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# HENNEKAM SYNDROME: LITERATURE REVIEW

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**Summary**

**Introduction** Hennekam syndrome is an autosomal recessive disease with lymphangiectasia, severe peripheral lymphedema, abnormalities of the face, cramps, mild growth and mental retardation.

**The aim of the study** to describe the clinical characteristics of Hennekam syndrome.

**Search strategy.** The databases of Scopus, Web of Science, and PubMed were used to conduct a comprehensive literature search. Complete publications that had been released in peer-reviewed journals up through May 2023 were chosen. Search parameters included the terms "Hennekam syndrome" and "Lymphedema-Lymphangiectasia-Mental Retardation Syndrome." Thus, 83 publications were discovered, from which 53 articles were chosen.

**Results**: The literature describes more than 50 cases Hennekam syndrome. Lymphedema, resulting hypoplasia lymphatic system usually appears at birth and in early infancy, in the form of swelling of limbs, genitals, face and eyes. Intestinal lymphangiectasia can lead to protein-losing enteropathy, mild growth retardation, peripheral edema, and ascites. At biochemical study determined hypogammaglobulinemia, hypoalbuminemia, lymphopenia and increased alpha-1 antitrypsin. In this article, a review of the literature and descriptions of each reported case of Hennekam syndrome were made.

***Key words:*** *Hennekam syndrome, lymphangiectasia, lymphedema.*

**Резюме**

# СИНДРОМ ХЕННЕКАМА: ОБЗОР ЛИТЕРАТУРЫ

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**Введение** Синдром Хеннекама представляет собой аутосомно-рецессивное заболевание с лимфангиэктазией, тяжелой периферической лимфедемой, аномалиями лица, судорогами, умеренным ростом и умственной отсталостью.

**Цель исследования** — описать клинические характеристики синдрома Хеннекама.

**Стратегия поиска.** Для проведения всестороннего поиска литературы использовались базы данных Scopus, Web of Science и PubMed. Были выбраны полнотекстовые публикации, опубликованные в рецензируемых журналах до мая 2023 года. Параметры поиска включали термины «синдром Хеннекама» и «синдром лимфедема-лимфангиэктазия-умственной отсталости». Таким образом, было обнаружено 83 публикации, из которых были отобраны 53 статьи.

**Результаты.** В литературе описано более 50 случаев синдрома Хеннекама. Лимфедема, возникающая в результате гипоплазии лимфатической системы, проявляется обычно при рождении и в раннем детстве в виде отека конечностей, половых органов, лица и глаз. Кишечная лимфангиэктазия может привести к энтеропатии с потерей белка, легкой задержке роста, периферическим отекам и асциту. При биохимическом исследовании определяются гипогаммаглобулинемия, гипоальбуминемия, лимфопения и повышение уровня альфа-1-антитрипсина. В статье проведен анализ литературы и описание всех опубликованных случаев синдрома Хеннекама.

***Ключевые слова:*** *синдром Хеннекама, лимфангиоэктазия, лимфедема.*

**Түйіндеме**

# ХЕННЕКАМ СИНДРОМЫ: ӘДЕБИЕТТІК ШОЛУ

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**Кіріспе** Хеннекам синдромы лимфангиоэктазиямен, ауыр шеткергі лимфедемамен, бет әлпетіндегі ауытқулармен, құрысулармен, орташа бойлық және ақыл-ой кемістігімен жүретін аутосомды-рецессивті ауру.

**Зерттеудің мақсаты** - Хеннекам синдромының клиникалық сипаттамаларын сипаттау.

**Іздеу стратегиясы.** Әдебиетті жан-жақты іздеу үшін Scopus, Web of Science және PubMed дерекқорлары пайдаланылды. 2023 жылдың мамырына дейін рецензияланған журналдарда жарияланған толық жарияланымдар таңдалды. Іздеу параметрлері «Хеннекам синдромы» және «лимфедема-лимфангиоэктазия-ақыл-ой кемістігі синдромы» терминдерін қамтиды. Осылайша, 83 жарияланым табылды, оның ішінде 53 мақала іріктелді.

**Нәтижелер.** Әдебиетте Хеннекам синдромымен ауырған 50 астам науқас сипатталған. Лимфедема лимфа тамырларының дұрыс дамымауы әсерінен туған кезде немесе ерте нәрестелік кезеңде аяқтардың, жыныс мүшелерінің, беті мен көзінің ісінуімен көрінеді. Ішектік лимфангиэктазия әсерінен ақуыз жоғалтумен жүретін энтеропатия дамиды, бұл даудың артта қалуы және ісіну мен асциттің дамуымен жүреді. Биохимиялық зерттеу кезінде гипогаммаглобулинемия, гипоальбуминемия, лимфопения және альфа-1 антитрипсиннің жоғарлауы байқалады. Баспаға шыққан барлық клиникалық жағдайлар жинақталып, әдеби шолу жасалған.

***Түйінді сөздер:*** *Хеннекам синдромы, лимфангиоэктазия, лимфедема*.

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**Introduction**

Hennekam syndrome is characterized by a combination of lymphedema, intestinal lymphangiectasia and mental retardation with characteristic facial changes [45,46]. The literature describes more than 50 cases of Hennekam syndrome [2,33,50]. Hennekam syndrome (a syndrome lymphangiectasia-lymphedema-mental retardation) autosomal recessive disorder caused by homozygous or heterozygous mutation in CCBE1 gene on chromosome 18q21 [9,17,19,27,40]. It is characterized by generalized lymphatic dysplasia of various organs of the intestine, pericardium, limb and facial dysmorphism and mental retardation [3,23,24,26].

**The aim of study** to describe the clinical characteristics of Hennekam syndrome.

**Search strategy.**

The PubMed, Web of Science, and Scopus databases were used to conduct a thorough literature search. Up to May 2023, complete publications that had been published in peer-reviewed journals were chosen. The terms "Hennekam syndrome" and "Lymphedema-lymphangiectasia-mental retardation syndrome" were used as search criteria. As a result, 83 publications were found, of which 53 articles were selected.

**Results**

**Published clinical cases description**

First *Gabrielli O. et al.* (1991) published a clinical case of a boy born in a marriage second cousin and sister with anomalies of the face, syndactily of fingers, varus feet, and cryptorchidism. The child has profuse diarrhea, as well as the characteristic flat face, flat nasal septum, hypertelorism, epikant, small mouth and ears, teeth anomalies. The child was hospitalized at age 4 years with edema of feet, hypoalbuminaemia and lymphopenia. In 9 years old a child diagnosed with conductive hearing loss [20].

*Yasunaga M. et al.* (1993) described 7 year old boy with protein-lossing gastroenteropathy with characteristic typical signs of Hennekam syndrome, but without mental retardation and lymphedema [52].

*Cormier-Daire V. et al.* (1995) described a girl with intestinal lymphangiectasia, severe lymphedema of the extremities, facial abnormalities, seizures, mild mental retardation and characteristic facial changes, in contrast to the cases of a child described earlier found kidney malformation and coronary craniosynostosis [11].

*Angle B.* (1997) provided a clinical case of a girl with Hennekam syndrome with lymphedema, abnormalities of the face, intestinal lymphangiectasia and moderate mental retardation, which also had abnormalities not previously described - a congenital heart defect, prolapse of the rectum, vesicoureteral reflux, hearing loss [6].

*Erkan T.* (1998) described the I7-month-old girl with peripheral edema, normal mental development, hemangiomas in her arms, trunk and legs. Biochemical study showed iron deficiency anemia, hypoproteinemia, hypogammaglobulinemia and elevated levels of alpha-antitrypsin. Endoscopy and intestinal biopsy showed signs of intestinal lymphangiectasia [16].

*Scarcella A. et al.* (2000) described two sisters with Hennekam syndrome with facial anomalies, enteropathy with protein deficiency and intestinal lymphangiectasia. The sisters had different anomalies - primary hypothyroidism, hypertrophic pyloric stenosis, early death. Hepatosplenomegaly and limb lymphedema developed in the first month after birth. Lethal outcome of older sister was due to severe sepsis, severe hypoalbuminemia with periodic gastroenteritis and respiratory infection. An autopsy showed lymphangiectasia of mediastinum, pleura, peritoneum and intestinal lymphangiectasia. Hepatomegaly of fetus was diagnosed in younger sister, who died at 3 months from heart failure due to severe refractory hypoproteinemia [43]. In the same year Huppke A.P. reported two brothers with Hennekam syndrome, which, along with the typical symptoms of the disease MRI study revealed hyperintense of subcortical brain damage [25].

*Forzano F. et al.* (2002) described an Italian patient with severe lymphedema of the lower extremities, genitals, face, exudative enteropathy, cramps, mild mental retardation. He had a flat face, hypertelorism and advanced nasal septum. He suggested that the patient has a severe form of Hennekam syndrome [18].

At the same time *Van Balkom I.D.C. et al.* (2002) published an article describing the 8 patients with the Hennekam syndrome and compared with the previous 16 clinical cases. Lymphedema often had a hereditary character, was sometimes asymmetrical, and often gradually progressed. Complications as erysipelas often observed. Lymphangiectasia observed most often in the intestine, sometimes in the pleura, pericardium, thyroid, and intestine. Some patients had congenital malformations of the heart and blood vessels. In addition to the characteristic features observed glaucoma, dental abnormalities, hearing loss and kidney abnormalities. Psychomotor development from normal to severe mental retardation. Frequently observed cramps [49].

Also Hennekam syndrome has been described in infants with hereditary lymphedema, facial abnormalities, and intestinal lymphangiectasia (*Bellini C. et al.* (2003)) [7]. At birth, the child was observed with severe respiratory distress due to non-immune fetal hydrops, congenital chylothorax and pulmonary lymphangiectasia.

*Al-Gazali L.I. et al.* (2003) [2] described 4 children from Arab families with the various manifestations of Hennekam syndrome middle ear anomalies, anomaly of pulmonary venous drainage, hypoplasia of the inferior vena cava, polysplenia, cross ectopic kidney, liver median location, as well as numerous cavernous hemangiomas. Al-Ghazali assumed infringement in the development of blood vessels and lymphatic system leads to changes in the fetal fluid dynamics as a result of which there is a disturban of the facial skull morphogenesis. *Nisli K. et al.* (2008) have also described a patient with Hennekam syndrome with pericarditis and anomalous drainage of the pulmonary veins [36].

In 2010, *Connell F.* [10] published a clinical case of 6 year old girl from the UK with a generalized lymphedema. During the intrauterine development of the child appeared hydrops with pleural effusion and ascites, resulting in 33 weeks of gestation performed peritoneal shunting. At birth, a child marked swelling and took a semi-ventilation. Despite a diet with medium chain triglycerides in the child developed severe diarrhea at the age of 1 month. As a result, the child transferred to total parenteral nutrition and infusion of albumin, as well as receiving thyroid hormone replacement therapy for the treatment of hypothyroidism. Histological examination showed dilatation and inflammatory bowel disease. In 6 years, the child observed generalized edema with ascites and a steady decline in serum albumin

*G. Lakshminarayana* 2011 described a case in India along with the typical facial anomalies observed anodontia (missing teeth) and bilateral renal lymphangiectasia [29]. The first case in Morocco described the girl born from a cousin and sister, which was observed from 7 years with recurrent leg lymphedema secondary infection. The child was hospitalized in 14 years with complaints of mild edema of the lower extremities. In lymphography revealed the absence of lymph flow in both lower limbs. Given the anomaly of the face and mild mental retardation child diagnosed Hennekam syndrome [15].

*Rao B.* presented a case of 20 year-old man complaining of abdominal distension with ascites, bilateral leg edema, macrocephaly, swelling of the left half of the face, hypertrophy of the left half of the tongue, dental anomalies, acanthosis nigricans, and acrohordon, syndactyly [39].

In 2015, described a clinical case of 5 weeks the boy from Pakistan with edema, ascites and hypoalbuminemia. It diagnosed with primary intestinal lymphangiectasia secondary protein-losing enteropathy. Considering the related marriage of parents conducted a genetic analysis, which showed the presence of mutations CCBE1. Author emphasized that in addition to the classic version of Hennekam syndrome are less severe cases wich characterized with intestinal lymphangiectasia and moderate edema [19].

On examination, the patient 21-year-old revealed bilateral pleural effusion, edema of both feet and eyelids, scrotum, anomalies of face- broad forehead and face, dents bridge, and micrognathia, epikant. In the study of pleural

effusion chylothorax diagnosed on the basis of triglycerides level (650 mg/dL). At lymphoscintigraphy marked slow lymph flow to both lower extremities. Diagnosis was based on facial anomalies, lymphedema, epilepsy, chylothorax, and mild mental retardation [8].

In 5 affected individuals of closely related families with Hennekam syndrom, including 3 patients with Dutch ancestry, 1 Omani patients and 1 Iraqi patient, *Alders et al* (2009) have deciphered the candidate gene CCBE1 and identified homozygosity for a missense mutation in all 5 patients [3, 4]. The presence of kinship parents equal sex ratio, absence of vertical transmission of all this suggests autosomal recessive inheritance path.

**Pathogenesis**

It has been suggested that multiple facial anomalies can be explained by the effects of fetal lymphedema with hypoplasia or aplasia of the lymphatic vessels, lymphatic obstruction or early migration of nerve tissue [23]. Furthermore, gastrointestinal protein loss result in stunted growth, resulting in loss of metabolites, such as calcium and magnesium spasms arise. Although there is no true lymphatic vessels in the brain, there are cells in the dura, adventitia cervical blood vessels and surrounding tissues, which provide access to common cord lymphatic system. Violation of this system may cause some mild edema of the brain and, therefore, contribute to the emergence of seizures and developmental delays. However, other features of the syndrome, such as dental anomalies, glaucoma, or brain abnormalities is difficult to explain, as a complication. The causative gene can also have different functions in different tissues, which explains the primary manifestation of malformations.

**Diagnosis**

Endoscopy, video capsule endoscopy, radionuclide lymphangiography, and magnetic resonance imaging are among the diagnostic procedures used to identify intestinal lymphangiectasia. Genetic testing, typical facial anomalies helps to diagnosis Hennekam syndrome.

**Differential diagnosis**

Hennekam syndrome should be differentiated from Noonan's syndrome, which is characterized by developmental delay, facial abnormalities, pulmonary artery stenosis, the irregular shape of the chest. In 1972 Wallet described the 6 year-old boy with severe lymphedema and lymphangioectasia of intestines and lungs. When Noonan syndrome is marked short neck with pterygium fold or low growth of hair, hypertelorism of eye slits, low growth. Facial microanomalies include antimongoloid incision of eye slits, ptosis, epicanthus, low-set ears, wrinkled curl, malocclusion, cleft soft palate uvula, gothic sky, micrognathia and microgeny [21].

Hennekam syndrome should be differentiated from lymphedema-cholestasis syndrome [1], an autosomal recessive congenital chylothorax with edema that develops in the first few days of life [51]. In this syndrome, congenital lymphedema is observed with an unusual face, atrial septal defect, and congenital pulmonary lymphangiectasia without peripheral lymphedema and semidiaphragmal eventration very small mouth, and other dysmorphic features [41,42,49].

Congenital lymphedema may also be present in autosomal-dominant disease Milroy, syndrome distihiasis-lymphedema [37] syndrome of microcephaly, lymphedema [47], the syndrome of hypoparathyroidism, nephropathy, lymphedema [38], lissencephaly-cerebellum syndrome hypoplasia-lymphedema [24] velocardiofacial syndrome, ectodermal dysplasia with immunodeficiency, osteoporosis and lymphedema [14], and Turner syndrome.

We have previously published case series of HS with intestinal inflammation and other autoimmune conditions such hypothyroidism, celiac disease, and type 1 diabetes [34].

**Treatment**

Treatment usually depends on the symptoms [52]. Hennekam syndrome appointed albumin infusion, a diet containing medium chain triglycerides. Al Sinani et al. reported the successful use of octreotide to reduce losses and hypoalbuminemia intestinal protein [5]. Pulmonary lymphangiectasia difficult to treat. Lymphedema is sometimes require surgery. The prognosis depends on the severity of clinical symptoms, severe symptoms can lead to early death [30-32,44].

**Conclusion**

As can be seen from the discussion above, Hennekam syndrome is a rare cause of intestinal lymphangiectasia. Doctors pediatricians, gastroenterologists should be mindful about Hennekam syndrome in the presence of intestinal lymphangiectasia, lymphedema, and distinctive facial anomalies.

***Conflict of Interest.*** *The authors declare that they have no conflict of interest.*

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