Intestinal Enterokinase Deficiency in Pediatrics


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Abstract: Congenital enteropeptidase deficiency (CEP), also known as enterokinase deficiency. CEP is an uncommon autosomal recessive genetic disorder mostly characterized by severe chronic diarrhea after delivery, hypoproteinemia, and failure to grow. Enteropeptidase activity is anticipated to play a significant role in protein digestion. For growth and appropriate development in newborns with a congenital lack of the enzyme, pancreatic enzyme replacement treatment or an amino acid combination must be given. Only 13 cases of enterokinase insufficiency have been recorded since it was originally characterized in 1969. Couples should be informed that prenatal screening is an option and that EKD has a favourable prognosis. However, if an EKD patient is born, parents should be aware of the feeding issue and offer the proper pancreatic exocrine secretion medication. One research found that all patients had been diagnosed as newborns 25 years ago. Even when the pancreatic-enzyme replacement was stopped, they appeared to lead regular lives as adults, free of gastrointestinal issues and with normal body weight. This can be explained by the fact that trypsin, once liberated from its precursor, encourages additional trypsinogen activation in a positive-feedback manner. Better pharmaceutical preparations such as enteric-coated minimicrospheres and delayed-release capsules are used for better results as it maintains the enzyme and prevents its breakdown by stomach acidity. This review aims to summarise current knowledge of pathophysiology, causes, and treatment of Intestinal Enterokinase Deficiency in Pediatrics

Keywords: Congenital Enteropeptidase Deficiency, Enterokinase Deficiency, Pediatrics, Diarrhea, Pancreatic-Enzyme

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1. INTRODUCTION

Congenital enteroprotease deficiency (CEP), also known as enterokinase deficiency, is an incredibly uncommon autosomal recessive genetic disorder mostly characterized by severe chronic diarrhea after delivery, hypoproteinemia, and failure to grow. EKD is brought on by loss-of-function mutations in the transmembrane protease serine 15 (TMPRSS15) gene (OMIM#606635). A problem with intestinal protein absorption results from the absence of enterokinase (EK), which inhibits trypsinogen from being activated. Only around ten instances have been recorded globally for EKD, which was initially characterized by Hadorn et al. (1969). The Human Genome Mutation Database (HGMD) reports that only four variations have been recorded since it was originally characterized in 1969. There have only been 13 cases of enterokinase insufficiency (proenteropeptidase). For growth and appropriate development in newborns with a congenital lack of the enzyme, pancreatic enzyme replacement treatment or an amino acid combination must be given. On the other hand, pancreatitis, both acute and chronic, may result from duodenopancreatic reflux of proteolytically active EP. The ability to purify entersoprotease from an inactive precursor (proenteropeptidase). 4, 5 For growth and appropriate development in newborns with a congenital lack of the enzyme, pancreatic enzyme replacement treatment or an amino acid combination must be given. On the other hand, pancreatitis, both acute and chronic, may result from duodenopancreatic reflux of proteolytically active EP. 6-9 The primary function of pancreatic enzymes is to break down proteins, fats, and carbohydrates into smaller molecules that the small intestine can absorb. The pancreas plays a crucial role in the pathophysiology of pancreatic diseases.

1.1 Pathophysiology

Protein absorption is severely hampered by enterokinase deficiency. Enterocytes have proteinase-activated receptor two on their apical and basolateral membranes. Trypsin activation of this receptor causes enterocytes to release eicosanoids, which have a local effect on the epithelial development of the intestinal wall. Consequently, enterokinase localization on the luminal surface of the duodenal villi may, in addition to its solely digestive function, promote enterocyte development by producing active trypsin on the cell surface. The gene for beta-amyloloid precursor protein appears to be located nearby in the human genome in band 21q21.2. The human proenteropeptidase gene spans approximately 88 kb of genomic DNA sequence. It has 25 exons (24 introns). Like enterokinase deficiency, duodenase mutations that result in faulty activation of proenteropeptidase may cause illness. Only four genetic variants in the TMPRSS15 gene have been associated with the HGMD thus far due to the disease’s rarity and the limits of available diagnostic techniques. The codons at Ser712 in the macrophage scavenger receptor-like domain (MSCR) domain and Arg857 in the serine protease domain on the heavy chain were prematurely terminated due to the compound heterozygous nonsense variants c.2135C > G; p. (Ser712) and c. 2569C > T; p.(Arg857) in two siblings from a Western European family. Another patient was found to have the heterozygous deletion variant c.2707 2708del [p.(Val903Phefs29)] in exon 23 and the heterozygous nonsense variant c.781C > T; p.(Gln261)) in exon 8, which caused Gln261 to terminate prematurely in the heavy C1r/s motif and frameshift of amino acids in the serine protease domain.

1.2 Congenital Abnormalities Of Exocrine Pancreas

The pancreas is an endocrine and exocrine gland that functions in tandem. Acinar cells manufacture and store pancreatic enzymes, and ductal cells, which secrete fluid and electrolytes, make up the exocrine tissue. Exocrine pancreatic insufficiency (EPI) is typically seen in babies with malabsorption symptoms such as failure to thrive, chronic diarrhea, anaemia, or hypoalbuminemia. The most common test to detect pancreatic insufficiency (PI) patients is faecal elastase-1. Congenital EPI etiologies can be classified into three classes based on the basic pathophysiologic mechanisms: (a) exocrine pancreatic tissue injury, (b) pancreatic hypoplasia or agenesis, or (c) isolated enzyme deficiency. Cystic fibrosis (CF) is a multisystemic autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. So far, over 2000 CFTR mutations have been described. The most common, affecting at least one allele in more than
65% of CF patients, is a 3-base-pair deletion that results in the loss of a phenylalanine at position 508 of the protein (F508del). CFTR mutations have been divided into six types based on their major effect on CFTR function or processing. In many countries, CF is identified through neonatal screening, which detects high serum trypsinogen levels. Patients with cystic fibrosis may have a persistent cough, rectal prolapse, steatorrhea, failure to thrive, or male infertility later in life. Sweat tests and CFTR sequencing are used to make the final diagnosis of CF.

Sweat tests and CFTR sequencing are used to make the final diagnosis of CF. The second most common cause of congenital EPI is Shwachman-Bodian-Diamond syndrome (SBDS). The Shwachman-Bodian-Diamond syndrome gene has biallelic mutations in about 90% of SBDS patients (SBDS, SBDS type I). Recently, biallelic mutations found in elongation factor-like GTPase I have expanded the molecular spectrum of SBDS.

Patients with SBDS who underwent pancreas necropsy showed indications of acinar hypoplasia, significant fat infiltration, and the preservation of ductal cells and Langerhans islets despite the absence of fibrosis or inflammation. Parallel to this, quantitative pancreatic function studies in SBDS patients revealed normal fluid and anion outputs but significantly decreased enzyme secretion regarding total acinar secretion. Supportive treatment, including PERT and supplementation with liposoluble vitamins, addresses EPI in SBDS patients. About 45% of patients eventually experience a slight improvement in exocrine function, which allows them to stop taking PERT.17-19 Shwager syndrome is a rare multisystemic autosomal recessive condition brought on by biallelic mutations in the COX4I2 gene, which codes for a part of the mitochondrial respiratory chain's terminal enzyme, cytochrome c oxidase. Exocrine pancreatic insufficiency, dyserythropoietic anaemia, and calvarial hyperostosis are the disease's hallmark symptoms. The condition has been identified in 4 patients to date, all of whom present with failure to thrive and steatorrhea shortly after delivery. The pancreas appeared atrophic and obese on imaging. EPI (supplementation of pancreatic enzyme and liposoluble vitamins) and repeated anaemia transfusions are the mainstays of illness care.

### 1.3 Johanson-Blizzard Syndrome

The frequency of Johanson-Blizzard syndrome (JBS), a multisystemic autosomal recessive illness, is thought to be 1/250,000. Later research revealed that JBS is brought on by homozygous or compound heterozygous mutations in the Nrecognin 1 (UBR1) gene, which codes for one of a small number of ligases involved in the N-end rule pathway and is a component of ubiquitin-protein ligase E3. As a result, wild-type UBR1 identifies, binds, and marks the N-terminal residue of proteins, which causes the proteasome to degrade the protein. Unfolded protein buildup in the ER and improper protein breakdown is thought to be caused by mutated UBR1 and contribute to ER stress.20 Inflammatory infiltrates and progressive acinar tissue loss was seen in the pancreas of JBS patients. It has been demonstrated that this pathogenic process begins in the fetus. Patients with JBS who underwent quantitative pancreatic function tests had considerably lower enzyme secretion but preserved fluid and anion outputs. Serum trypsinogen levels were also significantly below the ranges considered to be normal. The EPI and hypo- or aplasia of the nasal wings are the two defining characteristics of JBS. Other characteristics include craniofacial malformations, short stature, developmental delay, congenital heart disease, elevated liver enzymes, genito-urinary disorders, and kidney defects. Patients with JBS who have EPI are treated with PERT and liposoluble vitamin supplements. Supplemental endocrine hormones may also be necessary.24

### 1.4 Aplasia, Hypoplasia, And Dysplasia

Aplasia denotes the presence of a simple, basic organ structure. Agenesia, in contrast, denotes the absence of every component of an organ. An undeveloped bodily component is said to have hypoplasia. An organ or bodily component developing improperly is referred to as dysplasia. An extremely uncommon condition of pancreatic development is primary agenesis of the pancreas. Its incidence range is unknown. In addition to postnatal diabetes mellitus and malabsorption, total pancreatic absence is also frequently linked to intrauterine growth retardation, which may be related to the fact that insulin is a key intrauterine development factor. The condition is typically lethal very quickly. Monogenic conditions such as pancreatic agenesis are possible (OMIM 260370).25 Despite not being a pancreatic enzyme, enterokinase is essential for activating pancreas-derived zymogens in the duodenum. Hence enterokinase deficit manifests as a pancreatic protease failure. One family's diagnosis of this illness (OMIM 226200) has been linked to mutations in the proenteropeptidase gene PRSS7. With very few exceptions, these isolated enzyme deficits have an extremely low number of reported instances and a lack of molecularly verified abnormalities. This would suggest additional lipolytic, proteolytic, and glycolytic activity sources that can make up for specific inadequacies. Enzyme replacement therapy is highly effective in all cases of isolated pancreatic enzyme insufficiency.26

### 1.5 Ductal Anomalies

Congenital anomalies of the pancreas and pancreatic duct may not be identified until maturity, and they are frequently found incidentally in asymptomatic people. A developmental anomaly of the pancreas and pancreatic duct should be considered in adult patients with persistent and unexplained signs and symptoms like abdominal pain, nausea, and vomiting brought on by recurrent pancreatitis or gastric outlet obstruction. Imaging is also advised in these cases. Many patients use magnetic resonance cholangiopancreatography (MRCP) for noninvasive evaluation of the biliary tree and pancreatic duct. It could show the pancreatic duct's path and discharge pattern and simplify diagnosing pancreatic developmental defects.27–29

14% of people have pancreas divisum, which is caused by the dorsal and ventral ducts failing to fuse during embryological development. Type 1 or the conventional divisum, type 2 (where dorsal drainage predominates in the absence of the duct of Wirsung), and type 3 (where there is an incomplete divisum with a minor connecting branch) have all been described as three variations. The majority of the pancreatic gland in the pancreas divisum drains into the minor papilla through the duct of Santorini, while the posterior head and uncinate process drain into the major papilla through the duct of Wirsung with the CBD.28,29

### 1.6 Annular Pancreas
The ventral bud’s difficulty in spinning with the duodenum leads to the envelopment of the duodenum, which causes an annular pancreas. In this anomaly, the pancreatic head is continuous with a band of pancreatic tissue that either entirely or partially encircles the second half of the duodenum. Because of extensive duodenal blockage, the annular pancreas typically manifests in newborns who vomit. However, about 50% of older patients may never have symptoms, with the aberration only becoming apparent by chance. When present, symptoms often begin in the third to a sixth decade and include abdominal pain, vomiting due to a blocked gastric outlet, upper gastrointestinal bleeding from a peptic ulcer, pancreatitis, or, in rare cases, jaundice due to a blocked biliary system. In this anomaly, the pancreatic head is continuous with a band of pancreatic tissue that either entirely or partially encircles the duodenum on CT and magnetic resonance imaging (MRI), continuing the pancreatic head. However, a diagnosis of an annular pancreas does not necessitate the visualization of a full ring of pancreatic tissue around the duodenum. Suspicion of an annular pancreas should be raised in the context of gastric outlet obstruction. These patients most likely have a narrow band of pancreatic tissue embedded in the duodenum wall that cannot be observed on CT or MRI scans.21

1.7 Heterotopic Pancreas

Pancreatic tissue situated outside of the pancreas’ typical anatomical position is known as heterotopic pancreas. It typically resides in the upper digestive tract. There are very few cases of the heterotopic pancreas. The preoperative diagnosis is challenging. Any location in the abdominal cavity is capable of harbouring a heterotopic pancreas. With the stomach, duodenum, or jejunum accounting for more than 90% of cases, it is typically seen in the upper gastrointestinal system. The colon, spleen, or liver are uncommon locations. The submucosa-buried nature of the heterotopic pancreas makes it challenging to identify from GIST12,21. In our cases, heterotopic pancreatic tissue had a diameter of 1.5–2 cm rather than the typical 1–2 cm. Patients with heterotopic pancreas may appear normal or experience gastrointestinal discomfort. It can also show clinical symptoms in a few uncommon pancreatic conditions, such as pancreatitis, islet cell tumours, pancreatic cancer, and pancreatic cyst. Diagnosis aids include the gastroscope, CT scan, and echo gastroscope. According to the literature, an echogram is often used to diagnose this disease. In the differential diagnosis of GIST, the heterotopic pancreas should be considered. Surgical excision is the first and best option for a heterotopic pancreas because medical treatment is ineffective.34 Endoscopic biopsies are frequently unremarkable, making it difficult to differentiate between the gastric heterotopic pancreas and primary or metastatic cancer. Frozen sections should be taken quickly and frequently to confirm the diagnosis and prevent unnecessary radical surgery like Whipple’s procedure or subtotal gastrectomy. Some carcinoid syndrome symptoms could appear in a heterotopic pancreas, and they could be treated surgically to get rid of them.33

1.8 Pancreatic Insufficiency

Several hereditary disorders of the exocrine pancreas, which have been described as causes of pancreatic insufficiency, maldigestion, and steatorrhea, are as follows: Cystic fibrosis, Schwachman-Diamond syndrome, Johanson-Blizzard syndrome, Exocrine pancreatic dysfunction with refractory sideroblastic anaemia, Pancreatic aplasia/hypoplasia.31 Isolated exocrine pancreatic enzyme deficiencies Lipase Lipase-collipase Collipase Amylase Trypsinogen Cystic fibrosis is, by far, the most common. The ensuing exocrine pancreatic insufficiency can be primary or developmental and may include all of the exocrine pancreatic enzymes or only isolated enzyme deficiency.36

1.9 Schwachman-Diamond Syndrome

The Schwachman-Diamond syndrome was first described in 1964 and represents the second most common cause of pancreatic insufficiency.1, Its main features are pancreatic insufficiency, cyclic neutropenia, metaphyseal dysostosis, and growth retardation. Associated manifestations include dental abnormalities, renal dysfunction, hepatomegaly, abnormal lung function, delayed puberty, and ichthyosis. The estimated incidence is 1 in 10,000 to 20,000 live births, with no sex predominance, and the suggested mode of inheritance is autosomal recessive.16 Stunted growth is the most constant clinical feature of the syndrome. These patients are usually below the third percentile for height, but linear growth is maintained. Most often, the malabsorption is manifested during infancy with steatorrhea.37 Stools are greasy, pale, and foul-smelling. A negative sweat test excludes cystic fibrosis. An increased stool fat excretion or pancreozymin/secretin stimulation test that reveals very low or nonexistent pancreatic zymogen enzymes confirms the diagnosis. Patients with steatorrhea have less than 1% normal lipase secretion. Patients without steatorrhea have diminished lipase activity that is more than 10% of normal.38 In contrast with cystic fibrosis, the volume and bicarbonate content of the stimulated pancreatic fluid are usually normal, and its viscosity is normal. In some patients, spontaneous improvement occurs with the disappearance of steatorrhea, whereas in others, steatorrhea persists into adulthood. Pathologically, the pancreatic size is normal to small, with evidence of fatty infiltration. The ductal and the islet compartments are preserved with only residual acinar tissue left.39 The hematologic manifestations of Schwachman-Diamond syndrome are variable. Neutropenia, thrombocytopenia, and anaemia are present in 95%, 70%, and 50%, respectively. The neutropenia (<1500/mm3) is usually intermittent and occurs as often as every 1 to 2 days. Blood counts are performed twice weekly during a 3-week period to confirm the diagnosis. Although the quantitative neutrophil response to infection is appropriate, several qualitative neutrophilic anomalies are described, including defective motility.116 and unusual surface distribution of concanavalin A receptors that might contribute to abnormal chemotaxis of neutrophils. Impaired neutrophil chemotaxis can be improved with lithium therapy. These neutrophil abnormalities may explain the susceptibility of the patients to infection. Bone marrow examination reveals hypoplasia, fat infiltration, and myeloid maturation arrest.40,41
I.10 Johanson-Blizzard Syndrome

Johanson-Blizzard syndrome was described in 1971.60 Its main features are pancreatic insufficiency, nasal alar hypoplasia, absence of permanent teeth, short stature, congenital deafness, psychomotor retardation, ectodermal scalp defects, recto urogenital malformations, imperforated anus, and hypothyroidism. The mode of inheritance is autosomal recessive with no sex predilection. Only now, fewer than 40 patients have been described. The clinical picture is dominated by typical dysmorphism, malabsorption, failure to thrive, and, occasionally, clinical hypothyroidism. Although the genetic defect is unknown, most recently, the pathophysiology of the pancreatic defect was elucidated. Patients with the syndrome have preservation of fluid and electrolytes ductular output but a decreased acinar secretion of trypsin, colipase, and total lipase, consistent with a primary acinar cell defect. The preserved ductular output is similar to Schwachman-Diamond syndrome.

I.11 Epidemiology

There have only been 13 cases of primary enterokinase deficiency recorded. Similar clinical characteristics were described in three more individuals, but their intestinal enterokinase activity was not tested. The prognosis is favourable with appropriate care. The few recorded instances show no signs of sex preference. With one known exception, afflicted patients have diarrhoea and failure to thrive at birth. The exception was the afflicted boy’s sister, who started having symptoms at age five months and was diagnosed at age eight years.

I.12 Management

Parents who are carriers might be warned about the 25% chance of EKD in subsequent pregnancies. Couples should be informed that prenatal screening is an option and that EKD has a favourable prognosis. However, if an EKD patient is born, parents should be aware of the feeding issue and offer the proper pancreatic exocrine secretion medication. Trypsin activity in the duodenal fluid provided the basis for the conventional diagnosis of EKD. Patients may receive the incorrect diagnosis, or the appropriate therapy may be postponed due to the challenges in accessing the contents of the duodenal intestine and evaluating EK activity. Patient who lack intestinal enterokinase should get pancreatic enzyme supplementation. When enzymes are given either portioned with meals or just after meals, the effectiveness of enzyme replacement treatment for exocrine pancreatic insufficiency appears to be higher. Enzyme administration through entericoated minicircles prevents acid-mediated lipase inactivation and guarantees that enzymes are expelled from the stomach concurrently with nutrients. Delayed-release capsules minimally affect gastric transit and are meticulously titrated to fit the needs of patients. Further innovations include Relizorb, which uses a single-use cartridge form of lipase connected to existing enteral tube feed sets to facilitate digestion. Even though EKD is an uncommon congenital condition, pancreatic enzyme replacement treatment had positive results for the reported individuals. Nevertheless, some children go through diarrhoea and other symptoms during adolescence following full remission before returning to normal with an increase in the pancreatic enzyme replacement treatment dose. The tendency for self-healing and recurrence might be explained by the ageing population’s decreased need for protein digestion. Adult protein digestion needs can be met through feedback mediated by trypsin or alternative activation mechanisms unrelated to trypsin and EK. However, it is insufficient for newborns to digest protein, and recurrence may be linked to increased protein consumption during adolescence’s growth spurt. In one research, all the patients had been diagnosed as newborns 25 years ago. Even when the pancreatic-enzyme replacement was stopped, they appeared to lead regular lives as adults, free of gastrointestinal issues and with normal body weight. Protein digestion relies only on enteropeptidase activity during infancy since all mutations discovered anticipate the abolishment of enzymatic function. It has been demonstrated in the past that trypsinogen possesses an innate ability to self-activate, albeit at a very sluggish pace. Additionally, previous research has shown that trypsin, once liberated from its precursor, encourages additional activation of trypsinogen in a positive-feedback manner. This explains the finding that individuals with enteropeptidase deficiency had active trypsin, chymotrypsin, and carboxypeptidase A found in their stools. Given that the infant’s proportionate requirement for protein digestion is substantially larger, the self-activation of trypsinogen and the activation by trypsin independent of enteropeptidase activity may not be sufficient for protein digestion in humans. Genetic analysis now offers an effective tool for early EKD diagnosis because to the use of highthroughput sequencing and the knowledge of the genetic basis of the illness. EKD in the differential diagnosis should be included when babies with persistent diarrhoea, hypoproteinaemia, and normal intestinal histology do not improve after receiving standard care. Even before the availability of genetic studies, infants could be treated with pancreatic exocrine secretion. Patients with this genetic condition can live longer and with a higher quality of life if they receive early diagnosis and treatment.

I.13 Enteropeptidase Inhibition

Strong and reversible enteropeptidase inhibitor SCO-792 has a slow dissociation rate from enteropeptidase. It effectively prevents protein digestion and, as a result, prevents the rise in plasma branched-chain amino acids. In vitro, it also reduces trypsin activity. Since trypsin is an essential enteropeptidase downstream molecule, it is anticipated that it will be essential in treating pancreatitis. The enteropeptidase inhibitor SCO792 significantly aids in weight loss by improving insulin sensitivity and glucose management. Additionally, SCO-792 improves the lipid profiles in the liver and plasma. Therefore, enteropeptidase inhibition may be a cutting-edge therapy alternative for diabetes and obesity. In the treatment of chronic renal disease, enteropeptidase inhibitors have promise. SCO-792 reduces albuminuria and prevents glomerular filtration rate decrease. Additionally, SCO-792 reduces interstitial fibrosis and improves glomerulosclerosis in the kidney. This shows that using SCO-792 improves renal parameters in individuals with chronic kidney disease quite well.
2. CONCLUSION

Exocrine pancreatic insufficiency is a term used to describe a rare condition called enterokinase deficiency. The number of recognized causes has grown significantly beyond cystic fibrosis due to improved diagnostic methods, including specific genetic testing. Early diagnosis enables the implementation of the necessary care to stop malnutrition's severe, long-term consequences. In addition, these patients can grow and develop thanks to improvements in pancreatic enzyme supplementation without experiencing any noticeable illness symptoms or pharmaceutical side effects.

3. AUTHOR CONTRIBUTION STATEMENT

Dr. Ahmed Abdelsamie Fadl conceptualized and designed the study. Dr. Abdulhalim Ahmed Alabdullatif and Dr. Aldebani.Moluk Nabeel S searched databases for literature. Dr. Alqaghtani Mohammed Abdullah S and Dr. Dania Ebrahim Khalil Maki screened and filtered selected studies. Dr. Alharbi Maryam Eyadah and Dr. Waleed Yahya Sufi and Dr. Abdullah Majed Saleh Alharbi wrote the manuscript. Dr. Nada Mohammed J Alzahrani and Dr. Mohammed Ali A Alshamrani and Dr. Ahmed Abdullah Bugshan and Dr. Abdulrahman Ibrahim A Altowairqi revised the manuscript. Dr. Jalal Mohammed Alsameen and Dr. Waad Musayid B Alsaeedi emailed the journal for publication.

4. CONFLICT OF INTEREST

Conflict of interest declared none.


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