Rauðkyrningar í vélinda hjá börnum

Úlfur Agnarsson

!

Esophageal Eosinofilia – orsakir skv. American College of Gastroenterology

- Eosinophilic gastrointestinal diseases
- PPI-responsive esophageal eosinophilia
- Celiac disease
- Crohn's disease
- Infection
- Hypereosinophilic syndrome
- Achalasia
- Drug hypersensitivity
- Vasculitis
- Pemphigus
- Connective tissue diseases
- Graft vs. host disease
- PPI, proton-pump inhibitor.

Vélinda bakflæði

- Rauðkyrningar eiga ekki að vera í vélinda

- Tilvist þeirra í vélinda var talið tengt bakflæði

GE reflux → PPI - REE

- damage to the tight junctions due to acid exposure
- results in increased permeability with dilation of intracellular spaces and may allow for allergen penetration
- triggers subsequent recruitment of eosinophils to the esophageal epithelium

- direct anti-inflammatory effect of the PPI on the esophageal epithelium
- recent report has shown that in esophageal cell lines, exposure to omeprazole in cells stimulated with cytokines such as IL-13 and Il-4 can block the secretion of eotaxin-3, which is thought to play an integral role in development of EoE .

PPI-REE

- **PPI-responsive esophageal eosinophilia** — The pathogenesis of esophageal eosinophilia in such patients is not well understood. It is also **unclear** if PPI-responsive esophageal eosinophilia and eosinophilic esophagitis are distinct diseases. In a study that evaluated differences in major basic protein, **tryptase**, and **eotaxin-3** levels in patients with PPI-responsive esophageal eosinophilia, eosinophilic esophagitis, and controls, there were significant differences in protein levels when patients with eosinophilic esophagitis were compared with controls but not with patients with PPI-responsive esophageal eosinophilia In addition, some patients with an initial response to PPIs subsequently develop recurrent symptoms and eosinophilia consistent with eosinophilic esophagitis Interestingly, **PPIs block STAT6**, which is involved in binding of the eotaxin-3 promoter in esophageal epithelial cells, suggesting that **the response to PPIs in** some patients may in part be due to an anti-eosinophil effect .

PPI -REE

- several pediatric and adult studies have described a histologic response to PPI therapy that is consistently in the 30–50%range

- more than one-third of all patients with esophageal eosinophilia on biopsy will respond to a PPI, and patients in this category should not be diagnosed with EoE.

PPI-REE verður að EoE ?

- **PPI-REE has not been shown to be associated with an antigenic or immunologic cause of esophageal eosinophilia** and cannot be labeled as an EoE phenotype at this time
- long-term follow up of these patients is lacking

- one small case series highlighting this issue follows four pediatric patients with PPI-REE . Despite continued therapy with PPI, patients developed symptoms warranting repeat endoscopy, which ultimately demonstrated recurrent esophageal eosinophilia consistent with EoE.

EoE

- Eosinophilic esophagitis — Diagnostic criteria have been proposed in at least two consensus guidelines, which were similar in their recommendations].
- **Symptoms related** to esophageal dysfunction
- **Eosinophil**-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥15 eosinophils per high power field
- Mucosal eosinophilia is **isolated to the esophagus** and **persists after two months of treatment with a PPI trial**
- Secondary causes of esophageal eosinophilia have been excluded
- A **response to treatment (dietary elimination; topical glucocorticoids) supports the diagnosis** but is not required

Eosinophilic esophagitis

- Fjöldi eo. > 15 phpf bendir til EoE

- Nýgengi jókst úr 0.45 /100.000 1991-95 í 9.5 /100.000 2001-5
- Hjá börnum jókst nýgengi úr 0.91 /10.000 2000 í 1.28/10.000 2003

- Algengara í drengjum

EoE í börnum - einkenni

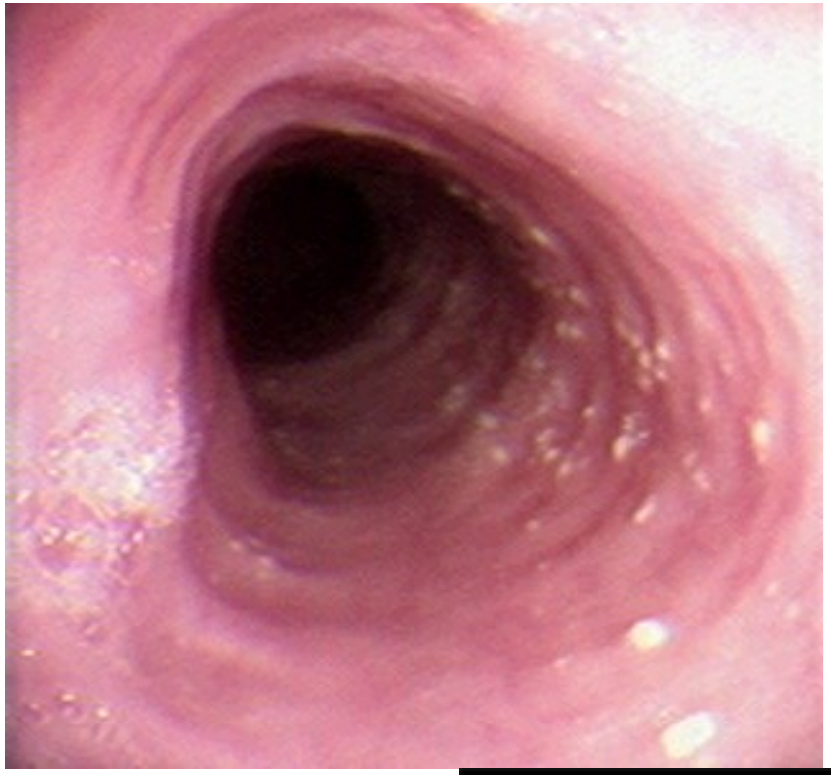
- Feeding dysfunction (median age 2.0 years)
- Vomiting (median age 8.1 years)
- Abdominal pain (median age 12.0 years)
- Dysphagia (median age 13.4 years)
- Food impaction (median age 16.8 years)

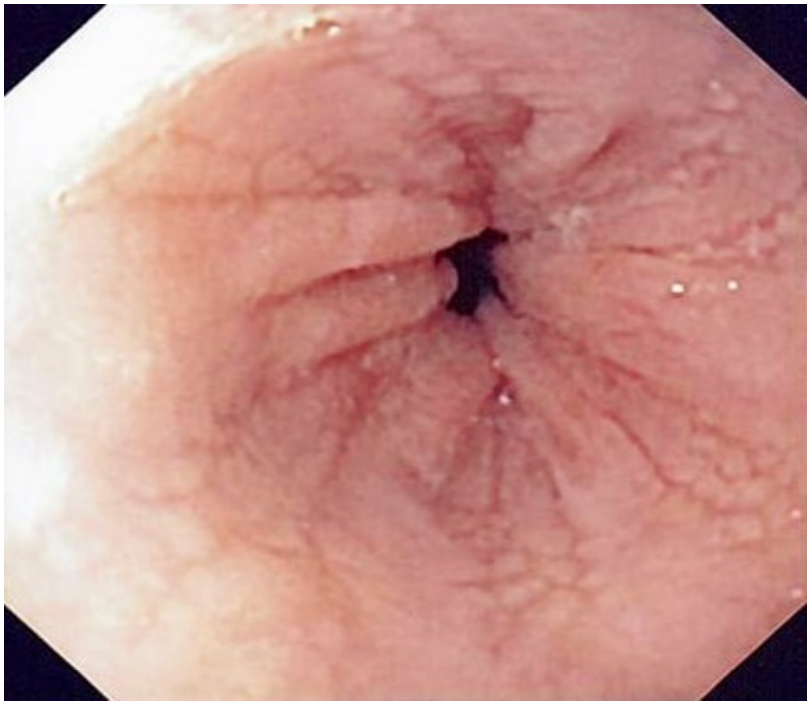
EoE – fullorðnir - einkenni

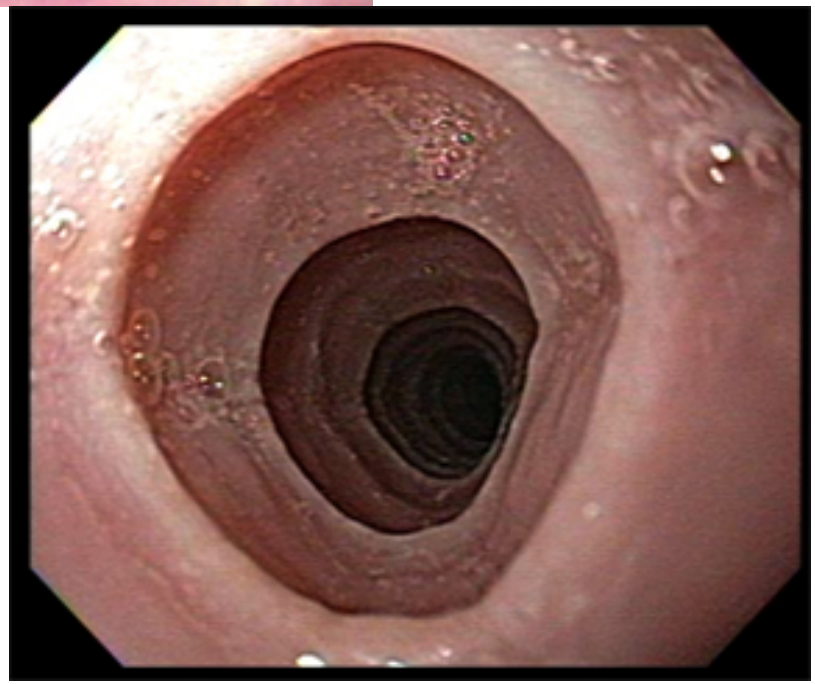
- Dysphagia
- Food impaction
- Chest pain that is often centrally located and does not respond to antacids
- Gastroesophageal reflux disease-like symptoms/refractory heartburn
- Upper abdominal pain

EoE við speglun

- Stacked circular rings ("feline" esophagus) :44 percent
- Strictures (particularly proximal strictures) : 21 percent
- Attenuation of the subepithelial vascular pattern: 41 percent
- Linear furrows : 48 percent
- Whitish papules (representing eosinophil microabscesses) : 27 percent
- Small caliber esophagus: 9 percent

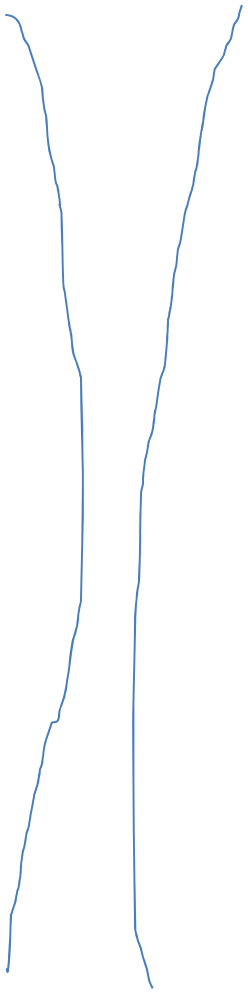






Evidence Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE

- *Major features*
- ***Edema*** *(also referred to as decreased vascular markings, mucosal pallor)* Grade 0: Absent. Distinct vascularity present Grade 1: Loss of clarity or absence of vascular markings
- ***Fixed rings*** *(also referred to concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealization)* Grade 0: None Grade 1: Mild-subtle circumferential ridges Grade 2: Moderate-distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm) Grade 3: Severe-distinct rings that do not permit passage of a diagnostic endoscope
- ***Exudates*** *(also referred to as* ***white spots, plaques****)* Grade 0: None Grade 1: Mild-lesions involving less than 10% of the esophageal surface area Grade 2: Severe-lesions involving greater than 10% of the esophageal surface area
- ***Furrows*** *(also referred to as* ***vertical lines, longitudinal furrows****)* Grade 0: Absent Grade 1: Vertical lines present
- ***Stricture*** Grade 0: Absent Grade 1: Present (specify estimated luminal diameter)
- *Minor features*
- ***Crepe paper esophagus*** *(mucosal fragility or laceration upon passage of diagnostic endoscope but not after esophageal dilation)* Grade 0: Absent Grade 1: Present
- ***Narrow-caliber esophagus*** *(reduced luminal diameter of the majority of the tubular esophagus)* Grade 0: Absent Grade 1: Present



Greining á EoE- verður að fá vefjasýni

- A meta-analysis of endoscopic findings in EoE from 100 publications encompassing a total of 4,678 patients with EoE and 2,742 controls found that **the sensitivity, specificity, and predictive values of endoscopic findings alone are insufficient for diagnosis of EoE**
- In addition, the inter- and intra-observer reliability of detecting these findings is only in the fair range , and the endoscopic appearance may be normal in 10–25% of patients with EoE
- Therefore**, mucosal biopsies of the esophagus should be obtained in all patients in whom EoE is a clinical possibility regardless of the endoscopic appearance.**

EoE - vefjaskoðun

- Histology —Esophageal eosinophilia in the absence of clinical features is not sufficient to make a diagnosis of eosinophilic esophagitis.
- During endoscopy, biopsies should be obtained from the distal esophagus as well as either the mid or proximal esophagus . The sensitivity of biopsies for diagnosing eosinophilic esophagitis depends upon the number of biopsies obtained
- In a report of 66 adults, **the sensitivity was 100 percent after obtaining five biopsies compared with 55 percent with one biopsy .**
- A second study found that the **sensitivity for two, three, and six biopsies was 84, 97, and 100 percent, respectively .**

EoE - endurskoðun frá 2013

- **the MAIN new information will be the new attitude towards response to PPI**
- **dilemmas in long term steroid safety**
- **safety of dilation**
- and suggestions for endoscopic and clinical evaluation so that registries and multi centre studies may have a consistent scoring.

EoE – rannsókn og meðferð

- Ofnæmispróf og aftur ofnæmispróf – RAST – prick – Epicutan
- Ofnæmispróf inn í vélindað

- PPi lyf
- Sérfæði
- Fluticason
- Sterar iv / oralt

EoE - tilfelli 1

- **6 mánaða drengur** fékk hitavellu, **blóðugan niðurgang** og byrjaði að **hafna allri fæðu**. Þyngdist illa. Var á brjósti og illa gekk að næra hann til að byrja með og var það gert með magaslöngu í gegnum nefið. Þannig var hann nærður í í 2-3 vikur og var settur á Nutramigen mjólk.

- Ofnæmis próf (RAST) endurtekin sýna svörun gagnvart mjólk, eggjum og fiski og þarf drengurinn að vera áfram á Nutamigen mjólk - sennil. næsta árið. Kom ekki aftur.

EoE tilfelli 1

- Líða 6 ár. Kemur vegna kviðverkja við naflann og smá ógleði sl. 1 1/2 viku.
- Þessa viku hefur hann verið með niðurgang nokkrum sinnum á dag. Saga um að vera afar lengi að borða og að það hafi staðið í honum matur í sumar og haust. Hefur ekki kastað upp. Matarlyst hefur alltaf verið misjöfn og hefur það ekki breyst.

EoE tilfelli 1

- Fyrir neðan efsta 1/3 hluta vélinda er áberandi tunnugerðar munstur og einnig langsum línur niður eftir vélindanu. Magi er eðlilegur og bulbus duodeni og pars descendens duodeni sömuleiðis. Tekin eru 2 sýni úr duodenum. Við J-sveigju virðast maga-vélindamót ágætlega þétt. Þannig ekki merki um hiatus herniu. Tekið er 1 sýni frá vélinda á bakaleiðinni. Þar sem drengurinn er orðinn mjög órólegur nást ekki fleiri sýni.

- Niðurstaða: Er með esophagitis líklega eosinophiliskan esophagitis. Beðið verður eftir niðurstöðum úr þessu eina sýni en líklega þarf að fá drenginn til ofnæmislæknis og setja hann á sérstakt fæði ásamt því sem hann heldur áfram á Nexium.
- Í sneiðum greinist slímhúðarbiti úr vélinda með þéttri íferð eosinophila í þekju (24 per HPF). **Breytingin samrýmist eosinophilic esophagitis.**

EoE tilfelli 2

- 13 ára drengur með sögu um að það hafi staðið í honum frá því hann var pínulítill. Mjög lengi að borða, slefar mikið og er í vandræðum með að koma niður mat. Fór að standa í honum þegar hann var 2-3 ára gamall. Nú þarf hann að tyggja vel og lengi. Ákveðið er að gera hjá honum speglun með þessa sögu.

- Lýsing: Fyrst er notað Olympus nasal gastroscope. Premedication er Xylocaine hálssprey, Midazolam 5mg og Leptanal 40+20µgr i.v. Farið niður með tækið niður í skeifugörnina sem er að sjá eðlilegt, tekið sýni þaðan. Magi er að sjá alveg eðlilegur og við J-sveigju eru ágætlega þétt maga-vélindamót og ekki merki um hiatus herniu. Engin bólga í maga. Farið er upp í vélinda og **er trachealisering** í öllu vélindanu. Engin sár sjást. Slímhúðir eru þokkalega eðlilegar að útliti hvað roða varðar. Tekin eru sýni úr neðri og efri hluta vélinda.

EoE tilfelli 3

- 7 ára gömul stúlka hefur asthma bronchiale og exema og hefur sögu um eggjaofnæmi en er víst komin yfir það núna og fær eðlilega fæðu.
- Sagan um meint bakflæði nær aftur um það bil 1 1/2 ár - uppköst á kvöldin, gjarnan eftir matinn og reyndar einnig á öðrum tímum dagsins eftir aðrar máltíðir t.d. morgunmat.
- Þá er hún oft með skál eða disk fyrir framan sig og gubbar í hann. Átta mig ekki alveg á hvort hún kúgist mikið eða bara skyrpir en þetta hefur verið áberandi hjá henni.
- Hún hefur verið sett á bakflæðislyf fyrir ári síðan Pariet og síðan nú á Rabeprazol en hefur það haft misgóð áhrif og þegar skammturinn var aukinn úr 10 mg x 1 í 10 mg x 2 þá lagaðist ástandið fyrst töluvert - en nú hefur dregið úr áhrifum þess og hefur þetta ekki haft nein áhrif upp á síðkastið.

EoE tilfelli 3

- Það er greið intubation niður í munn og vélinda. Efst uppi er ekkert óeðlilegt að sjá **en þegar kemur að miðbik vélindans og niður að neðri enda þess er langsum lína nokkuð áberandi og virðist vera bjúgur eða þroti í slímhúðinni.** Sé engin sár með vissu. Engin áberandi hyperemia. Farið er niður í maga sem er að sjá alveg eðlilegur og gerð J-sveigja og eru magavélindamót ágætlega þétt. Ekki hiatus hernia. Farið inn í bulbus duodeni sem er að sjá eðlilegur og inn í pars descendens duodeni.

EoE - tilfelli 4 - að utan

- I'd like your advice on treatment in a **10 year old boy** with EoE with persistent EoE and narrowing of the entire esophagus.
- He **was referred** to me by **a pediatric allergist**, who already knew the boy from the age of one year old. He had symptoms of **dysphagia for at least 2 years but was a slow and fussy eater since he was a toddler**. He **has stunted growth**, but normal weight for height. The first EGD **showed narrowing of the entire esophagus,** only a 5,9 mm scoop could pass and also >60 eos/HPF oon 3 levels. I created a mucosal tear of the upper part of the esophagus because of first introducing the regular scoop fort his age (9,6mm), so I placed a NG tube and he received only Neocate per tube for one week after which we let him eat thick solids and expand what he could eat. I also gave 4 weeks of high PPI and rescoped him after 4 weeks. No improvement in narrowing or eosinophilia, so he was started on 2 FED (milk and wheat) for 8 week. Rescope showed no improvement, so I expanded to 6FED for 8 weeks, with improvement of number of eosinophils (ca 30/HPF) but no improvement of the narrowing. Added flixotide swallowed, slight further improvement. So I deceded to give him **a course of high dosage of prednisolon (like in IBD, 4 weeks 1 dd 40 mg, followed by deminishing dose and rescoped him at 1 dd 15 mg**. Improvement of the eosinophils to 5 eos proximally, 10 in the middle and 15/HPF distally (coming from resp 30, 30 and 40 eos/HPF. So marked improvement, but unfortunately no improvement in the narrowing.

Tilfelli 4 – að utan

- My questions are:
- - What shall I do with the dosage of prednisolon? Because of his small height, I don't want him to long on oral prednisolon. Shall I start him on a **higher dose of viscous budesonide 2 dd 2 mg** (or more?)

- - Shall I look at his adrenal/cortisol axis?
- - Do I start him **on maintenance azathioprin?**

- - Since the narrowing of the esophagus is ful length, I don't want to dilate him, **and I'm wandering if the stricturing is permanent, with influx of eos in the muscle of the esophagus causing scar tissue.**
-
- He and his parents do not want an elemental diet, he is taking 1 liter of Neocate orally (strawberry flavor) since I started the diagnostics and is growing but not yet cathing up in height.
.

EoE tilfelli 5

- 12 ára stúlka með eosinophiliskan esophagitis og líklega eosinophiliska bólgu í þörmum líka sem greindist þegar hún var í Malasíu, bjó þar. Hefur nú verið í eftirliti hjá okkur og verið nokkuð oft spegluð. **Er með bólgur sérstaklega distalt í vélinda en hennar aðal kvartanir eru mikill slappleiki og þreyta, beinverkir út um allan líkamann, í útlimum bæði ofan og neðan og líklega í fleiri beinum en verið skoðuð af gigtarlækni þar sem ekki hefur fundist nein skýring.** Fer samt í leikfimi, hefur ekkert misst úr skólanum. Er á alveg geysilegu fáfæði, fær fáar tegundir.
- Í sneiðum greinast slímhúðarbitar úr vélinda. Í vélindaþekju sést **þétt íferð eosinophila (meira en 50 per HPF**). Nokkur spongiosa greinist einnig í þekju.
  Breytingin samrýmist eosinophilic esophagitis. Bólga í þörmum er horfin a.m.k. í bili.

EoE tilfelli 5

- Hjá ofnæmislækni:
- Varðandi tíð einkenni með magaverkjum, nokkuð oft höfuðverki með og ógleði þá er margt sem bendir til þess að þarna sé einnig um migreni að ræða. Hún fékk meðferð með Periactin á sínum tíma þegar hún var yngri.
- Ræði þetta því við barnataugalækni og hann er sammála hugmynd minni að prófa að setja inn Postofen þegar hún fær þessi einkenni eða að prófa fyrirbyggjandi meðferð með Amitriptylini
- Ef að Postofen dugar ekki þá mun ég vísa henni í athugun hjá taugalækni barna.
- **Hvaða almennu einkenni eru þetta ???**

Extraintestinal Manifestations in Children With Gastrointestinal Food Allergy

G. Domínguez-Ortega, O. Borrelli, R. Meyer, R. Dziubak, C. De Koker, H. Godwin, C. Fleming, N. Thapar, M. Elawad, F. Kiparissi, A.T. Fox, and N. Shah

TRACT

ctives: The presence of extraintestinal manifestations (EIM) in chil- with gastrointestinal (GI) food allergy (GIFA) is greatly debated. In the t study we assessed the prevalence of EIM in children with GIFA and gated whether their presence is helpful in the allergy-focused history- process.

ds: The medical records of all children with a proven diagnosis of were reviewed along with those of children diagnosed as having natory bowel disease (IBD) as controls. Data regarding age at onset, iagnosis, atopic family history, atopic comorbidities, GI symptoms, were recorded.

Data from 436 children with GIFA and 74 children with IBD were in the analysis. EIM were documented in 368 children with GIFA, fatigue (53.0%), allergic shiners (49.1%), mouth ulcers (39.0%), /hypermobility (35.8%), poor sleep (34.4%), night sweats (34.4%), (22.7%), and bed-wetting (17.7%). The proportion of patients was higher in the GIFA

Food allergy (FA) is defined as an adverse immun occurring reproducibly on exposure to a given Gastrointestinal (GI) food allergies (GIFA) may caus of clinical manifestations, and depending on the underl anism they are classified as immunoglobulin E (IgE) non-IgE–mediated, and mixed immune reactions (believed that in the United Kingdom between 2.2% a infants in the first year of life experience FA, affectin respiratory, and/or GI tract (4). Commonly reported GI of GIFA include vomiting, diarrhoea, constipation, bl abdominal pain (1,5). The suspicion of non-IgE–mediat mostly reliant on clinical history, physical examination ination diet with subsequent food challenge, given scre such as skin prick tests, specific

System einkenni

- Höfuðverkir - oft daglega –lítur illa út –
- Þreyta - slappleiki
- Slæmur svefn
- Nætur sviti
- Dökkir baugar undir augum
- Munnsár
- Nocturnal enuresis
- Liðverkir – hypermobilitet í liðum

TABLE 3. Comparison of extraintestinal manifestation prevalence between patients with IBD and gastrointestinal food-allergic patients with and without atopy

	IBD versus atopic GIFA, %		IBD versus nonatopic GIFA, %	
EIM	IBD group, n = 74	GIFA atopic, n = 306	IBD group, n = 74	GIFA nonatopic, n = 130
Allergic shiners	13.50	53.90***	13.50	37.70***
Fatigue	20.30	57.20***	20.30	43.10**
Night sweats	4.10	37.60***	4.10	27.70***
Poor sleep	6.80	37.30***	6.80	27.70***
Mouth ulcers	14.90	43.80***	14.90	27.70
Joint pain/hypermobility	18.90	39.50***	18.90	26.90
Bed-wetting	5.40	19.30**	5.40	13.80
Headache	12.20	26.80*	12.20	13.10

EIM = extraintestinal manifestation; GIFA = gastrointestinal food allergy; IBD = inflammatory bowel disease.
*** $P < 0.001$.
** $P < 0.01$.
* $P < 0.05$.

typically attributed to atopy, especially to allergic rhinitis. We have found allergic shiners to be more frequently reported in both GIFA groups, atopic and nonatopic, than in the IBD group, and, even more remarkably, no significant difference was found between atopic and nonatopic GIFA allergic shiners. Atopy coexists with the chronic fatigue syndrome in >50% of adult patients (13), in whom possible cellular immune mechanisms have been implicated, although, again, it has not been described in the paediatric age group. We have shown that fatigue is the most frequent EIM in patients with GIFA and that its presentation is significantly higher irrespective of being atopic or nonatopic compared with the IBD group. A recen [illegible] children has shown that atopy (21), and IBD (29) previously, which could explain the lack statistically significant difference between the GIFA group a IBD group.

Several studies have described joint hypermobility in ad patients with GI symptoms and other nonspecific compla including autonomic dysfunction symptoms (migraine, alle rash, nocturia, dysuria, flushing, night sweats, fever, lymph g pain, and poor sleep) (30,31). The joint–gut axis has previo been described in children [illegible] children with GIFA ha EIM in o[illegible] shared mech[illegible] toms described in studies in [illegible] dy (17) has shown adult patient[illegible] were found to h[illegible] We ha[illegible] fo high incidence of [illegible]

Extraintestinal Manifestations

The proportion of patients with EIM was higher in the GIFA group than in the IBD group (368/436 [84.4%] vs 40/74 [54.1%], $P < 0.001$). Segregating the GIFA group into children with and without atopic comorbidities, this proportion was also higher in both atopic (276/306, 89.9%) and nonatopic (93/130, 71.5%) children compared with children with IBD (54.1%, $P < 0.001$ and <0.05, respectively). The majority of children with GIFA (231/53%) had ≥ 3 of these EIM (atopic group 180 [58.8%], nonatopic group 51 [39.2%]) versus the IBD group: 7 (9.5%), $P < 0.001$. The prevalence of each EIM in both patients with GIFA and patients with IBD is shown in Table 2.

(16), joint pain/hypermobility (19,20), headache (21,22), and enuresis (23), although the mechanisms are not fully understood. We have described the presence of all of them in a large cohort of children with GIFA. The majority of them (70.2%) were classified as atopic because they had a known diagnosis of asthma, eczema, or allergic rhinitis. Those who were classified as nonatopic GIFA also presented an increased number of EIM compared with the IBD group; therefore, in the absence of a positive atopic history, these EIM could by themselves lead the clinician in the suspicion of GIFA.

The first report of EIM in atopy related to allergic shiners and was published in 1966 (14). Since then, allergic shiners have been

TABLE 2. Comparison of extraintestinal manifestation prevalence between gastrointestinal food-allergic patients and patients with IBD and within allergy subgroups

	GIFA versus IBD, %		Atopic GIFA versus nonatopic GIFA, %	
EIM	IBD group, n = 74	GIFA group, n = 436	GIFA atopic, n = 306	GIFA nonatopic, n = 130
Allergic shiners	13.5	49.1***	53.9	37.7**
Fatigue	20.3	53***	57.2	43.1**
Night sweats	4.1	34.6***	37.6	27.7
Poor sleep	6.8	34.4***	37.3	27.7
Mouth ulcers	14.9	39***	43.8	27.7*
Joint pain/hypermobility	18.9	35.8**	39.5	26.9*
Bed-wetting	5.4	17.7*	19.3	13.8
Headache	12.2	22.7	26.8	13.1**

EIM = extraintestinal manifestation; GIFA = gastrointestinal food allergy; IBD = inflammatory bowel disease.
*** $P < 0.001$.
** $P < 0.01$.
* $P < 0.05$.

Endir

stool did not resolve. Therefore, all 16 infants were receiving amino acid by 4 months of age (Fig. 1).

be rechallenged

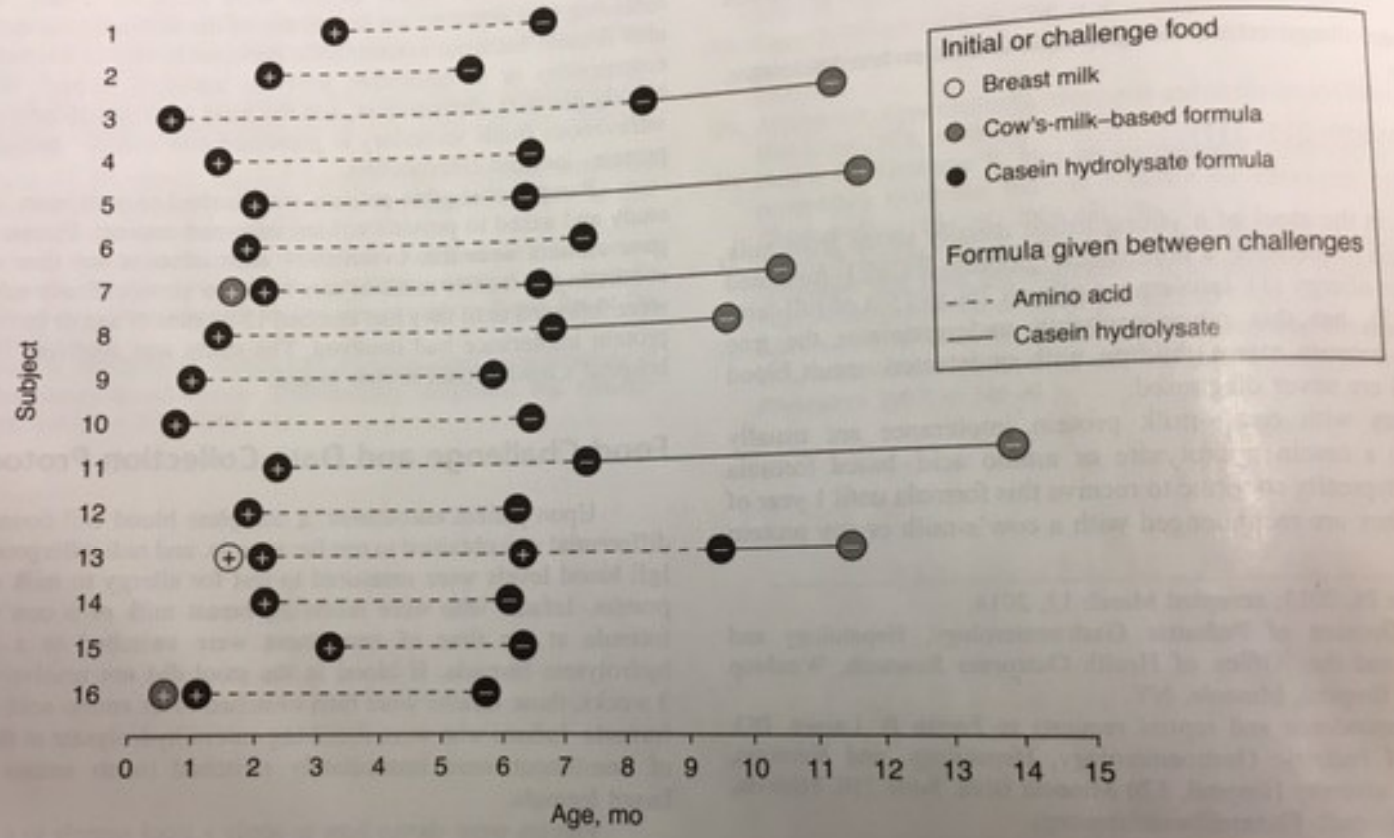


FIGURE 1. Stool guaiac test results. Circles indicate test result at enrollment and following each food challenge. Connecting lines indicate formula given between challenges. For example, upon enrollment at 3 months of age, subject 1 tested positive on a diet of casein hydrolysate formula, was successfully switched to amino acid formula, then tested negative when rechallenged with casein hydrolysate formula at 6 months. N = 16.

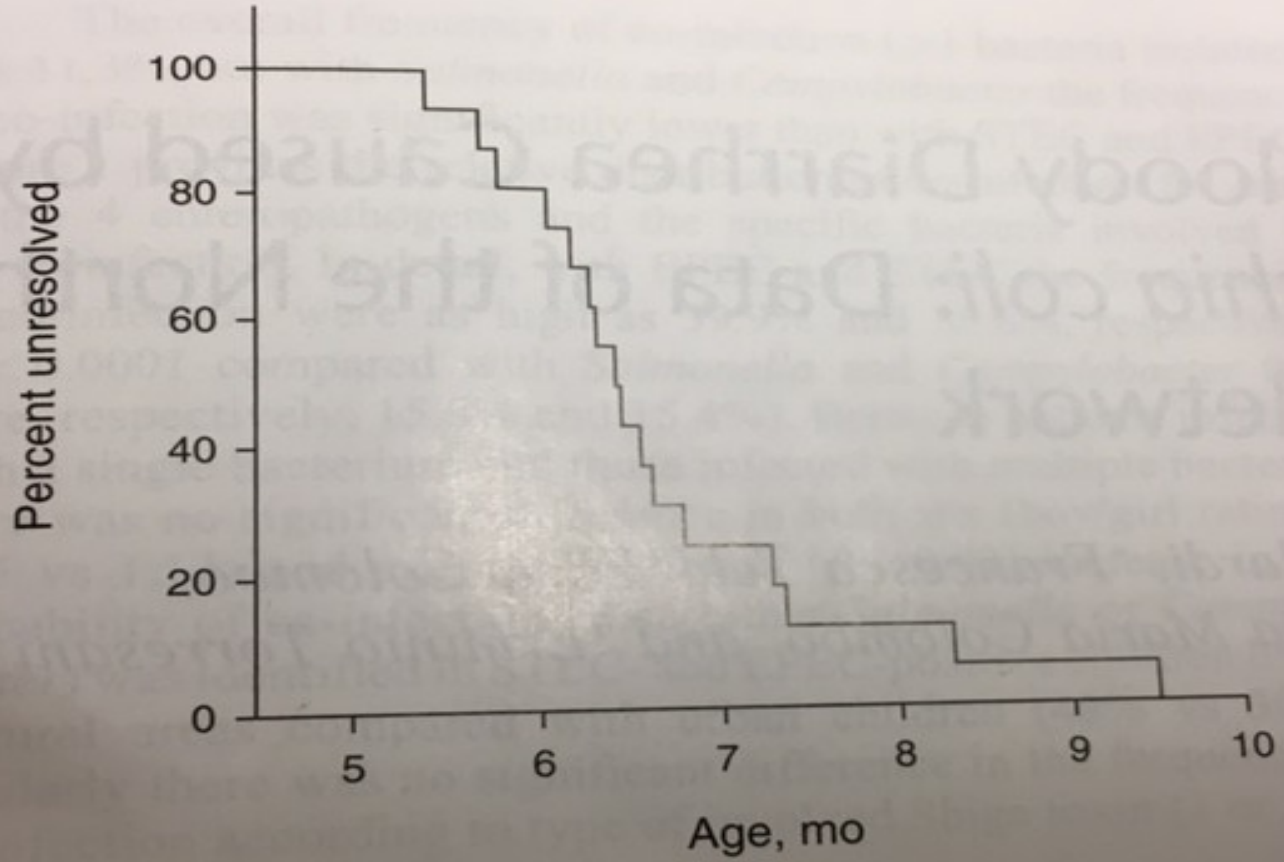


FIGURE 2. Duration of milk protein intolerance. Graph shows percentage of infants with unresolved milk protein intolerance as a function of age. The remainder (100 – percent unresolved) had negative stool guaiac tests after rechallenge with casein hydrolysate. N = 16.