Journal of Digestive Diseases and Hepatology
Messova AM, et al. J Dig Dis Hepatol 6: 183.
www.doi.org/10.29011/2574-3511.100083
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Case Report

Growth Failure, Micronutrient Deficiency and Autoimmunity – A New Phenotype of Hennekam Syndrome

Messova AM, Lindley KJ, Köglmeier J*

Great Ormond Street Hospital for Children NHS Foundation Trust London, United Kingdom

***Corresponding author**: Köglmeier J, Great Ormond Street Hospital for Children NHS Foundation Trust London, United Kingdom

Citation: Messova AM, Lindley KJ, Köglmeier J (2022) Growth Failure, Micronutrient Deficiency and Autoimmunity-A New Phenotype of Hennekam Syndrome. J Dig Dis Hepatol 6: 183. DOI: https://doi.org/10.29011/2574-3511.100083

Received Date: 9 September 2022; **Accepted Date:** 20 September 2022; **Published Date:** 23 September 2022

Abstract

Hennekam syndrome (HS) is a lymphatic system disorder associated with protein losing enteropathy [1]. High protein minimal fat diet is a known therapeutic approach. Whilst a mild malabsorption syndrome is well-known, intestinal inflammation, severe growth failure and autoimmune disorders are not described. We report three patients with HS. Two had intestinal inflammation, micronutrient deficiencies and growth failure refractory to anti-inflammatory medication and oral supplementation. Intestinal mucosal healing and satisfactory catch-up growth was achieved with Parenteral nutrition (PN). One child developed Coeliac disease. The clinical course of all three was complicated by other autoimmune phenomena including hypothyroidism and type 1 diabetes.

Keywords: Hennekam syndrome; Lymphangiectasis; Lymphedema; Protein losing enteropathy; Inflammation; Micronutrients; Nutrition; Autoimmune

Introduction

Hennekam syndrome is a are autosomal recessive disorder of lymphatic development. Rupture of intestinal lymphatics is causing protein-losing enteropathy [1]. Three subtypes divided according to underlying causative gene mutation affecting the VEGF-C/VEGFR-3 signalling pathway important for lymphangiogenesis are described - CCBE 1, FAT4 and ADAMTS3 [2,3].

HS presents with limb oedema, lymphangiectasis in the intestine and other organs, characteristic facial features and variable learning difficulties [1].

Methods

The index case presented with intestinal inflammation, micronutrient deficiencies and growth arrest refractory to anti-inflammatory medication and required frequent albumin infusions. Rehabilitation of nutrition status and growth was achieved on long term PN. A further two were identified from the clinic database and case notes reviewed respectively. Written consent for data publication was obtained from patients/carers who were informed about this manuscript.

Results

Case 1

A 10-month-old boy presented with diarrhoea, abdominal distension and respiratory distress. Investigations revealed pleural effusions, ascites, portal vein thrombosis, hypoalbuminemia and low peripheral lymphocyte count. He had facial dysmorphism (broad nasal bridge, midface hypoplasia). Stool alpha-1-antitrypsin was elevated. Upper and lower gastrointestinal endoscopy and video capsule (VCE) revealed ulceration in duodenum and jejunum together with lymphangiectasis (Figure 1). He received steroids twice and started on Azathioprine. Genetic testing showed a homozygous mutation in the CCBE1 gene (c.305G>C (p.Cys102Ser) and confirmed HS. He required daily 20% albumin infusions despite Octreotide and minimal fat high protein diet (MFHP) with medium chain triglyceride (MCT) oil. From the age of four, his growth arrested. He was found to be hypothyroid and had profound fat-soluble vitamin and trace metal deficiencies not responsive to high dose oral supplementation. Despite normal thyroid function on thyroxine, his height remained unchanged. Aged 7 parenteral nutrition was started. Repeat endoscopies showed midgut lymphangiectasia with only mild inflammatory changes in the duodenum. Coeliac screen was negative.

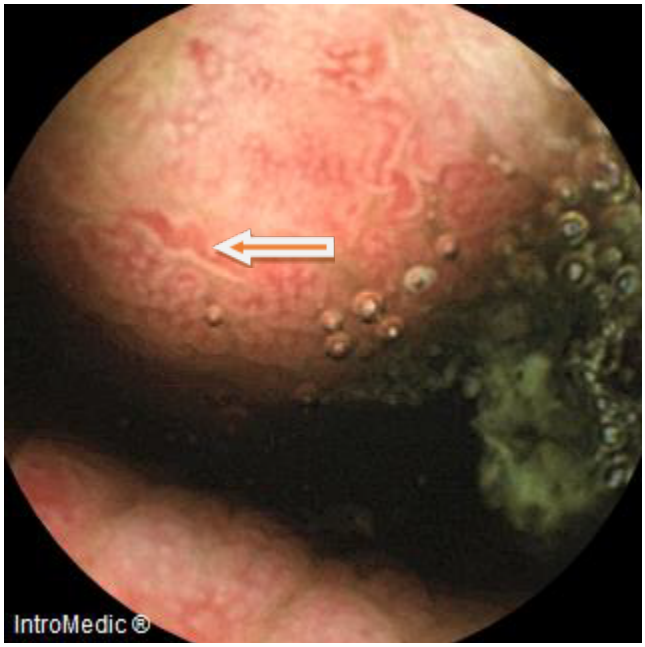

Figure 1a: Ulceration in jejunum (VCE). VCE (video capsule endoscopy) of case 1 - arrow indicates ulceration in jejunum

He was discharged on home PN and demonstrated good catch-up growth in Figure 2 and correction of micronutrient deficiencies.

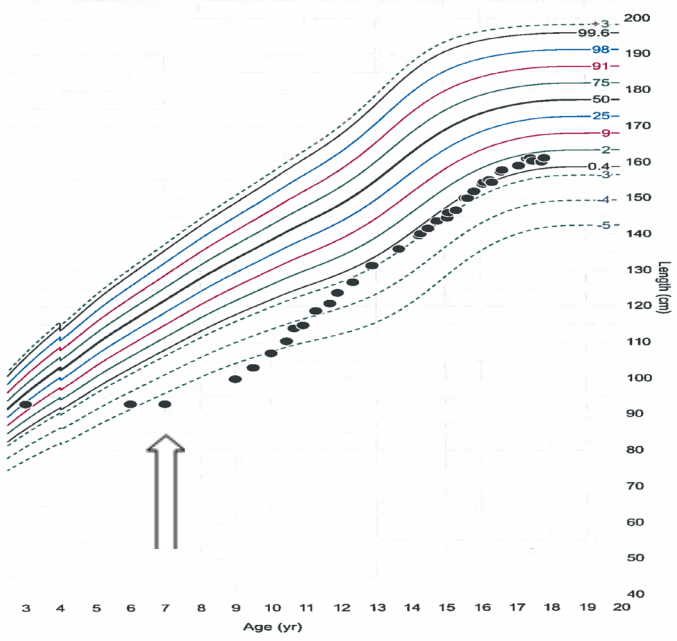

Figure 2: Growth chart patient 1-arrow indicates start of PN.

Anti-inflammatory medication and octreotide were discontinued. No inflammation was seen on follow up endoscopy. He is 17.5 years of age and remains on PN. Attempts to reduce parenteral support resulted in increased albumin requirements and micronutrient deficiency.

Case 2

A 5 months old girl presented with poor weight gain and left adrenal neuroblastoma, which was fully resected. She had facial oedema with dysmorphic features and low albumin levels. Her faecal alpha-1-antitrypsin was raised suggestive of a protein losing enteropathy. Pan endoscopic assessment of her gastrointestinal tract revealed inflammation in duodenum and terminal ileum together with mid gut lymphangiectasia (Figure 3).

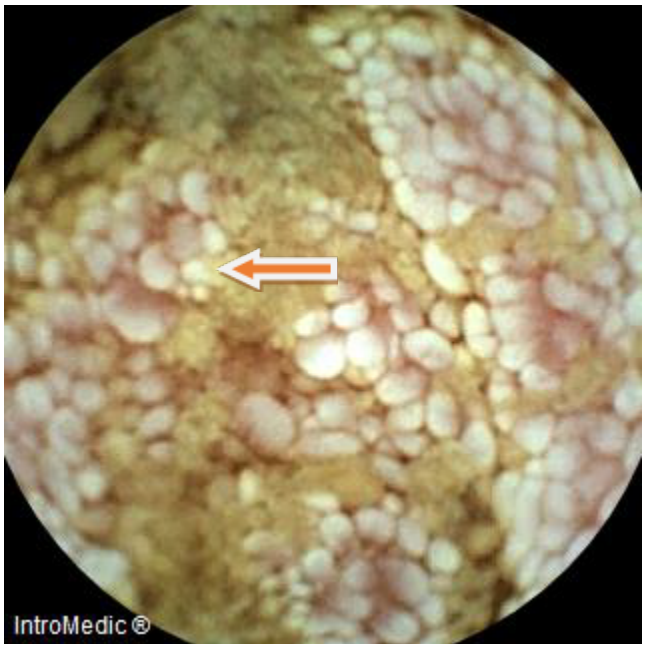

Figure 3: VCE case 2-arrow indicates midgut lymphangiectasia.

Genetic testing confirmed HS (c.521G>A, p.Cys174Tyr). She was treated with octreotide but continued to require twice weekly 20% albumin infusions. She received steroids twice and Azathioprine. Minimal MFHP+MCT diet was started. Aged 4 she developed insulin dependent diabetes and hypothyroidism.

Despite good blood sugar control and thyroxine, she did not grow for 18 months and had profound micronutrient deficiencies unresponsive to oral supplementation. Repeat endoscopy revealed resolution of the inflammatory infiltrate but ongoing midgut lymphangiectasia. Home PN was started aged 7.6 years. Growth in Figure 4 and micronutrient deficiencies improved.

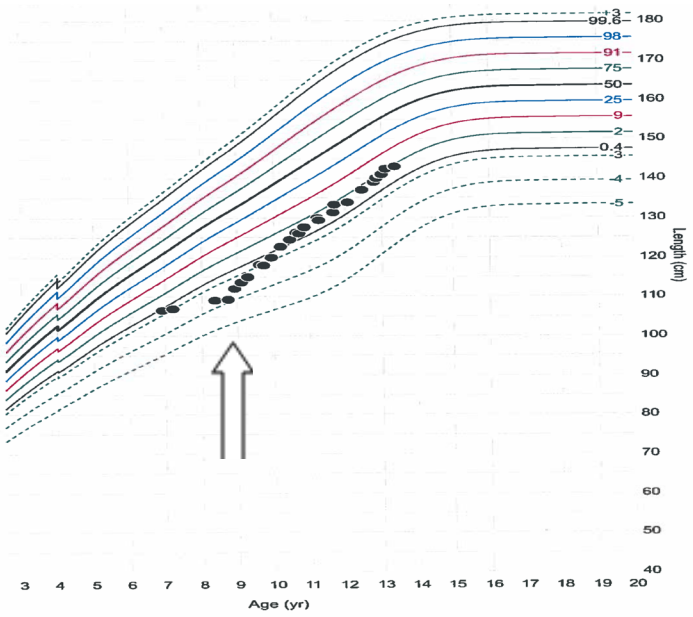

Figure 4: Growth chart patient 2- arrow indicates start of PN Immunosuppression was discontinued without reoccurrence of intestinal inflammation.

PN was withdrawn aged twelve. She is 13 years and remains stable on oral micronutrient supplementation and thyroxine, receives albumin infusions twice a week and has good diabetic control.

Case 3

Genetic screening of her younger sister showed a homozygous mutation in the CCBE1 gene (c.521G>A). She had mild facial dysmorphism and loose stools. MCT formula was started when breast milk stopped and solids (MFHP) commenced aged 6 months. Height/weight increased along the 91st centile; albumin infusions were given only every three weeks.

When 3.5 years she developed type 1 diabetes. Albumin requirement increased to three infusions/week, growth slowed down and micronutrient levels dropped. Pan endoscopy revealed midgut lymhangiectasia and duodenitis with partial villous atrophy and increase in intraepithelial lymphocytes. Tissue transglutaminase antibodies were significantly elevated (>128 U/ml; normal <6.9) and a gluten free diet started. She is now five. Albumin requirements have gone down (2/week); growth is normal.

Discussion

The lymphatic system plays an important role in body fluid and tissue homeostasis. In HS, malformed lymphatics result in blockage of the lymphatic circulation. Accumulation of fluids in multiple parts of the body including face, extremities and major organs are the consequence [4].

Facial dysmorphism thought to be caused by abnormal lymphatics during the development of the bone and soft tissue structures of the face and variable learning difficulties are characteristic [3]. Lymphangiectasia is most common in the intestine. In addition, peripheral lymphoedema is often seen. In utero, lymphatic endothelia cells differentiate from veins through action of the PROX1 and SOX18 transcription factors followed by the development of the lymphatic system through the involvement of several other proteins [6]. Defective protein function can result in lymphoedema.

To date 27 genes participating in lymphatic system development have been identified, including CCBE1, FLT4 and ADAMTS3, which are responsible for the development of HS [2,3]. Our patients all had mutations in the CCBE1 gene and classical phenotypic features of facial dysmorphism and intestinal lymphangiectasia leading to protein losing enteropathy. However, the youngest child had a much milder clinical presentation highlighting the phenotypic variability even amongst members of the same family [4].

Her early diagnosis and treatment highlight the importance of early recognition and start of therapy. Two children developed hypothyroidism, which may be explained by abnormal lymphatics in the thyroid gland. Iodine is predominantly absorbed in the stomach and upper small intestine. In addition, the midgut lymphangiectasia seen in both children could have impaired iodine absorption. The sisters also developed type 1 diabetes. Abnormalities of the endocrine pancreas have not previously been described in HS but may be related to abnormalities in the lymphatic system of the pancreas. Hypothyroidism and type 1 diabetes are thought to be autoimmune driven disorders. All three children also had a varying degree of intestinal inflammation (one coeliac disease) not known to be associated with HS. Inflammatory Bowel Disease (IBD) is caused by immune dysregulation in the gut.

HS may hence be associated with autoimmune disorders such as hypothyroidism, type 1 diabetes, coeliac disease and IBD. The underlying pathophysiology in HS has not been discussed before. The clinical case of the two older children was complicated by severe growth failure and micronutrient deficiencies, which did not respond to anti-inflammatory medication and high dose vitamin/trace metal supplementation.

Both received a synthetic somatostatin analogue (octreotide), known to reduce blood flow to the splanchnic area via vasoconstriction and been shown to reduce the lymphatic leak in patients with a thoracic duct injury [5]. However, our patients did not respond to octreotide. PN prescribed alongside MFHP+MCT diet on the other hand proved to be very successful.

Both children demonstrated catch up growth and normalisation of micronutrients. One child developed micronutrient deficiencies, slowing of growth and increased albumin requirements following the onset of type 1 diabetes and Coeliac disease. She is currently stable on a gluten free diet and oral supplementation.

Conclusion

Our case series highlights the potential association of HS with intestinal inflammation and other autoimmune phenomena such as hypothyroidism, coeliac disease and type 1 diabetes. Growth failure and micronutrient deficiencies were common and nutrition status could be rehabilitated with PN in those most severely affected.

References

1. Hennekam RC, Geerdink RA, Hamel BC, Hennekam FA, Kraus P, et al. (1989) Autostomal recessive intestinal lymphangiectasia and lymphedema, with facial anomalies and mental retardation. Am J Med Genet 34: 593- 600.
2. Alders M, Hogan BM, Gjini E, Salehi F, Al-Gazali L, et al. (2009) Mutations in CCBE1 cause generalized lymph vessel dysplasia in humans. Nat Genet 41: 1272-1274.
3. Brouillard P, Dupont L, Helaers R, Coulie R, Tiller GE, et al. (2017) Loss of ADAMTS3 activity causes Hennekam lymphangiectasis-lymphedema syndrome 3. Hum Mol Genet 26: 4095- 4104.
4. Al-Gazali LI, Hertecant J, Ahmed R, Khan NA, Padmanabhan R (2003) Further delineation of Hennekam syndrome. Clin Dysmorphol 12: 227-232.
5. Al Sinani S, Al Rawahi Y, Abdoon H (2012) Octreotide in Hennekam syndrome associated intestinal lymphangiectasia. World J Gastroenterol 18: 6333- 6337.