Title: “The gut-everywhere axis: extraintestinal manifestations and non-gut symptoms of gastroenterological diseases”

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Abstract

Extraintestinal manifestations (EIMs) of gastrointestinal (GI) diseases are numerous and fascinating. They can affect almost any organ in the body and are caused by various different mechanisms.

Over the last decade the awareness of the ability of the gut to effect other parts of the body has become more widespread, the “gut-brain axis” being a powerful example. However, there are many different gut axes including less well known connections, such as the gut-liver axis, the gut-skin axis, the gut-joint axis, the gut-eye axis, the gut-immune axis and the gut-lung axis.

The gut-skin, gut-joint and gut-eye axes are particularly interesting when it comes to the EIMs seen in Coeliac disease and Inflammatory Bowel Disease (IBD), which are well known.

Some EIMs relate directly to the GI disease activity and effective treatment of the intestinal disease will lead to a resolution of the EIMs. However, some EIMs seen in IBD occur independently of disease activity.

The exact mechanisms and pathogenesis of EIMs remains complex and not fully understood.

In this review paper we will briefly review and discuss the EIMs associated with Coeliac disease and IBD, as well as non-gut symptoms and signs seen in other less commonly known GI diseases such as congenital enteropathies and intestinal lymphangiectasia.

This review paper aims to equip paediatricians and health care professionals with the knowledge needed to identify EIMs in children with GI disease presenting with symptoms and signs manifesting outside of the gut.

Key Words

Extraintestinal manifestations, children, coeliac disease, inflammatory bowel disease, paediatrics, dermatitis herpetiformis, erythema nodosum, pyoderma gangrenosum, uveitis, episcleritis, scleritis.

Manuscript

Extraintestinal manifestations (EIMs) of gastrointestinal (GI) diseases are numerous and fascinating. They can affect almost any organ in the body, and perhaps acted as inspiration for Hippocrates when he announced that “all disease begins in the gut”.

Awareness and identification of EIMs in the context of GI diseases in children is key not only for paediatric gastroenterologists, but also for general paediatricians and health care professionals. Some GI diseases may have a subtle and/or atypical presentation and present with EIMs which could easily be missed or overlooked leading to a delay in diagnosis and management.

This review paper provides an overview of some conditions across paediatric gastroenterology, where an extra GI component, when identified correctly and looked at holistically, will point towards a GI disease diagnosis.

Coeliac disease

Coeliac disease (CD) is a systemic autoimmune disease involving T cells in the context of a dysregulated mucosal response to gliadin, the protein in gluten. The disease is triggered in genetically susceptible individuals on exposure to gluten.

CD is a very common condition affecting 1% of the population. Like many other immune-mediated conditions, the incidence of CD is increasing and this is not just due to better diagnosis and awareness.

Ongoing research focuses on whether environmental determinants, such as infections and antibiotic use, could possibly play a role. The Western diet, known for its effects on the microbiome, intestinal permeability and mucosal inflammation, is also being investigated as a possible factor contributing to the increase in the development of CD.

The mechanism of EIMs in CD has different aetiologies. Some of the EIMs are caused by mucosal damage leading to malabsorption, whilst others are due to autoimmune responses such as autoantibodies originating in the gut affecting other parts of the body causing pathology.

Interestingly, the prevalence of EIMs, at around 60%, is similar in children and adults with CD[1]. However, the extra intestinal signs seen differ. Children present most often with short stature, headaches, fatigue and mood disturbances, whereas adults present most often with iron deficiency anaemia.

The most commonly known extra-intestinal feature of CD is dermatitis herpetiformis (DH)(Fig. 1A). However, in practice this is rarely seen in children.
In DH there is skin deposition of immune complexes and IgA autoantibodies against transglutaminases. DH causes an extremely pruritic blistering rash mainly affecting extensor surfaces of the skin. Blisters are rarely seen as the rash is so itchy that any blisters are destroyed by scratching. Patients with DH rarely present with GI symptoms but 72% will have enteropathy on biopsy. Treatment is the same as for CD, i.e. a strict gluten free diet.

In CD, short stature remains the most commonly associated EIM. It is usually seen in children with more severe disease or who have onset of the disease at a younger age. The way CD leads to short stature is multi-factorial, not only comprising of malnutrition and malabsorption, but also due to dysfunction of the insulin-line growth factor 1 (IGF1) axis.

Interestingly, when children with untreated CD were given growth hormone there was no increase in their IGF1. This could be explained by the effects of active inflammation (IL-6, interferon gamma and TNFa) on the growth axis, suppressing any increase in IGF1.

Anaemia is a common presentation of CD. Iron is absorbed mostly in the duodenum, therefore damage to the villi from CD will affect absorption. Treatment is very successful with a gluten free diet and iron supplementation.

Other EIMs seen in CD include delayed puberty and transaminitis.

Raised transaminases is the most common liver manifestation of CD. The prevalence is around 9-14% and the extent of mucosal damage in the duodenum, the anti-transglutaminase (TTG) level, the presence of anti-endomysial antibodies and malabsorption, all correlate with the severity of the hypertransaminasemia.
The transaminitis tends to respond excellently to a gluten free diet, with liver enzymes normalising completely in 75-95% of cases within one to two years.

A raised ALT has also been linked with a higher TSH and a correlation has been seen between raised transaminases in CD and thyroid disease. This possibly relates to the liver being involved with thyroid hormone transport, metabolism and deiodination.

Although other hepatic diseases such as autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cholangitis are seen more commonly in children with CD, they do not respond to a gluten free diet.

Osteopenia and osteoporosis is seen in paediatric patients with CD, with osteopenia affecting up to 75% of CD patients. The damaged duodenal mucosal can lead to poor absorption of vitamin D and calcium. This causes an increase in parathyroid hormone secretion that is commonly seen in children with CD. Inflammatory cytokines such as IL1, IL6 and TNFa also stimulate bone metabolism increasing osteopenia and increased bone turnover.

Children with CD may experience non-erosive arthritis, subclinical synovitis on imaging, myopathy and arthralgia. Arthralgia in CD is more commonly seen in children over the age of 12.

CD is also associated with other autoimmune diseases affecting the joints such as juvenile idiopathic arthritis, rheumatoid arthritis, Sjogren's and systemic lupus erythematosus.

Of all the EIMs seen in CD, the neurological manifestations are particularly interesting and affect 3-10% of children with CD. Headaches are the most common neurological EIM seen in CD and can affect up to 20% of children. Children presenting with persistent headaches should be screened for CD. Adherence to a gluten free diet will result in 76% of patients experiencing resolution of headaches.

Other far rarer neurological manifestations of CD in paediatrics include ataxia and neuropathy.

There has long been a discussion as to whether epilepsy is associated with CD. A cohort study by Ludvigsson et al. looking at whether biopsy confirmed cases of CD were associated with epilepsy found that CD was associated with 1.4 fold increase in the risk of developing epilepsy.

A particular type of epilepsy with occipital calcifications has been seen in children with CD (Fig. 2A).

Cerebellar ataxia is seen in young adults with CD. The pathogenesis is thought to involve anti-TG6 antibodies which may attack the cerebellar cells directly. However, children with CD without cerebellar ataxia may also test positive for these antibodies, therefore their role in cerebellar ataxia is not yet clear.

In children, distal neuropathy is also seen. The pathogenesis of the neuropathy is not certain but may involve anti-ganglioside antibodies as well as nutritional deficiencies such as B12 and micronutrient deficiencies. Children with neuropathy may have no enteropathy, which would suggest that malabsorption is not necessarily a contributing factor. Therefore, a possible explanation would be cross reaction between anti-gliadin antibodies and synapsin. (Table 1.)

Neurological and psychiatric complications have been observed in CD for over 40 years.
The increased risk of psychiatric disease does not seem to be just due to the stress and challenges associated with having a chronic health condition or needing to adhere to a strict gluten free diet.

Children with CD have an increased incidence of psychiatric diseases such as depression, anxiety, obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) prior to diagnosis. The pathogenesis for this may involve cross reactivity between brain tissue and anti-neuronal, anti TG6, anti-ganglioside and anti-gliadin antibodies.

Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease (IBD) is another gastrointestinal disease well known for its association with EIMs.
Up 30% of children with IBD (and up to 50% of adults suffer from EIMs. Interestingly, up to half of EIMs are seen prior to the development of the GI symptoms.

While some EIMs are specific to either Crohn's disease or ulcerative colitis (UC), others are common to both diseases.

Among the most widely known EIMs in IBD are those affecting the joints, skin and eyes. Less commonly seen are those involving the hepatobiliary tract, pancreas, lungs and heart.

Some EIMs can be dependent on the degree of GI disease activity, while others can be seen when the GI disease is in fact in remission. Therefore, some EIMs resolve on treatment whereas others will not. EIMs can be difficult to manage and often require referral to other specialties and MDT discussions.
Oro-cutaneous lesions seen particularly in Crohn's include aphthous ulcers, mucogingivitis, pyodermatitis pyostomatitis vegetans (PPV)(Figure 1B) and oro-facial granulomatosis (OFG)(Figure 1C). Pyodermatitis pyostomatitis is more commonly seen in adults and is very rare in children with IBD.

The most common skin conditions seen in IBD include psoriasis, erythema nodosum (Figure 1D), pyoderma gangrenosum (Figure 1E) and sweet syndrome. Erythema nodosum (Figure 1D) is seen in both CD (far more commonly) and UC. The sex ratio is children for erythema nodosum is 1:1 but in adults it is far more common in females.
Usually erythema nodosum improves with treatment of the GI disease. In rare cases, however, it has been observed in children with no GI symptoms[2].

Pyoderma gangrenosum (Figure 1E) is seen mainly in UC. It is caused by neutrophilic infiltration of the skin. It can occur in isolation, but usually it is seen in IBD or other inflammatory or neoplastic diseases. The lesions are very painful, deep and with necrosis at the ulcer base. In adults, pyoderma gangrenosum most commonly affects the lower legs, but in paediatrics it is seen mostly on the head, genital, peri-stomal and perianal areas.

Paediatric pyoderma gangrenosum often does not respond to treatments and can be difficult to manage. Anti-TNF treatment is currently the recommended first line treatment for severe pyoderma gangrenosum in children with IBD.

The eye is the third most affected organ with regards to EIMs in IBD. However, ocular EIMs affect children with IBD less than adults. An Iranian study showed that 6 out of 96 (6.2%) children with IBD had EIMs affecting their eyes[3].

Ocular EIMs include episcleritis (Figure 1B), scleritis (Figure 1C) and uveitis (Figure 1D). Anterior uveitis (Figure 1D) is the best known of these due to its potential to damage sight. It is also screened for in children with other autoimmune diseases such as juvenile idiopathic arthritis (JIA).

Episcleritis and anterior uveitis are the most common ocular EIMs seen in IBD.

Episcleritis is usually unilateral and causes redness and mild irritation of the eye (Figure 1B). It tends to correlate with active GI inflammation.

Scleritis is seen less commonly in IBD but if not treated can cause sight loss. It can present with a constant pain behind the eye and is a more painful condition than episcleritis. Often the pain is worse at night (Figure 1C). Scleritis is not related to GI inflammation activity and can occur when IBD is in remission.

Anterior uveitis (Figure 1D) usually causes bilateral eye pain, mild photphobia and blurred vision. As opposed to episcleritis, anterior uveitis activity is usually independent of GI inflammation. It is seen more frequently in children with Crohn's.

As with joint and skin EIMs, ocular manifestations can precede GI symptoms. Children presenting with isolated anterior uveitis should be reviewed regularly for the development of IBD.

Joint involvement includes IBD related arthralgia, IBD related arthritis (peripheral or axial), enthesitis or dactylitis. The most common forms of arthropathy seen in children with IBD are seronegative sacroiliitis and spondyloarthropathy (SpA)[4].

Hepatobiliary disease such as Primary Sclerosing Cholangitis (PSC) and Autoimmune Hepatitis (AIH) is seen in 5-10% of children with IBD.

PSC is a cholestatic liver disease characterised by inflammation and fibrosis of the biliary ducts. Although the disease course varies, it can eventually lead to cirrhosis and liver failure. Children with IBD and PSC have an increased risk of colorectal cancer and cholangiocarcinoma.

Pancreatitis is also seen but is rare. Pancreatitis when seen in IBD is usually as a side effect of Azathioprine treatment.

Endocrine EIMs (including growth failure, metabolic disease and pubertal delay) occur in IBD. They are often multi factorial, in part driven by inflammation and nutritional deficicits, but can also be iatrogenic from glucocorticoid use.

At present the pathogenesis of EIMs in IBD is not yet fully understood.
EIMs may result from extension of the immune responses in the gut, or they could be independent inflammatory events with the same genetic and environmental predisposition as IBD. (Table 1)

The microbiome in the gut can cause inflammation outside of the GI tract via molecular mimicry, bacterial translocation and microbial metabolite production. Examples of immune responses extending from the gut include bacterial antigen translocation, microbial antigen cross-reactivity, ectopic expression of adhesion molecules and chemokines, T cell trafficking actuated by non specific adhesion molecules and circulating antibodies which can bind epitopes shared between the gut and extraintestinal sites. (Table 1)

The relationship between the microbiome and IBD is a dynamic one and works in both directions. The microbiome can drive IBD but intestinal inflammation in turn can cause dysbiosis further driving IBD.

In early gut microbiome dysbiosis, microbial penetration into the lamina propria can be seen. Late dysbiosis includes a decrease in microbial diversity, a decrease in beneficial bacterial species and an increase in pathogenic bacterial species and fungi. Significant dysbiosis can lead to mucosal adherence and translocation of intestinal contents including bacteria across the gut wall potentially triggering chronic inflammation.

Dysbiosis can cause gut immune cells to be activated and these cells may eventually translocate to other organs.

In PSC, specific gut bacteria have been found to disrupt the integrity of the gut wall leading to translocation of bacteria causing liver inflammation.

Exclusive enteral nutrition (EEN) is often used to induce remission in paedatric patients with Crohn's disease, one of its mechanisms of action being its ability to manipulate the microbiome.

Monogenic IBD

Monogenic IBD deserves a separate discussion. It includes a separate sub-group of patients where single genetic defects underlie chronic intestinal inflammation, which presents with an IBD phenotype.

Most cases of monogenic IBD are diagnosed in children below the age of six (very early onset IBD, VEO-IBD), however diagnoses in older children and adults are also reported.

Monogenic disorders are often associated with primary immune deficiencies. This group of children may therefore present with a history of recurrent and/or atypical infections.

The EIMs seen in monogenic IBD may include lymphadenopathy, hepatosplenomegaly and specific skin lesions.

In monogenic IBD caused by IL-10 signalling defects, typical features include complex, refractory perianal disease, skin folliculitis and/or arthritis at a very young age.

Some forms of monogenic IBD are caused by disorders of immunomodulation. These cases present with prolonged diarrhoea and malabsorption as a consequence of immune mediated intestinal mucosa damage.

Immune dysregulation, Polyendocrinopathy, Enteropathy and X-linked syndrome (IPEX) is a syndrome caused by genetic defects leading to FOXP3 deficiency and resulting in T cell hyperactivation.
It usually presents in boys comprising of a triad of severe dermatitis, diabetes and enteropathy.
Children with IPEX may present with an early onset of IBD-like enteropathy as well as other autoimmune (AI) disorders such as AI anaemia, AI thrombocytopaenia, type 1 diabetes, AI thyroiditis and interstitial pneumonia.

Drug induced EIMs in GI disease

There are various EIMs caused by drugs used to treat GI disease. This is seen mainly in IBD where for example steroids may cause signs of Cushing syndrome such as striae, moon face, osteoporosis, stunting of growth and depression. Rarely the use of steroids can also cause avascular necrosis of the femoral head.

Infliximab and adalimumab are anti-TNF agents which have revolutionised treatment in IBD and rheumatological conditions. They have acted as extremely important steroid sparing agents and are often very successful at inducing and maintaining remission. However, cutaneous reactions are commonly seen to anti-TNF agents. These reactions include reactions at injection sites as well as immune mediated reactions such as skin folliculitis, new onset psoriasis (Fig. 1F), worsening of psoriasis and lupus-like syndrome.

Other rare conditions affecting the gastrointestinal tract which can also present with EIMs

Acrodermatitis enteropathica

Acrodermatitis enteropathica is a rare condition characterised by a congenital zinc deficiency from mutations of the SLC39A4 gene. It mainly affects the paediatric population, presenting with peri-orificial and acral dermatitis, alopecia and diarrhoea. Children with acrodermatitis enteropathica present with dermatitis most commonly affecting the feet and hands. About half will also have diarrrhoea and/or alopecia. Only one fifth present with the classic triad of dermatitis, diarrhoea and alopecia. The treatment, which is zinc supplementation, was discovered in 1974.

Intestinal lymphangiectasia

Intestinal lymphangiectasia is a rare condition that causes protein losing enteropathy (PLE). Symptoms arise because the rate of protein lost into the gut is higher than the amount of protein synthesised by the liver.

Intestinal lymphangiectasia can be either primary (congenital) or secondary (e.g. a result of chemotherapy, cardiac surgery, infection or toxins).

Children will present with chronic diarrhoea and generalised oedema due to low albumin. Diagnosis is based on GI endoscopy, biopsy and magnetic resonance imaging (MRI).

Paediatric congenital enteropathies

The paediatric congenital enteropathies, also known as the congenital diarrhoea disorders, are a heterogeneous group of inherited disorders which present early in life. They include the following examples.

Microvillus Inclusion Disease (MVID), is an autosomal recessive enteropathy causing uncontrollable secretory diarrhoea (with high output generally between 150ml and 300ml/kg/day). It is linked to gene variants in MYO5B, STX3, STXBP2, UNC45A. The majority of the children affected will require lifelong parenteral nutrition.

Congenital tufting enteropathy (CTE) is also an autosomal recessive disease resulting from mutations in the epithelial cell adhesion molecule (EpCAM) gene. It manifests with intractable secretory diarrhoea in the first months of life.

IDEDNIK syndrome (Intellectual disability, enteropathy, deafness, neuropathy, ichthyosis and keratodermis syndrome) caused by (autosomal recessive) mutations in AP1S1, presents as severe persistent diarrhoea, dehydration and salt wasting. These children also show reduced copper levels with accumulation of copper in the liver similar to seen in Wilson's disease.

Trichohepatoenteric syndrome is a rare autosomal recessive genetic disease caused by pathogenic mutations in TTC37 or SKIV2L gene. It manifests as a neonatal enteropathy with intractable watery diarrhoea, woolly and brittle hair, short stature, café au lait spots and dysmorphic features affecting the face. The diarrhoea starts in infancy and is not responsive to bowel rest. There can be GI inflammatory changes such as in VEO-IBD.

Enteroendocrine cell dysgenesis is an autosomal recessive inherited disorder, presenting with severe secretory diarrhoea from birth and malabsorption. Treatment consists of parenteral and enteral nutrition, as tolerated based on the disease phenotype.

Conclusion

This review highlights some of the known EIMs in common GI diseases, including CD and IBD. It also provides a brief overview of less known conditions within the sub-specialist field of paediatric gastroenterology, including congenital enteropathies and intestinal lymphangiectasia.

Research endeavours are ongoing to investigate the pathogenesis of these EIMs.

Familiarisation with the main non GI signs and symptoms associated with specific conditions is crucial to put the correct diagnostic and treatment pathways in place in a timely manner.

Signs should not be viewed in isolation; be it in an outpatient clinic or on an inpatient ward. An underlying gastrointestinal disease should be considered among other differential diagnoses in a child presenting with ocular or skin lesions. Equally, when reviewing a child with known gastrointestinal disease, screening for and asking about EIMs is fundamental for a complete assessment.

Our review highlights how the gut has far reaching effects on many different systems and organs in the body. The pathways through which this occurs are multiple and not yet fully understood but involve genetic factors, the gut barrier function, the immune system, and the gut microbiome.

List of clinical practice points

1. Coeliac disease (CD) can present with atypical extraintestinal manifestations (EIMs), even in the absence of GI symptoms. Paediatricians should have a low threshold for screening for CD in children presenting with short stature, headaches and rashes.

2. Iron deficiency anaemia is a common presentation of CD.

3. Children with CD have higher rates of psychiatric disease compared to the general population. We should consider screening for CD in children presenting with anxiety, depression and obsessive-compulsive disorder (OCD). All children presenting with an eating disorder should be screened for CD.

4. EIMs of IBD affecting the skin are common and include erythema nodosum, pyoderma gangrenosum and psoriasis.

5. Episcleritis and anterior uveitis are the most commonly seen ocular EIMs in IBD. Episcleritis usually correlates with active GI inflammation, while anterior uveitis is usually independent of GI inflammation.

6. An underlying gastrointestinal disease should be considered among other differential diagnoses in a child presenting with ocular or skin lesions.

7. Monogenic IBD is caused by specific genetic defects and tends to present before the age of 6 years. In addition to GI symptoms, these children may also present with immunodeficiency and a history of recurrent infections.

8. IPEX is a monogenic disorder caused by FOXP3 deficiency resulting in T cell hyperactivation. It usually presents in boys comprising of a triad of severe dermatitis, diabetes and enteropathy (very early onset-IBD).

9. Growth failure is the most common presenting symptom of chronic liver disease in children.

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