotor to drastic mental retardation (8).

Lymphangiectasia, which is one of the main pillars of the disease, manifests as systemic lymphedema which can cause hydrops fetalis, or result in milder forms of lymphatic edema in childhood. It preferentially affects intestines, which causes intestinal lymphangiectasia. Intestinal lymphangiectasia

is characterized with dilated intestinal, submucosal and subserosal lymphatic vessels and results in a protein-losing enteropathy, hypoproteinemia, hypoalbuminemia, and lymphocytopenia. Maldevelopment of the lymphatic system also affects limbs, the genitalia, the pleura, pericardium, thyroid gland, and kidneys. It is suggested that the presence of both lymphangiectasia and lymphedema would differentiate Hennekam syndrome from other congenital primary lymphatic disorders (3,6,9).

In 1999, Rockson et al reported the Lymphoscintigraphic Manifestations in a 13 year old girl with Hennekam Syndrome, and explained that slight degrees of congenital lymphedema occur with some regularity in the general population and may reflect a normal developmental variability in the regression of fetal lymphedema, but the lymphedema and intestinal lymphangiectasia in Hennekam syndrome reflect the intrauterine lymphatic dysfunction related to the underlying genetic mutation(10). It is hypothetically possible that birth care providers observed some degree of edema caused by the syndromic malformation in our patient, but ignored that, assuming it as a natural variation.

Developmental pulmonary lymphangiectasia is a rare disorder which may be present at birth or later during childhood. It is infamous for its bad prognosis when clinically symptomatic, although microscopic changes may exist in patients with different variations of the syndrom (9). In addition to the cardiac and valvular consequences of pulmonary lymphangiectasia, there are reports of patients that demonstrated congenital cardiac and blood vessel anomalies (ASD, VSD, vascular aneurysm or cyst and intracerebral infarctions), indicating a disturbance of angiogenesis in at least a subgroup of the phenotypes. It is also believed that the primitive lymphatic sacs develop out of veins, and that various genes play roles in the development of both blood and lymph vessels (8,11).

Laboratory findings may include anemia, hypoproteinemia, hypogammaglobulinemia, elevated level of alpha-l antitrypsin excreted in the feces, all of which result from lymphovascular dysfunction, and abnormalities that are related to possible organ dysfunction like kidney or thyroid (12).

Conclusion

Hennekam syndrome is an autosomal recessive disorder characterized with lymphatic development and dysmorphic features including round flat face, flat bridge of the nose, hypertelorism, and low set ears. These features are believed to be secondary to in utero lymphatic perturbations when the facial structures are being formed.

Classic phenotype includes lymphangiectasia (particularly of the intestine), lymphedema, characteristic dysmorphic features, and mental disabilities. But there are also reports of cases presenting normal cognition or facing other abnormalities like cardiovascular, kidney, and thyroid.

Our patient is a case of this syndrome as a result of a homozygous mutation in the FAT4 gene, which is the cause of this syndrome in almost 20% of the cases. The cardiac anomalies observed, including ASD and aneurysmal IAS, support the hypothesis of shared genetic and embryonic development pathways of both blood and lymph vessels.

Acknowledgement: Authirs thank the childeren and her familiy.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical consideration: The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, and was conducted according to the Declaration of Helsinki. Undersigned informed consent form was obtained from patient prior to the enrollment regarding the identifiable publication of the patient.

Data availability statement: The data sets used and/or analyzed during the current study are available from the corresponding authors per request.

Author contributions: B.A. contributed in conception, design and drafting of the manuscript. Z.S. contributed in data collection. Z.S. contributed in drafting of the manuscript. and B.A. supervised the study. All authors approved the final version for submission.

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