Piima talumatus, ülevaade teadusuuringutest

Host A, Halken S. Cow's milk allergy: where have we come from and where are we going? Endocr Metab Immune Disord Drug Targets. 2014 Mar;14(1):2-8. **Lehmapiimaallergia: kust me tuleme ja kuhu läheme?**

Eelmise sajandi 30. ndatest alates on kogunenud palju teaduslikku kirjandust lehmapiima allergia kohta (*cow´s milk proteine allergy* CMPA). Viimase kümne aasta jooksul on diagnostilised vahendid ja ravi palju edasi arenenud. Kasutatakse sümptoomide kaotamist eliminatsiooni testiga ja nende või mittesoovitavate reaktsioonide tekkimist piimavalgu provokatsioonitestiga. Edasiarenenud diagnostilised testimised kasutavad epitoope ja *microarray* tehnoloogiat ning võivad parandada tulevikus CMPA diagnostilist korrektsust, määratledes spetsiifilisi IgE antikehi lehmapiima spetsiifiliste allergeeni komponentide vastu. Varases lapsepõlves on CMPA esinemissagedus arenenud maades 2-3%, CMPA-le viitavaid sümptoome on 5-15%-l imikutest, mis viitab kontrollitud eliminatsiooni- ja provokatsiooni protseduuride teostamise vajadusele. Reprodutseeritavad kliinilised reaktsioonid piimavalgule tekivad 0,5%l rinnapiimal olevatel lastel. Enamusel imikutest arenevad piimaallergia sümptoomid enne esimest elukuud, sageli 1nd jooksul pärast lehmapiimal baseeruva toidusegu andmist lapsele. Enamus lastest omavad 2 või rohkem sümptoomi kahe või rohkema organsüsteemi poolt. 50-70%-l on nahasümptoomid ja 20-30%-l hingamisteede sümptoomid, mis tekivad umbes 1 tunni jooksul pärast piimatoote tarbimist (vahetud reaktsioonid) või läheb aega üle tunni (hilised reaktsioonid). CMPA prognoos on hea, remissiooni sagedusega 45-50% 1 aastal, 60-75% teiseks eluaastaks ja 85-90% kolmandaks eluaastaks. Ebasoovitavaid rekatsioone teistele toiduainetele tekib 50%-l ja allergia sissehingatavatele ainetele 50-80%-l.

Peamine ravi on piima eemaldamine toidust, imikutel on oluline leida head piimavabad toidusegud. Dokumenteeritud ulatuslikult hüdrolüseeritud segud (üksikutel aminohapetel baseeruvad) on soovitavad, osaliselt hüdrolüseeritud segusid ei tohiks kasutada, sest need on uuringutes näidanud kõrget antigeensust ja allergeensust, kutsudes esile mittesoovitavaid sümptoome. Lamba- ja kitsepiim annavad tugevat ristreaktsiooni, osad lapsed aga taluvad teiste imetajate piima nagu nt mära ja eesli piima. Sojavalk on sama allergeenne kui piimavalk ja imikutele sojaga piimasegusid ei soovitata, sest esineb suur risk sojaallergia tekkimiseks, samas aga sojapiima talutakse päris hästi vanemas eas. Hiljutised ravimeetodid on suukaudne immunoteraapia (OIT), haarates järjest suurenevates kogustes piimaallergeeni tarbimist desensitiseerimise (tundetuks muutmise) eesmärgil ja piimavalgule taluvuse tekitamiseks. OIT võib suurendada reaktsiooniläve piimavalgule, kuid ikkagi on üleval küsimus turvalisusest ja pikaaegsest efektiivsusest. Anti-IgE teraapia Omalizumab´iga võib parandada OIT turvalisust ja efektiivsust ning ja olla kasulik monoteraapias.

Since the 1930's the scientific literature on cow's milk protein allergy (CMPA) has accumulated. Over the last decade new diagnostic tools and treatment approaches have been developed. The diagnosis of reproducible adverse reactions to cow's milk proteins (CMP), i.e. CMPA, still has to be confirmed by controlled elimination and challenge procedures. Advanced diagnostic testing using epitope and microarray technology may in the future improve the diagnostic accuracy of CMPA by determination of specific IgE against specific allergen components of cow's milk protein. The incidence of CMPA in early childhood is approximately 2-3% in developed countries. Symptoms suggestive of CMPA may be encountered in 5-15% of infants emphasizing the importance of controlled elimination/milk challenge procedures. Reproducible clinical reactions to CMP in human milk have been reported in 0.5% of breastfed infants. Most infants with CMPA develop symptoms before 1 month of age, often within 1 week after inter introduction of CMP-based formula. The majority has two or more symptoms from

two or more organ systems. Approximately 50-70% have cutaneous symptoms, 50-60% gastrointestinal symptoms and 20-30% respiratory symptoms. Symptoms may occur within 1 hour after milk intake (immediate reactions) or after 1 hour (late reactions). The prognosis of CMPA is good with a remission rate of approximately 45 to 50% at 1 year, 60 to 75% at 2 years and 85 to 90% at 3 years. Associated adverse reactions to other foods develop in up to 50% and allergy against inhalants in 50 to 80%. The basic treatment of CMPA is avoidance of CMP. In early childhood a milk substitute is needed. Documented extensively hydrolysed formulas are recommended, whereas partially hydrolysed formulas should not be used because of a high degree of antigenicity and allergenicity associated with adverse reactions. In case of intolerance to extensively hydrolysed formulas and multiple food allergies a formula based on aminoacids is recommended. Alternative milk substitutes such as sheep's and goat's milk should not be used because of a high degree of cross reactivity with CMP. Milk from other mammals such as mare and donkey may be tolerated by some children with CMPA. Soy protein is as allergenic as CMP and soy formula is not recommended for young children with CMPA because of a great risk of development of allergy to soy, whereas soymilk is normally tolerated in older children with CMPA. Recent treatment modalities are oral immunotherapy (OIT) involving the ingestion of increasing amounts of milk allergen on a regular basis to desensitize and potentially permanently tolerize patients to CMP. OIT can increase the reaction thresholds to CMP, but questions about safety and long-term efficacy remain. Anti-IgE therapy with Omalizumab may improve the safety and efficacy of OIT and may provide benefit in monotherapy.

Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, Nowak-Węgrzyn A. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol. 2014 Aug;134(2):382-9. **Toidust tingitud enterokoliidi (food protein-induced enterocolitis syndrome) (FPIES) kliinilised jooned ja lahenemine- 10-aastane kogemus**

See on mitte-IgE-vahendatud toiduallergia. See diagnoos jääb tavaliselt hiljaks, sest klassikalised allergia sümptoomid puuduvad ning biomarkereid ei ole palju avastatud.

6k – 45.a. isikud olid uuringus FPIESdiagnoosiga ja neile teostati suukaudne provokatsioonitest *(oral food challenges* (OFCs)). Kes testis ei osalenud, nendel uuriti meditsiinilisi märkmeid. 160-st 54% olid mehed, keskmine vanus 15 kuud. Teostati 180 OFCs 15-le toidule 82 isikul; 30% uuritavast populatsioonist omas FPIES, mida kinnitas OFC. **Tavalisemad toidud olid lehmapiim (44%), soja (41%), riis (22.5%) ja kaer (16%). Enamus (65%) reageerisid 1 toidule, 26% kahele ja 9% kolmele toiduainele või rohkemale.** Enamusel esines atoopia, 39% omasid IgE sensitisatsiooni teisele toidule. 39 isikut **(24%) omasid positiivset spetsiifilist IgE taset toidule, mis indutseeris FPIES**. Laste hulgas spetsiifilise IgEga lehmapiimale muutus 41%-l piimast tingitud FPIES mingiks teiseks IgE-vahendatud fenotüübiks mingi aja jooksul. Keskmine iga, mil taluvus saavutati, oli **4.7 a riisile ja 6.7 aastat sojale**. **Keskmine iga, mil piimale taluvus saavutati isikute puhul, kel ei olnud piimaseptsiifilist IgE taset, oli 5.1 aastat, kusjuures mitte ükski nendest, kellel esines piimaspetsiifiline IgE, ei saanud uuringu ajal taluvaks. EPIES tüüpiliselt laheneb 5 eluaastaks. Piima FPIES, eriti koos piimaspetsiifilise IgE tõusuga on pikaajalise kuluga ning akuutsete reaktsioonidega.**

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy. FPIES diagnosis is frequently delayed because of the absence of classic allergic symptoms and lack of biomarkers. We sought to characterize the clinical features and resolution of FPIES in patients evaluated in our practice. Subjects 6 months to 45 years of age with FPIES were prospectively

recruited for oral food challenges (OFCs). Medical records were searched to identify the subjects who did not participate in OFCs. Among 160 subjects, 54% were male; median age at diagnosis was 15 months. We performed 180 OFCs to 15 foods in 82 subjects; 30% of the study population had FPIES confirmed based on OFC results. The most common foods were cow's milk (44%), soy (41%), rice (22.5%), and oat (16%). The majority (65%) reacted to 1 food, 26% reacted to 2 foods, and 9% reacted to 3 or more foods. The majority were atopic, and 39% had IgE sensitization to another food. Thirty-nine (24%) subjects had positive specific IgE levels to the food inducing FPIES. Among children with specific IgE to cow's milk, 41% changed from a milk FPIES to an IgE-mediated phenotype over time. The median age when tolerance was established was 4.7 years for rice, 4 years for oat, and 6.7 years for soy. Median age when milk tolerance was established for subjects with undetectable milk-specific IgE levels was 5.1 years, whereas none of the subjects with detectable milk-specific IgE became tolerant to milk during the study (P = .003). EPIES typically resolves by age 5 years. Milk FPIES, especially with detectable food-specific IgE, can have a protracted course and eventually transition to acute reactions.

Venter C, Groetch M. Nutritional management of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014 Jun;14(3):255-62. **Toitumuslik toimetulek toidust tingitud enterokoliidi sündroomiga *(food protein-induced enterocolitis syndrome)* FPIES.**

Seotud toidud on: piim, soja ja teraviljadest eriti riis. Toiduainete hulk erineb indiviiditi, kuid enamus raporteid viitab peamiselt 1-2 toiduainele. Toitumuslik ravi on komplitseeritud, sest FPIES võivad vallandada nii tüüpilised kui ebatüüpilised toiduained. Oluline on eemaldada tekitav toiduaine menüüst, hoida adekvaatsena teiste toiduainete tarbimine ja piisav toitainete saamine ning kindlustada lapse kasvamine ja arenemine.

To summarize the latest information on the nutritional management of food protein-induced enterocolitis syndrome (FPIES), focusing on the foods implicated and how to avoid these whilst maintaining a nutritionally sound diet. A number of foods are implicated in FPIES such as milk, soy and grains, particularly rice. The number of foods implicated in FPIES per individual differs, but the majority of reported cases have two or fewer food triggers involved. FPIES is a complex presentation of non-IgE-mediated food allergy. Dietary management is complicated as both common food allergens as well as atypical food allergens can trigger FPIES. Sound nutritional advice is required to ensure appropriate food avoidance, adequate consumption of other foods and sufficient nutritional intake to maintain and ensure growth and development.

Fiocchi A, Claps A, Dahdah L, Brindisi G, Dionisi-Vici C, Martelli A. Differential diagnosis of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014 Jun;14(3):246-54. **Toiduvalgust indutseeritud enterokoliidi sündroomi diferentsiaaldiagnoos**

Ägeda ja kroonilise toidu poolt indutseeritud enterokoliidi sündroomi FPIES *(food protein-induced enterocolitis syndrome*) potentsiaalsed diferentsiaaldiagnoosid, andes ülevaate publitseeritud uuringutest.

Järjest rohkem on publitseeritud selle diagnoosiga juhtumeid viimastel aastatel. Kuna haigusel on mittespetsiifilised sümptomid, siis diferentsiaaldiagnostiliselt tulevad kõne alla akuutsel juhul sepsis, teised infektsioonhaigused, akuutsed gastrointestinaalsed (mao-sooletrakti) GI episoodid, kirurgilised

esmaabi vajavad seisundid, toiduallergia. Kroonilisel juhul maskeerib FPIES malabsorptsiooni sündroomi, metaboolseid häireid, esmast immuunpuudulikkust, neuroloogilisi seisundeid, koagulatsioonidefekte ja teisi mitte IgE vahendatud toiduallergiaid. **Klinitsiste tuleb suunata sellele diagnoosile mõtlema. Diagnoosi hilinemine on enamusel juhtudel tingitud vähesest teadmisest selle haiguse kohta.**

Uuringu sissejuhatusest (viited http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4011629/): Selle haiguse patogeenes on intrigeeriv, mitmeid hüpoteese on püstitatud, pannes vastutuse rakuliselt vahendatud immuunsusele või humoraal-spetsiifilistele immunoloogilistele muutustele, või neutrofiilidele, trombotsüütidele ja/või eosinofiilide düsfunktsioonile. Osad vahendusained nagu serotoniin, võivad olla haaratud [1]. Ükskõik, mis on mehhanism, on haiguse algus sageli plahvatuslik ja haigus lapse elukvaliteeti tõsiselt häiriv [2]. Väga harva on esimene diagnoos õige [3]. Kuigi FPIES diferentsiaaldiagnoosi peetakse oluliseks juba mitmeid aastaid [4], ei ole siiani esitatud täielikku ülevaadet. Vale diagnoos võib mitmete kuude jooksul tuua kaasa uusi akuutseid episoode [5], või isegi viia dramaatiliselt mittekorrektsete diagnostiliste/terapeutiliste sekkumisteni [6]. Siiani on FPIES ikkagi peetud võimalikuks toiduallergia manifestatsiooniks [7–9]. **Mida pikem on diagnoosi viibimine, seda suuremad riskid ja kulutused. Seda haigust on ju väga lihtne ravida ja diagnoosimine on samuti lihtne- teadmine on ainuke, mida vajate.** Kohaste sekkumiste toimet on kirjeldatud [60], oluline on harida haigla pediaatreid ja üldarste, et lühendada esimese episoodi ja diagnoosi vahelist aega [2].

Abstract: To assess all the possible differential diagnosis of food protein-induced enterocolitis syndrome (FPIES), both in acute and chronic presentation, reviewing the data reported in published studies. There is an increase of reported cases of FPIES in recent years. As the disease presents with nonspecific symptoms, it can be misunderstood in many ways. The differential diagnosis includes, in acute presentations, the following: sepsis, other infectious diseases, acute gastrointestinal episodes, surgical emergencies, food allergies. In its chronic forms, FPIES may mimic malabsorption syndromes, metabolic disorders, primary immunodeficiencies, neurological conditions, coagulation defects, and other types of non-IgE-mediated food allergy. A thorough clinical evaluation, including symptoms, signs, and laboratory findings, is necessary to lead the clinicians toward the diagnosis of FPIES. The major reason for delayed diagnosis appears to be the lack of knowledge of the disease.

Introduction: Among the mysteries that surround the FPIES, pathogenesis is the most intriguing. Several hypotheses have been proposed, attributing the responsibility to cell-mediated or humoral-specific immunologic alterations, or to neutrophils, platelets, and/or eosinophils dysfunction. Some mediators, such as serotonin, may be involved [1]. Whatever the mechanism(s) is, the presentation of the disease is often explosive and the disease is severely hampering the patient's quality of life [2]. Thus, the condition must not go unnoticed, and a diagnosis is called for. However, because of several reasons, the first diagnosis is seldom the right one [3]. Although the differential diagnosis of FPIES has been considered an important issue for many years [4], a complete review of the conditions possibly confused with FPIES is lacking. Misdiagnoses may delay the identification of FPIES for months, exposing the children to the repetition of acute episodes [5], or even leading to dramatically incorrect diagnostic/therapeutic interventions [6]. Yet, FPIES is indicated as a possible manifestation of food allergy in all the guidelines on the topic [7–9]. The present article aims to review the possible diagnostic hypotheses proposed for FPIES before its correct identification. The diagnosis of FPIES is often difficult and delayed, and patients may undergo extensive workups for their symptoms. This is very common in non-IgE-mediated food allergies [10], but particularly typical of this syndrome: FPIES does not have an identification biomarker nor an unequivocal, typical symptom.

Feuille E, Nowak-Węgrzyn A. Definition, etiology, and diagnosis of food protein-induced enterocolitis syndrome (FPIES). Curr Opin Allergy Clin Immunol. 2014 Jun;14(3):222-8. **FPIES ehk toidust indutseeritud enterokoliidi sündroomi definitsioon, etioloogia ja diagnoosimine**

(Food protein-induced enterocolitis syndrome) FPIES on siiani veel kehvasti mõistetud mitte -IgE-vahendatud ülitundlikkus toidule, mõjutades peamiselt imikuid ja väikelapsi. On uusi **andmeid patofüsioloogiast, mis viitavad kohalikule taskaalutusele TNF-α ja TGF-β vahel.** Patsiendid omavad sageli mitmesuguseid sümptoome: korduv oksendamine, dehüdratatsioon, letargia ja madal kaaluiive. Vaatamata haiguse tõsidusele hilineb diagnoos väga sageli ning patsientidele teostatakse ekstensiivseid ja invasiivseid teste.

Suukaudse provokatsioonitesti kriteeriumite ülevaatamiseks ja modifitseerimiseks on vaja multitsentrilisi uurimusi, samuti on vaja uurimusi EPIESI reaktsioonide patofüsioloogiast, et kindlustada arusaam tõenduspõhisest lähenemisest diagnoosile ja toimetulekule haigusega.

Registries are needed to understand the phenotype, triggers, and prevalence of FPIES. Food protein-induced enterocolitis syndrome (FPIES) is a poorly understood non-IgE-mediated food hypersensitivity, primarily affecting infants and toddlers. There are few data regarding pathophysiology of FPIES that suggest local intestinal imbalance between TNF-α and TGF-β. Patients frequently present with multiple reactions, which are characterized by projectile, repetitive emesis, dehydration, lethargy, and failure to thrive. Despite the severity of presentation, the diagnosis is frequently delayed, and patients often undergo extensive and invasive evaluation prior to reaching the diagnosis. Reviews published in the last year provide a general approach to diagnosis and management of FPIES and aim to increase awareness and understanding of FPIES among general pediatricians. Multicenter studies are necessary to reevaluate and modify the oral food challenge criteria. Research on the pathophysiology of FPIES reactions is necessary to provide insight into the evidence-based approach to diagnosis and management of FPIES. Registries are needed to understand the phenotype, triggers, and prevalence of FPIES.

Järvinen KM, Nowak-Węgrzyn A. J Allergy Clin Immunol Pract. 2013 Jul-Aug;1(4):317-22. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. **FPIES: praegused toimetuleku strateegiad ja kirjanduse ülevaade**

Teatud FPIES jooned kattuvad toiduvalgust indutseeritud enteropaatia (*food protein-induced enteropathy*) ja proktokoliidi ning ka anafülaksiaga. FPIES ei ole hästi tuntud pediaatrite ja kiirabitöötajate poolt, enamasti arvatakse lapsel olevat viiruslikku GI haigust, sepsist või kirurgilist haigust ning diagnoos hilineb kuid. Selles uurimuses kirjeldatakse iseloomulikke jooni läbi juhtumite, kuigi juhuvalikuga kliinilisi uurimusi toimetuleku võimaluste kohta ei ole, on **detailselt kirjeldatud olemasolevat kirjandust ja autorite kogemusi.**

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic. FPIES is elicited most commonly by milk and soy proteins; however, rice, oat, and other solid foods may also elicit FPIES. Certain FPIES features overlap with food protein-induced enteropathy and proctocolitis, whereas others overlap with anaphylaxis. FPIES is not well recognized among pediatricians and emergency department physicians; the affected children are often mismanaged as having acute viral gastrointestinal illness, sepsis, or surgical disease, delaying diagnosis of FPIES for many months. The

aim of this review is to provide case-driven presentation of the features of FPIES. Although randomized clinical trials on management options are missing, the relevant current literature and authors' experience are reviewed in detail.

Leonard SA, Nowak-Wegrzyn A. Manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome. Pediatr Ann. 2013 Jul;42(7):135-40. **FPIES ilmingud, diagnoos ja toimetulek.**

CME EDUCATIONAL OBJECTIVES 1. Recognize manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome (FPIES) in an outpatient setting. 2. Assess nutritional needs and provide anticipatory guidance for dietary management. 3. Recognize the indications of when to refer for assessment of resolution of FPIES using physician-supervised food challenges. Food protein-induced enterocolitis syndrome (FPIES) is an under-recognized non-immunoglobulin E (IgE)-mediated gastrointestinal food allergy affecting primarily infants and toddlers. An abnormal response to food antigen resulting in local inflammation is thought to lead to increased intestinal permeability and fluid shift. The primary features of acute FPIES are repetitive, projectile vomiting, lethargy, pallor, diarrhea, and dehydration. Chronic FPIES is typically seen in young infants with continued exposure to cow's milk or soy-based formula. Biomarkers are lacking and patients may undergo extensive workups for their symptoms, which often leads to a delay in diagnosis and puts infants at risk for feeding difficulties, nutritional deficiencies, and failure to thrive. This review will provide a guide in how to recognize the clinical features of and manage FPIES.

Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. Clin Exp Allergy. 2012 Aug;42(8):1257-65. **66 Itaalia lapse mutitsentriline retrospektiivne uuring toiduvalgust indutseeritud enterokoliidi sündroomi *(Food Protein-Induced Enterocolitis Syndrome)*** FPIES korral: erinev toimetulek erinevate fenotüüpide korral.

Uuring viidi läbi 7 a jooksul (2004-2010). Diagnoos pandi haigla andmete baasil. 66-l lapsel leiti FPIES. Diagnooside hulk suurenes märkimisväärselt 2008 – 2010. Koguti kokku 165 FPIES episoodi (keskmine oli lapse kohta 2 episoodi, üldse erinevatel lastel 1-10). **Lehmapiim** oli kõige tavalisem vallandaja (65%), sellele järgnesid **kala, muna, riis, soja, mais, linnuliha ja kitsepiim**. 56 (85%) last reageeris üksikule toidule ja sümptoomide tekke aeg oli keskmiselt 2,4 tundi (SD 0.7 h). **Oksendamine** oli kõge tavalisem sümptoom (98%). OFC diagnoosiga patsientide hulgas reageeris 78% pärast söömist tervele allergeense toidu portsjonile vanuse kohta**. Naha prick test (SPT) vallandavale toidule oli negatiivne 97% juhtudest.** 32/66st (48%) saavutas taluvuse keskmiselt 29 kuuks (SD 17 months). Taluvuse saavutamise aeg piimale oli märkimisväärselt madalam kui teistele toitudele.

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated paediatric disorder triggered by the ingestion of specific food proteins. Many features of this syndrome are not yet well defined. The aim of our study was to describe demographic features, causative agents, clinical features, treatments and outcomes of children suffering from acute FPIES at three Italian of Pediatric Allergology Centers. A retrospective study was performed over a 7-year period (2004-2010). Hospital medical record databases and hospital outpatient electronic charts were screened for the diagnosis of FPIES. Information on the first and subsequent FPIES' episodes was collected. We diagnosed 66 children with FPIES. The number of diagnoses significantly increased between 2008 and 2010

(P < 0.001). We collected a total of 165 FPIES episodes (median per child 2, range 1-10). Cow's milk was the most common trigger food (65%), followed by fish, egg, rice, soy, corn, poultry and goat's milk. Fifty-six (85%) children reacted to a single food. Mean documented time from ingestion to symptom onset was 2.4 h (SD 0.7 h). Vomiting was the most common symptom (98%). Among patients diagnosed with OFC, 78% reacted after eating a whole serving size of the trigger food per age. Skin prick tests (SPT) for trigger foods were negative in 97% of cases. Thirty-two/66 children (48%) achieved tolerance at a mean age of 29 months (SD 17 months). Age of achieved tolerance for cow's milk was significantly lower compared to that of other foods (24 ± 8 vs. 53 ± 17 months, P < 0.0006). This article provides new insights on FPIES in Italy by describing its largest series, and shows how a significant increase in the FPIES diagnosis has been observed in the last few years. We also discussed selected management aspects of this syndrome where different phenotypes can be found.

Kokkonen TS, Augustin MT, Kokkonen J, Karttunen R, Karttunen TJ. Serum and tissue CD23, IL-15, and FasL in cow's-milk protein-sensitive enteropathy and in coeliac disease. J Pediatr Gastroenterol Nutr. 2012 Apr;54(4):525-31. **Seerumi ja kudede CD23, IL-15 ja FasL lehmapiimatundliku enteropaatia ja tsöliaakia CD korral**

Eesmärk oli uurida CMSE (cow's-milk-sensitive enteropathy) ja CD (tsöliaakiahaiguse) patogeneesi ja leida uusi seerumi markereid. Me uurisime CD23, IL-15, ja FasL kontsentratsiooni veres ja tootmist sooles. Lõime hüpoteesi, et **seerumi CD23, valk, mida toodavad lümfifolliikulid, võib olla seotud lümfonodulaarse hüperplaasiaga (LNH), mis on iseloomulik CMSE-le**. Eeldasime, et interleukiin (IL)-15 ja **FasL, on funktsionaalselt seotud IEL proliferatsiooni ja apoptoosiga** intraepiteliaalsetes lümfotsüütides (IELs), ja tõusnud IEL esineb mõlema, nii CMSE kui CD puhul.

Uurisime 23CMSE-ga last, 20 mitteravitud CD, ja 14 kontrolli. Seerumi sCD23 tõus esines mitteravitud CMSE ja tsöliaakia (CD) korral. CD23 toodeti limaskesta germinaalkeskustes, kuid CD23ei olnud seotud LNH olemasoluga. **CMSE korral on trend seerumi sFasL hulga suurenemisele ja kõrged tasemed seostusid LNH-ga ja korreleerusid IEL numbriga. Limaskesta kõrged endoteliaalsed veenulid, mis külgnevad lümfifolliikulitega, näitasid intensiivset FasL tootmist.**

Seerumi sCD23 on tõusnud mitteravitud CMSE ja CD korral ja võib ka anda informatsiooni hattude atroofia tõsiduse kohta. CMSE puhul oli kõrge seerumi FasL mis viitab nii LNHle kui IELs tõusule - sellele, et CMSE patogeensis on oluline FasLvahendatud mehhanism. Hilisemaid uurimusi on tarvis, et hinnata, kas intensiivne FasL tootmine limaskesta kõrgemates endoteeli veenides on regulatoorne element mukosaalses immuunsuses.

The aim of the study was to explore pathogenesis and find new serum markers for cow's-milk-sensitive enteropathy (CMSE) and coeliac disease (CD). We assessed the intestinal expression and serum concentration of CD23, IL-15, and FasL. We hypothesised that the serum levels of CD23, a protein expressed in the lymphoid follicles, would be associated with lymphonodular hyperplasia (LNH), a feature characteristic of CMSE. We also presumed that interleukin (IL)-15 and FasL, functionally connected with proliferation and apoptosis of the intraepithelial lymphocytes (IELs), would relate with the increased numbers of IELs present in both CMSE and CD. Twenty-three children with CMSE, 20 with untreated CD, and 14 controls were studied for CD3, α/β- and γ/δ-expressing IELs, and for duodenal and ileal expression of CD23, FasL, and IL-15 by immunohistochemistry, and for serum concentration of sCD23, sFasL, and sIL-15 by enzyme-linked immunosorbent assay. There was a trend for increase in sCD23 serum levels in untreated CMSE and in CD (P = 0.074; P = 0.077). CD23 was expressed in the mucosal germinal centres, but sCD23 was not related to presence of LNH. In CMSE,

there was a trend for increase in serum sFasL (P = 0.07) and high levels associated with LNH (P = 0.025) and correlated with the IEL numbers (P < 0.05). Mucosal high endothelial venules adjacent to lymphoid follicles showed an intensive FasL expression. Serum sCD23 shows a trend of increment in CMSE and CD, and in the latter, sCD23 level may provide information about the severity of villous atrophy. In CMSE, high serum sFasL indicates both LNH and an increase of IELs, suggesting importance of FasL-mediated mechanisms in the pathogenesis of these features characteristic of CMSE. Further studies are necessary to evaluate whether intensive FasL expression in mucosal high endothelial venules presents a regulatory element in mucosal immunity.

Leonard SA, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome: an update on natural history and review of management. Ann Allergy Asthma Immunol. 2011 Aug;107(2):95-101; quiz 101, 162. **FPIES: ajalugu ja toimetuleku ülevaade**

Vaadeldi PubMedis publitseeritud artikleid 1978 – mai 2011, kasutades võtmesõnu: *food-induced enterocolitis* ja *FPIES*. Uuteks publikatsioonideks loeti 3-a vanused artiklid. Esinemine on 0.34% esimesel eluaastal võrreldes 0.5% lise IgE-vahendatud lehmapiima allergiaga. Tüüpiliselt algab enne 6.elukuud toiduseguga toidetud imikul korduvate oksendamiste, kõhulahtisuse, dehüdratatsiooni ja letargiaga 1-5 t pärast toidu tarbimist**. Selle ajani oli kirjeldatud neli rinnapiimal oleva lapse juhtumit**. Peamised toiduained on piim, soja ja riis. Diagnoos pannakse kliinilise ajaloo baasil ja kui tarvis, tehakse suukaudne provokatsioonitest. Tavaliselt kasvatakse sellest koolieaks välja. Oluline on õige ja varajane diagnoosimine, sest teised põhjused **annavad samasuguseid sümptoome. Oluline on ka hilisem jälgimine, kui toitu uuesti menüüsse lülitatakse.**

To review the clinical features, pathophysiology, and management of food protein-induced enterocolitis syndrome (FPIES) and to discuss new observations in epidemiology and natural history. PubMed searches were performed for articles published between 1978 and May 2011 using the keywords food-induced enterocolitis and FPIES. Articles were selected based on their relevance to the topic of this review. The newest developments in FPIES were defined by articles published in the past 3 years. FPIES is a non-IgE-mediated gastrointestinal food hypersensitivity thought to be cell-mediated, although the exact pathophysiologic mechanism requires further study. In a recent birth cohort, the incidence of cow's milk FPIES was 0.34% in the first year of life compared with 0.5% for IgE-mediated cow's milk allergy. FPIES typically presents before 6 months of age in formula-fed infants with repetitive emesis, diarrhea, dehydration, and lethargy 1 to 5 hours after ingesting the offending food. Four cases of FPIES in breastfed infants have recently been reported. The most common offending foods are cow's milk, soy, and rice. Diagnosis is based primarily on clinical history and, when unclear, physician-supervised oral food challenges. FPIES is usually outgrown by school age. Although management remains avoidance of the offending food, observations that natural history varies for different foods has redefined the timing of reintroduction. Early recognition of FPIES and removal of the offending food are imperative to prevent misdiagnosis and mismanagement of symptoms that may mimic other causes. Close follow-up is required to determine when foods may be added back into the diet.

Chaabane M, Bidat E, Chevallier B. A new case of food protein-induced enterocolitis syndrome. Arch Pediatr. 2010 May;17(5):502-6. **Toiduvalgust indutseeritud enterokoliidi juhtum.** [Article in French]

Piimavalgust tingitud enterokoliit (*Food protein-induced enterocolitis syndrome)* EPIES algas esimesel elupäeval mittespetsiifiliste ja väikeste sümptoomidega. Küsitavad olid kolm toiduainet: lehmapiim, soja ja nisu. FPIES diagnoosi kahtlustati 9 kuul, pärast 3 hospitaliseerimist oksendamiste, vahel

letargia ja hüpotensiooni tõttu, mis tekkisid umbes 2t pärast lehmapiima tarbimist. **Sümptoomid ei olnud seotud positiivse IgE ja nahatestidega.** Siis tekkisid sümptoomid ka nisu ja soja peale. Tänu hilisele diagnoosile esines ka kolm anafülaktilise šoki juhtumit.

FPIES on mittetavaline rakuliselt vahendatud toiduallergia reaktsioon. Sellele sündroomile on iseloomulikud GI (gastrointestinaalsed ehk mao-sooletrakti) sümptoomid, eriti tõsine oksendamine, vahel aga seondub ka anafülaktilise šokiga. Tavaliselt tekivad sümptoomid 2t pärast toidu tarbimist. Reaktsioonid algavad varases eas (1 elukuul) ja tavaliselt hääbuvad kolmandaks eluaastaks 38-100% juhtudel. Tavaliselt tekitavad seda lehmapiim ja soja, diagnoosi on raske panna, sest suukaudne väljakutse on ainuke, mis kinnitab diagnoosi. Ravi seisneb spetsiifilise toiduaine vältimises. Tõsised reaktsioonid vajavad šoki ravi ja kortikosteroide.

We report a case of food protein-induced enterocolitis syndrome (FPIES) with milk whose signs of milk intolerance began in the 1st days of life, consisting in minor and nonspecific symptoms. The 3 foods in question were cow's milk, soja, and wheat. The diagnosis of FPIES was suspected at the age of 9 months, after 3 hospitalizations for vomiting, sometimes associated with lethargy and hypotension, which occurred around 2h after cow's milk ingestion. Symptoms were not associated with positive specific IgE and cutaneous tests. Signs then occurred with soja and wheat. Because of the late diagnosis, 3 anaphylactic shock episodes occurred. FPIES is an uncommon cell-mediated food allergy reaction. This syndrome is characterized by gastrointestinal symptoms, especially severe vomiting, sometimes associated with anaphylactic shock. Usually signs occur 2h after ingestion. These reactions begin early, in the 1st months of life, and regress by the age of 3 years in 38-100% of cases depending on the responsible food. They are usually induced by cow's milk and soy proteins. Diagnosis is difficult and delayed because of nonspecific symptoms. Oral food challenge is the only examination that confirms the diagnosis. Treatment involves the exclusion of the specific food involved. Severe reactions require treatment of shock and adjunction of corticosteroids.

Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. Arch Dis Child. 2009 Jun;94(6):425-8. **Prospektiivne jätkuuring suukaudse väljakutsega toiduvalgust indutseeritud enterokoliidi sündroomi puhul**

Eesmärk oli määratleda lehmapiima ja soja taluvuse määr ja anda juhiseid järgneva suukaudse toiduga väljakutse/provokatsioonitesti teostamiseks (*follow-up oral food challenges (FU-OFCs*)) infantiilse toiduvalgust indutseeritud enterokoliitilise sündroomi (*infantile food protein-induced enterocolitis syndrome* (FPIES)) korral. Analüüsiti 23 patsiendi andmeid infantiilse FPIESga, kellele teostati kaks või rohkem FU-OFCs ja keda jälgiti üle 2 aasta vanuseks saamiseni. Esimene FU-OFCs teostati 6-kuuselt ja patsiendid jaotati soja ja piima väljakutse gruppi. Teine ja kolmas FU-OFCs teostati 2 kuuliste intervalliga ristuval ja ümberlülituslikul viisil.

Taluvusmäär lehmapiimale ja sojale oli 27.3% ja 75.0% kuuendal elukuul, 41.7% ja 90.9% 8 kuuks ja 63.6% ja 91.7% 10 kuuks vastavalt. Patsiendid kasvasid sellest talumatusest välja 20. ja 14. elukuuks. Infantiilse FPIES puhul esimese FU-OFC peaks tegema sojale 6-8 elukuul ja lehmapiimale üle 12 kuuselt. **Nad kasvavad välja 2 aastaga.**

To determine tolerance rates to cow's milk and soy and to suggest guidelines for follow-up oral food challenges (FU-OFCs) in infantile food protein-induced enterocolitis syndrome (FPIES). The authors analysed the data of 23 patients with infantile FPIES who underwent two or more FU-OFCs and were followed up until over 2 years of age. The first FU-OFCs were performed at 6 months of age, and patients were randomly allocated to cow's milk (n = 11) or soy (n = 12) challenge starting groups.

Second and third FU-OFCs were performed at 2-month intervals in a crossed and switched-over manner. Tolerance rates to cow's milk and soy were 27.3% and 75.0% at 6 months of age, 41.7% and 90.9% at 8 months and 63.6% and 91.7% at 10 months, respectively. Patients outgrew cow's milk and soy intolerance at age 20 and 14 months. In infantile FPIES, the first FU-OFC should be performed with soy at 6-8 months of age and cow's milk FU-OFC should be conducted at over 12 months of age. Infants with FPIES were observed to outgrow food sensitivities during the first 2 years of life.

Nowak-Wegrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2009 Aug;9(4):371-7. **Toiduvalgust indutseeritud enterokoliidi sündroom FPIES**

Teadmine FPIES kohta: Riis on peamine tahke toiduaine, mis põhjustab FPIES. Imik võib olla hüpotermiline ja omada trombotsütoosi. Hüpoalbumineemia ja kaalu juurdevõtmine vähem kui 10 g/päevas aitab diferentseerida kroonilist infantiilset lehmapiima FPIES infektsioossetest põhjustest. Maomahla leukotsüüdid üle 10 raku vaateväljas on leitud imikutel positiivse suukaudse väljakutse korral piimale. **EPIES on mitte-IgE-vahendatud GI toidu ülitundlikkuse häire. Toiduvalgu poolt aktiveeritud soole lümfotsüüdid toodavad põletikulisi tsütokiine, mis resulteerivad suurenenud soole läbilaskvuse, malabsorptsiooni, düsmotiilsuse, oksendamise, diarröa, valu ja *failure to thrive´*ga**. Vähenenud soole transformeeruv kasvufaktor beeta (*transforming growth factor beta*) ja tõusnud TNFalfa võivad olla olulised FPIES puhul. Lehmapiim ja soja on tavaliseimad FPIES põhjused, kuid ka teravili (riis, oder ja kaer), kala, linnuliha ja aedvili võivad olla põhjuseks. Enamus laheneb 3 eluaastaks.

To review current knowledge and recent advances in food protein-induced enterocolitis syndrome (FPIES). Rice is the most common solid food causing FPIES. Rice FPIES is associated with more severe reactions than other foods. Infants presenting acutely may be hypothermic (<36 degrees C) and have thrombocytosis. Finding of hypoalbuminemia and weight gain less than 10 g/day helps to differentiate chronic infantile cow's milk FPIES from infectious causes. Gastric juice leukocytes more than 10 cells per high-power field are found in infants with positive oral food challenge to cow's milk. FPIES is a non-IgE-mediated gastrointestinal food hypersensitivity disorder. Food protein-activated intestinal lymphocytes elaborate inflammatory cytokines that result in increased intestinal permeability, malabsorption, dysmotility, emesis, diarrhea, pain, and failure to thrive. Decreased intestinal transforming growth factor beta and increased TNFalpha may be important in FPIES. Cow's milk and soy are the most common causes of FPIES, but cereal grains (rice, oat, and barley), fish, poultry, and vegetables may also cause FPIES. The majority of FPIES resolve by age of 3 years.

Mehr SS, Kakakios AM, Kemp AS. Rice: a common and severe cause of food protein-induced enterocolitis syndrome. Arch Dis Child. 2009 Mar;94(3):220-3. **Riis on tavaline ja tõsine FPIES põhjustaja**.

Uuriti ja võrreldi riisi ja lehmapiima/soja poolt põhjustatud FPIES´i. Retrospektiivne uuring Austraalias, lastehaiglas 16 aastase perioodi jooksul. 14 last 26 episoodiga riisile võrreldi 17 lapse ja 30 episoodiga lehmapiimale (n = 10) või sojale (n = 7). Riisiga FPIES korral oli rohkem teiste toitude poolt põhjustatud FPIES (36%) kui piima/soja korral (0%). Riis põhjustas ka rohkem episoode enne diagnoosi saamist ja tekitas tõsisemaid reaktsioone, mis vajasid intravenoosset vedeliku manustamist. **Riisi peetakse tavaliselt hüpoallergiliseks toiduaineks, kuid ta ei ole ainult FPIES põhjustaja, ta on ka tõsisemate reaktsioonide tekitaja kui piim/soja.**

To examine and compare the characteristics of food protein-induced enterocolitis syndrome (FPIES) caused by rice and cow's milk/soy. Retrospective study of children presenting with FPIES to the Children's Hospital at Westmead, NSW, Australia, over a 16-year period. There were 14 children with 26 episodes of rice FPIES compared with 17 children with 30 episodes of cow's milk (n = 10) or soy (n = 7) FPIES. Children with rice FPIES were more likely to have FPIES caused by other foods (36%) than children with FPIES caused by cow's milk/soy (0%). Rice caused more episodes of FPIES before a correct diagnosis was made (median 4 (range 1-4) vs median 2 (range 1-4)) and triggered more severe reactions with higher rates of intravenous fluid resuscitation (42% vs 17%) than reactions caused by cow's milk/soy. This study highlights the emerging importance of rice, a food commonly thought to be "hypoallergenic", as a significant trigger of FPIES. Paediatricians should be aware that rice not only has the potential to cause FPIES, but that such reactions tend be more severe than those caused by cow's milk/soy.

Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. Pediatrics. 2009 Mar;123(3):e459-64. **Toiduvalgust tingitud enterokoliidi sündroom: 16 aastane kogemus**

Uuriti selle akuutse sündroomi kõiki aspekte (demograafilised iseärasused, põhjustavad toidud, kliinilised ilmingud, ravi ja tulemused) retrospektiivses uuringus Austraalias 16 a jooksul.

Keskmine iga, millal sündroom algas, oli 5.5 kuud. Lastel olid eelnevalt mitmed episoodid, enne kui korrektne diagnoos pandi. 21 last reageeris 1 toidule, 6 last kahele toidule. Põhjuseks oli 35-l lapsel riis (n = 14), soja (n = 12), lehmapiim (n = 7), aed- ja puuviljad (n = 3), lihad (n = 2), kaer (n = 2), ja kala (n = 1). 66 episoodi peamine sümptoom oli oksendamine (100%), sellele järgnes letargia (85%), kahvatus (67%) ja kõhulahtisus (24%). Temperatuur <36 kraadi C oli 24% -l episoodidest. Trombotsüüdid >500 x 10(9) per L oli 63% episoodidest. Ainult 2 last 19st vajasid kiirabi algsete reaktsioonide tõttu. Lisauuringud olid tavalised, 34%l teostati kõhuõõne uuring (*abdominal imaging*), 28% sepsise hindamine ja 22% konsulteeriti kirurgi poolt. Prognoos oli hea koos lahenemisega 2 tavalise toiduaine osas (riis ja soja) kolmandaks eluaastaks.

Tavaline on diagnoosi hilinemine ja valediagnoos. Lastele tehakse sageli mittevajalikke valulikeke uuringuid, **selle sündroomi puhul on tavalised märgid madal kehatemperatuur ja trombotsütoos.**

The goal was to examine the demographic characteristics, causative foods, clinical features, treatments, and outcomes for children presenting with acute food protein-induced enterocolitis syndrome. This was a retrospective study of children with food protein-induced enterocolitis syndrome who presented to the Children's Hospital at Westmead (Sydney, Australia) over 16 years. Thirty-five children experienced 66 episodes of food protein-induced enterocolitis syndrome. The mean age at initial presentation was 5.5 months. Children frequently experienced multiple episodes before a correct diagnosis was made. Twenty-nine children reacted to 1 food, and 6 reacted to 2 foods. Causative foods for the 35 children were rice (n = 14), soy (n = 12), cow's milk (n = 7), vegetables and fruits (n = 3), meats (n = 2), oats (n = 2), and fish (n = 1). In the 66 episodes, vomiting was the most common clinical feature (100%), followed by lethargy (85%), pallor (67%), and diarrhea (24%). A temperature of <36 degrees C at presentation was recorded for 24% of episodes. A platelet count of >500 x 10(9) cells per L was recorded for 63% of episodes with blood count results. Only 2 of the 19 children who presented to an emergency department with their initial reactions were discharged with correct diagnoses. Additional investigations of food protein-induced enterocolitis syndrome episodes presenting to the hospital were common, with 34% of patients undergoing abdominal imaging, 28% undergoing a septic evaluation, and 22% having a surgical consultation.

Prognosis was good, with high rates of resolution for the 2 most common food triggers (ie, rice and soy) by 3 years of age. Misdiagnosis and delays in diagnosis for children with food protein-induced enterocolitis syndrome were common, leading many children to undergo unnecessary, often painful investigations. Decreased body temperature and thrombocytosis emerge as additional features of the syndrome.

Boné J, Claver A, Guallar I, Plaza AM. Allergic proctocolitis, food-induced enterocolitis: immune mechanisms, diagnosis and treatment. Allergol Immunopathol (Madr). 2009 Jan-Feb;37(1):36-42.
Allergiline proktokoliit, toidust indutseeritud enterokoliit: immuunmehhanismid, diagnoos ja ravi

Termin toiduallergia viitab IgE vahendatud immuunreaktsioonile, mis tekib teatud toidu tarbimise järgselt. Viimastel aastatel kirjeldatakse palju mitteIgEvahendatud toiduallergiat. Sagedus ei ole täpselt teada, kuid arvatakse, et kõigist lehmapiima allergiatest **on 60% mitte-IgE-vahendatud mehhanismiga. Latentsperiood toidu tarbimise ja sümptoomide** vahel on pikem kui IgE allergia puhul ja allasuv immunopatoloogiline mehhanism ei ole päris selge, kuigi on aktsepteeritud T-rakuline vahendaminse. Pikaleveninud või kroonilistel juhtudel esinevad gastrointestinaalsed (GI) probleemid: allergiline proktokoliit, enterokoliit ja toiduvalgust tingitud enteropaatiad. Sümptoomid ilmnevad peamiselt esimestel elukuudel ja on progresseeruvad ning ise ennast piiravad paari aasta jooksul. **Kõige tavalisem tekitaja on piim, aga on viidatud ka kalale, munale ja riisile, ning iga lapse toidus olev valk võib seda tekitada. Sümptoomid kaovad pärast toiduaine menüüst eemaldamist.** Soovitav on kasutada täielikult hüdrolüüsitud valguga toidusegu, selle mittetalumisel elemendilist aminohapete segu.

The term food allergy refers to the immune reaction (mediated by IgE or otherwise) that develops in response to the ingestion of a concrete type of food. Among the different potential manifestations of an allergic reaction, those exclusively affecting the gastrointestinal system are described. In recent years, the study of non-IgE-mediated food allergy has grown in relevance. These disorders are almost always of a transient nature, inherent to (though not exclusive of) nursing infants, and with gastrointestinal symptoms that may have variable repercussions upon the nutritional state of the patient. The prevalence of such reactions is not known, though some studies report that up to 60 % of all cases of allergy to cow's milk proteins (CMPs) are due to non-IgE-mediated mechanisms. The latency period between the time of ingestion and the appearance of the first clinical manifestations is greater than in the case of IgE-mediated reactions, and the underlying immunopathological mechanism has not been clearly established although it is accepted that T cell mediation is involved. The gastrointestinal problems derived from these delayed or chronic reactions comprise allergic proctocolitis, enterocolitis and food protein enteropathies. These digestive disorders tend to appear in the first months of life, and are of a progressive and generally self-limiting nature, with resolution at about two years of age. The most commonly implicated food is milk and, in our setting, there have also been reports implicating fish, egg and rice although such reactions can be triggered by any protein introduced into the infant diet. These manifestations disappear after removing the causal protein from the diet. When the causal proteins are CMPs, a highly hydrolysed infant formula is supplied as substitute, and if the latter is not tolerated, an elemental amino acid-based formula is prescribed.

Armisén M, Vidal C, López-Rosés L, Rodríguez V, Bartolomé B. Eosinophilic esophagitis due to allergy to sheep and goat milk proteins. Rev Esp Enferm Dig. 2008 Jan;100(1):53-6. **Eosinofiilne ösofagiit lamba- ja kitsepiimavalgu allergia tõttu.** [Article in Spanish]

Eosinofiilne ösofagiit on põletikuline söögitoru haigus, mille puhul esineb kõrge number eosinofiilseid leukotsüüte limaskestas. See on täiskasvanutel ebatavaline, aga düsfaagia ja toidu mõju on sagedased sümptoomid. Me kirjeldame meest, kellel esines pikaaegne vahelduv düsfaagia pärast teatud tüüpi kitse- ja lambajuustu tarbimist ning kes vajas seetõttu ibuprofeeni. Biopsia andis eosinofiilse infiltratsiooni ja allergiatestid näitasid IgE antikehi kitse- ja lambapiimale. Kohalik steroidravi fluticasoniga ja nende piimatoodete elimineerimine viis sümptoomide täieliku kadumiseni. 4 kuu pärast ei olnud ka biopsias enam eosinofiile.

Eosinophilic esophagitis is an inflammatory disease of the esophagus characterized by the presence of high numbers of eosinophils in the esophageal mucosal layer (> 20 high-power field). It is uncommon in adults but in such cases intermittent dysphagia and food impaction are the most common presenting symptoms. We report the case of a male with long-standing intermittent dysphagia after eating selected goat and sheep cheese types, who required medical help following the impaction of an ibuprofen pill in the esophagus. A biopsy demonstrated the presence of eosinophilic inflammation, and allergy testing showed specific IgE against proteins in the milk of goats and sheep. Topical steroid therapy with oral fluticasone, and the elimination of these dairy products from the diet induced complete symptom resolution, and biopsy specimens taken 4 months later showed no eosinophils.

Kagalwalla AF, Shah A, Ritz S, Melin-Aldana H, Li BU. Cow's milk protein-induced eosinophilic esophagitis in a child with gluten-sensitive enteropathy. J Pediatr Gastroenterol Nutr. 2007 Mar;44(3):386-8. Novembre E, Vierucci A. Milk allergy/intolerance and atopic dermatitis in infancy and childhood. Allergy. 2001;56 Suppl 67:105-8. **Piima allergia/talumatus ja atoopiline dermatiit imiku- ja lapseeas.**

Ebasoovitavad reaktsioonid piimavalgule viitavad lehmapiima allergiale/talumatusele (CMPA *cow´s milk proteine allergy*/CMPI *cowś milk proteine intolerance*), sest sümptoomide alusel ei ole neid seisundeid võimalik eristada ning pole olemas ühte laboratoorset testi, mis neid diagnoosiks, vajalik on korrektne provokatsioonitest.

Atoopiline dermatiit (AD) on kõige tavalisem CMPA/CMPI sümptoom, **kolmandikul ADga lastest on CMPA/CMPI diagnoos eliminatsiooni dieedi või väljakutse testi alusel ja 40-50% alla 1-aastastest lastest CMPA/CMPI-ga omavad AD-d**. Paljud lapsed nendest omandavad täieliku taluvuse mõne aastaga, **kuid need, kellel jääb talumatus püsima, omavad sagedamini perekondlikku atoopilise haiguse ajalugu ja nendel lisanduvad väga sageli teised allergilised haigused nagu riniit või astma ning mitmesed toidutalumatused.** Simultaanne allergilise taluvuse arenemine ühes organis ja talumatuse arenemine teises organis viitab geneetiliste, immunoloogiliste ja keskkondlike faktorite keerulisele rollile AD jt atoopiliste haiguste tekkes.

Adverse reactions to cow's milk proteins are usually indicated as cow's milk allergy/intolerance (CMPA/CMPI) because no differentiation is possible on the basis of symptoms, and there is no reliable single laboratory test available for the diagnosis of CMPA or CMPI. Elimination and challenge tests for cow's milk proteins using strict, well-defined diagnostic criteria are required for the diagnosis of CMPA/CMPI. Atopic dermatitis (AD) is one of the most common symptoms of CMPA/CMPI. Approximately one third of AD children have a diagnosis of CMPA/CMPI according to elimination diet

and challenge tests, and about 40-50% of children < 1 year of age with CMPA/CMPI have AD. Many children with AD and CMPA/CMPI develop a complete tolerance to CMP in a few years. Children with persisting forms of CMPA/CMPI have a more frequent history of familial atopic disease, change in CMPA/CMPI manifestations over time and very high frequency of multiple food intolerance and allergic diseases. Many children who outgrow their AD develop other allergic diseases, such as rhinitis or asthma. The simultaneous development of allergic tolerance in one organ and the intolerance or atopic disease in another organ suggest that genetic, immunologic and environmental factors play a complex role in the natural history of AD and other atopic diseases.

Maloney J, Nowak-Wegrzyn A. Educational clinical case series for pediatric allergy and immunology: allergic proctocolitis, food protein-induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestations of non-IgE-mediated cow's milk allergy. Pediatr Allergy Immunol. 2007 Jun;18(4):360-7. **Mitte-IgE-vahendatud lehmapiimaallergia väljendused: FPIES, allergiline proktokoliit, allergiline eosinofiilne gastroenteriit koos valgukaoga gastroenteropaatiaga.**

Lehmapiima allergia on kõige tavalisem allergia vorm imikutel ja **väikelastel. See on 50%-l juhtudest mitteIgE vahendatud.** Allergiline proktokoliit on halvaloomuline häire, mis manifesteerub verejooksudega muidu pealtnäha tervetel ja rinnapiimal või segudega toidetud lapsel. Sümptoomid lahenevad 48-72 tunniga lehmapiima valgu toidust eemaldamise järgselt.

FPIES esineb noortel segutoidul lastel sümptoomidega: krooniline oksendamine, diarröa ja puudulik kaaluiive (*failure to thrive)*. Lehmapiima uuesti andmine pärast selle toidust elimineerimist resulteerub 2-3 t pärast profuusse ja korduva oksendamisega, 20%- või tekkida äge hüpovoleemiline šokk, mis vajab vedeliku ülekandeid. Enamus lastest muutuvad taluvaks mõne aastaga; kuid piima andmine tuleb teostada arsti järelevalve all ning intravenoosse ravivõimaluse olemasolul. **Allergiline eosinofiilne gastroenteriit haarab imikuid, aga ka vanemaid lapsi ning täiskasvanuid. Kõhuvalu, oksendamine, diarröa, madal kaauiive või kaalu kadu on peamised sümptoomid.** Osadel patsientidel või areneda valgukaoga enteropaatia *(protein-losing enteropathy).* 50% mõjutatud lastest on atoopikud ja omavad toiduspetsiifilisi IgE antikehi, kuid naha *prick test* ja seerumi toidu-IgE tasemed korreleeruvad halvasti toidu menüüst elimineerimise vastusega. Elementaalne dieet baseerub aminohapete segul, see viib GI eosinofiilse põletiku lahenemiseni tüüpiliselt 6 nädalaga.

Cow's milk protein allergy is the most common food allergy in infants and young children. It is estimated that up to 50% of pediatric cow's milk allergy is non-IgE-mediated. Allergic proctocolitis is a benign disorder manifesting with blood-streaked stools in otherwise healthy-appearing infants who are breast- or formula-fed. Symptoms resolve within 48-72 h following elimination of dietary cow's milk protein. Most infants tolerate cow's milk by their first birthday. Food protein-induced enterocolitis syndrome presents in young formula-fed infants with chronic emesis, diarrhea, and failure to thrive. Reintroduction of cow's milk protein following a period of avoidance results in profuse, repetitive emesis within 2-3 h following ingestion; 20% of acute exposures may be associated with hypovolemic shock. Treatment of acute reactions is with vigorous hydration. Most children become tolerant with age; attempts of re-introduction of milk must be done under physician supervision and with secure i.v. access. Allergic eosinophilic gastroenteritis affects infants as well as older children and adolescents. Abdominal pain, emesis, diarrhea, failure to thrive, or weight loss are the most common symptoms. A subset of patients may develop protein-losing enteropathy. Fifty percent of affected children are atopic and have evidence of food-specific IgE antibody but skin prick tests and serum food-IgE levels correlate with response to elimination diet poorly. Elemental diet

based on the amino-acid formula leads to resolutions of gastrointestinal eosinophilic inflammation typically within 6 wk.

Augustin MT, Kokkonen J, Karttunen R, Karttunen TJ. Serum granzymes and CD30 are increased in children's milk protein sensitive enteropathy and celiac disease. J Allergy Clin Immunol. 2005 Jan;115(1):157-62. **Seerumi granzüümid ja CD30 on tõusnud piimavalgule tundliku enteropaatia ja tsöliaakia korral**

CMSE ja CD (tsöliaakiahaigus) seonduvad lokaalse immuunvastuse üleregulatsiooniga, k.a. tsütotoksiliste lümfotsüütide aktivatsiooniga. Me uurisime, kas seda saab määrata süsteemsel tasemel, analüüsides seerumis granzüüme A (GrA) ja B (GrB), lahustuvat Fas, ja CD30.

57 last, nendest lõpliku CMSE diagnoosiga 23 (18 mitteravitut ja 5 dieedil), 20 mitteravitud CD ja 14 kontrolli ilma GI (gastrontestinaalsete ehk mao-sooletrakti) haiguseta uuriti kaebuste suhtes ja endoskoopial. Duodeenumi biopsiat vaadeldi histoloogiliselt, CD3, alfabeta and gamma-delta T-rakkude retseptoreid (TCRs), ja seerumi analüüse ELISA meetodil.

GrA ja GrB kontsentratsioonid oli märkimisväärselt kõrged mitteravitud CMSE ja CD korral võrreldes kontrollidega. Mõõdetav GrB esines vaid 20% kontrollidel, kuid 100% CMSE patsientidel. CD30 oli sarnaselt tõusnud mõlema, nii mitteravitud CMSE kui CD juhtudel, samal ajal kui ravitud CMSE juhtudel oli see võrdne kontrollisikutega. Kõik grupid olid sarnase lahustuva Fas-ga. Duodenaal CD3 +, alfabeta- and gammadelta-TCRs hulk korreleerus seerumi granzüümide ja CD30 tasemega.

Soole immuunvastus CMSE ja CD korral manifestreeub seerumi GrA, GrB, ja CD30 tõusuga; nende markerite määramine on uus vahend diagnostikas ja ravivastuse hindamisel. Muidugi on tarvis enne rutiinset kasutamist lisauuringuid.

Cow's milk protein sensitive enteropathy (CMSE) and celiac disease (CD) associate with upregulation of local intestinal immune responses, including activation of cytotoxic lymphocytes. We investigated whether this upregulation can be detected at the systemic level by analyzing serum concentrations of granzymes A (GrA) and B (GrB), soluble Fas, and CD30. Fifty-seven children with a final diagnosis of CMSE in 23 subjects (18 untreated and 5 on a diet), 20 untreated CD patients, and 14 control subjects with no gastrointestinal disease were examined by endoscopy for gastrointestinal complaints. Duodenal biopsies were studied for basic histology, CD3, alphabeta and gammadelta T-cell receptors (TCRs), and serum samples by commercial ELISA assays. Concentrations of GrA and GrB were significantly higher in untreated CMSE and in CD as compared with the control subjects. Measurable GrB was present in only 20% of the control subjects but in 100% of patients with CMSE. CD30 was similarly increased in both untreated CMSE and CD cases, whereas in treated CMSE cases the concentrations were equal to the control subjects. All groups showed similar soluble Fas. The numbers of duodenal CD3 + , alphabeta- and gammadelta-TCRs correlated with the serum granzyme and CD30 levels. The intestinal immune response in CMSE and CD is manifested by the increase in serum GrA, GrB, and CD30; the measurement of these markers provides a new practical and objective complementary means for diagnosis and assessment of treatment response. However, this has to be confirmed by more studies before routine use.

Augustin MT, Kokkonen J, Karttunen TJ. Duodenal cytotoxic lymphocytes in cow's milk protein sensitive enteropathy and coeliac disease. Scand J Gastroenterol. 2005 Dec;40(12):1398-406.
Tsütotoksilised lümfotsüüdid duodeenumis lehmapiima valgule tundliku enteropaatia ja CD korral.

Lehmapiimale tundliku enteropaatia patogeneetiline mehhanism ei ole täpselt defineeritud *(cow's milk protein-sensitive enteropathy* (CMSE)), kuid tõusnud seerumi **granzüümi** tasemed ja **duodeenumi** intraepiteliaalsed lümfotsüüdid (IELs), mis toodavad TIA-1, viitavad ebanormaalsele lümfotsüütide tsütotoksilisuse kaasatusele. Et hinnata CMSE tsütotoksilisust, analüüsiti duodeenumi limaskestasiseste lümfotsüütide (IEL) tsütotoksilisi graanuleid. Võrdluseks uuriti CD (tsöliaakiahaigusega) haigeid, kellel on see lümfotsüütide tsütotoksilisus patogeneetiliselt eriti oluline.

54 GI sümptomaatikaga last uuriti endoskoopiliselt, 21 said lõpliku diagnoosi CMSE, 15 last olid ravimatu CD-ga ja 18 –l kontrollil ei olnud gastrointestinaalset (GI) haigust. Limaskesta proovides uuriti CD3, perforiini, granzüüme A and B and TIA-1.

Duodenaalse IEL tsütotoksiliste graanulite tootmine on iseloomulik CMSE-le, kuigi väiksemas mahus kui CD korral. Arvatakse, et tsütotoksilisus on haaratud CMSE soole düsfunktsiooni patogeneesi, kuid hattude ebanormaalsuste puudumise tõttu võivad enterotsüüdid ehk soolerakud olla mitte peamisteks sihtmärkideks. Nende rakkude kuhjumise mehhanism vajab edasist uurimist.

Pathogenetic mechanisms of cow's milk protein-sensitive enteropathy (CMSE) are poorly defined, but elevated serum granzyme levels and an increase in duodenal intraepithelial lymphocytes (IELs) expressing TIA-1 suggest the involvement of abnormal lymphocyte cytotoxicity. To evaluate cytotoxicity in CMSE we analysed the expression of cytotoxic granule components in duodenal IELs. For comparison, we studied subjects with coeliac disease (CD), in which lymphocyte cytotoxicity is pathogenically important. Fifty-four children were examined by endoscopy for gastrointestinal complaints. Twenty-one subjects had a final diagnosis of CMSE, 15 children had untreated CD and 18 controls showed no definite gastrointestinal disease. Mucosal samples furnished from the bulb and descending duodenum were stained for CD3, perforin, granzymes A and B and TIA-1. In both CMSE and CD, increase of mid-duodenal TIA-1, perforin and granzyme A expressing IELs was seen, the counts in CD being much higher, and increased expression was also seen in the bulb. Granzyme B expression was increased only in CD. In CMSE, no evidence of villous atrophy was seen. Increase in duodenal IELs expressing cytotoxic granules is a characteristic feature in CMSE, although to a lesser degree than in CD. Cytotoxicity is suggested to be involved in the pathogenesis of intestinal dysfunction in CMSE, but based on the absence of villous abnormalities may not be mainly targeted to enterocytes. The mechanisms leading to the accumulation of these cells in CMSE need further investigation.

Augustin MT, Kokkonen J, Karttunen TJ. Evidence for increased apoptosis of duodenal intraepithelial lymphocytes in cow's milk sensitive enteropathy. J Pediatr Gastroenterol Nutr. 2005 Mar;40(3):352-8.
Tõendid duodeenumi limaskesta lümfotsüütides suurenenud apoptoosi kohta lehmapiima-tundliku enteropaatia (CMDSE) korral

Aktiveeritud IEL (intraepiteliaalsete lümfotsüütide) poolt indutseeritud enterotsüütide/soole limaskestarakkude apoptoos on CD (tsöliaakiahaigel) korral suur. Väiksem IEL juurdekasv on märgatav normaalse hattude struktuuri juures lehmapiima tundlikkusega enteropaatia korral. Siiani ei ole keegi avaldanud informatsiooni apoptoosi määra kohta.

Mitteravitud CMDSEga 21 lapse endoskoopia tulemusi võrreldi 15 CD ja 18 kontrollgrupi lapse omadega. Apoptoosi uuriti TUNEL tehnika abil ja M30 antikehade abil, Ki-67 kasutati proliferatsiooni määra hindamiseks ja CD3(+) T lümfotsüütide hulga lugemiseks.

Duodeenumi keskosas oli intraepiteliaalselt ja lamina proprias CMSE patsientidel märkimisväärselt tõusnud TUNEL(+) rakkude tihedus, aga erinevust ei olnud M30(+) epiteliaalrakkude tiheduses võrreldes kontrollidega. CD korral olid aga mõlemad kõrged. Proliferatsiooni määras ei olnud tõusu CMSE korral. Ja märkimisväärseid korrelatsioone apoptoosi ja proliferatsiooni määras ei leitud.

TUNEL(+) hulga tõus ja M30(+) rakkude hulga mittemuutumine viitab sellele, et apoptoosi määr intraepiteliaalsetes lümfotsüütides, aga mitte enterotsüütides on tõusnud CMSE korral. See viitab CMPE patogeneesis intraepiteliaalsete lümfotsüütide homöostaasi häirele.

Enterocyte apoptosis induced by activated intraepithelial lymphocytes (IELs) is increased in celiac disease (CD). A lesser increment in intraepithelial lymphocytes associated with normal villous structure is also characteristic of cow's milk sensitive enteropathy (CMSE), but no information is available about the apoptosis rate of this condition. Endoscopic biopsy samples of 21 children with untreated CMSE were compared with samples from 15 children with CD and 18 controls. Apoptosis was analyzed using the TUNEL technique and the M30 antibody from duodenal bulb and mid-duodenum samples. Ki-67 was used to detect the proliferation rate and CD3(+) to count the overall number of T lymphocytes. In the mid-duodenum, CMSE patients showed a significantly increased intraepithelial and lamina propria density of TUNEL(+) cells, but no difference in the density of M30(+) epithelial cells was seen compared with controls. In CD subjects, TUNEL(+) counts in mid-duodenal villous epithelium were increased. CD3(+) intraepithelial lymphocytes were increased in both CMSE and CD and correlated with TUNEL(+) and M30(+) counts among all patients. No increase in proliferation rate was seen in CMSE, and no significant correlations between apoptosis and proliferation rates were detected. The observed increase in TUNEL(+) counts and the absence of any increase in M30(+) cells suggest that the apoptosis rate of intraepithelial lymphocytes, but not of enterocytes, is increased in the small IELs in CMSE. However, the number of intraepithelial lymphocytes is still elevated in CMSE, indicating that a disturbance of homeostasis of intraepithelial lymphocytes is important in its pathogenesis.

Høst A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Pediatr Allergy Immunol. 2002;13 Suppl 15:23-8. **Lehmapiima allergia/talumatuse ja atoopiliste haiguste kliiniline pilt lapseeas**

1749 Odenses sündinud vastsündinut jäid 1995.a. uurimusse, milles vaadeldi nendel lastel piimavalgu allergia/talumatuse arenemist (CMPA/CMPI) esimesel eluaastal. Kui allergia/talumatus avastati, viidi lapsed piimavabale dieedile nii kauaks kuni piimaga väljakutse test näitas uuesti taluvust. Kõigile tehti väljakutse test 12-kuuselt ja talumatuse jätkumisel iga kuu järel kuni 3-aastaseks saamiseni, edasi 1 aasta järel kuni 15-aastaseks saamiseni. **Samast kohordist valiti 276 imikut juhuslikult pärast sündi prospektiivsesse mittesekkumuslikku jätku-uuringusse, kus vaadeldi atoopilise haiguse suhtes sensitisatsiooni/tundlikkuse väljakujunemist lapseeas.** Standardiseeritud küsimustikud pärilikkuse, keskkondlike faktorite ja sümptoomide kohta täideti 0, 6, 12 ja 18 kuuselt ning 5, 10 ja 15 aasta vanuselt. Intervjuud ja füüsiline läbivaatus teostati 18 kuuselt, 5, 10 ja 15 aastaselt. Naha *prick test* ja spetsiifiline sIgE (Pharmacia CAP) testimine teostati 18 kuuselt, 5, 10 ja 15 aastaselt sissehingatavatele allergeenidele (kask, rohi, puju, koer, kass, hobune, *Dermatophagoides pteronyssinus, Dermatophagoides farinae, alternaria ja Cladosporium herbarum*). Veelgi enam, kopsufunktsiooni mõõtmine teostati 10 ja 15 aastaselt. Kontrollitud piima eliminatsiooni ja väljakutse

protseduuride alusel kinnitati CMPA/CMPI diagnoos 39-l imikul 117-st koos sümptoomidega, mis viitasid CMPA/I-le, mille **tulemusena saadi 1-aastaselt CMPA/I esinemissageduseks 2.2%.** Üleüldine prognoos oli hea, koos täieliku paranemisega 56% esimeseks eluaastaks, 77% teiseks eluaastaks, 87% kolmandaks, 92% viiendaks ja 10. aastaks ning 97% viieteistkümnendaks aastaks. **Lastel, kes olid nooremad kui 10 aastat, arenes 41%-l astma ja 31%-l rinokonjunktiviit**. Lapsed, kellel oli mitte-IgE-vahendatud CMPI, omasid head prognoosi, samas kui lapsed IgE-vahendatud CMPA-ga varases lapsepõlves omasid märkimisväärselt suuremat riski püsivale CMPA-le, teiste toiduallergiate tekkimisele, astma ja rinokonjunktiviidi tekkimisele. Varases imikueas oli taastekkiv/korduv hingamisprobleem *(wheezing)* kõige sagedasem haigus (20%), millele järgnes atoopiline dermatiit (14%) ja toiduallergia (7%) 18-ks elukuuks. **Arsti poolt diagnoositud astma esinemine tõusis 2%lt 1.5 eluaastal kuni 9%-ni 10. eluaastaks. Rinokonjunktiviidi esinemine suurenes <1% 1.5-aastaselt kuni 9% ni 10. eluaastaks.** Üldiselt oli olemasoleva atoopilise haiguse esinemissagedus 20% 1.5-aastaselt, halvenedes 14%-ks 5. eluaastal ja 25%-ks 10. eluaastaks. Sensitisatsioon sissehingatavatele ja /või toidu allergeenidele näitas madalat sensitisatsiooni määra asümptomaatiliste seas (3%, 10% ja 12%) võrreldes kõrgete sensitisatsiooni määradega (8%, 39% ja 30%) sümptomaatilistel atoopikutel 1.5a., 5a. ja 10.eluaastal vastavalt**. Kõrgeim senitisatsiooni määr (53%) oli olemasoleva astmaga lastel 10-aastaselt.**

A cohort of 1,749 newborns from the municipality of Odense, born during 1995 at the Odense University Hospital, were followed up prospectively for the development of cow's milk protein allergy/intolerance (CMPA/I) during the first year of life. Once a diagnosis of CMPA/I was confirmed, a milk-free diet was continued until a new milk challenge had shown development of tolerance. All infants with CMPA/I were rechallenged at 12 months of age and, in the event of continued clinical sensitivity to cow's milk protein, controlled rechallenges were performed every 6 months up to 3 years of age; and thereafter every 12 months until the age of 15 years. From the same birth cohort, 276 infants were randomly selected at birth for prospective non-interventional follow-up in order to investigate the natural course of sensitization and development of atopic disease during childhood. Standardized questionnaires on atopic heredity, environmental factors and presence of atopic symptoms were answered at 0, 6, 12 and 18 months and at 5, 10 and 15 years of age. Interviews on atopic history and environmental factors as well as physical examination were carried out at 18 months, 5, 10 and 15 years of age. Skin prick test and specific sIgE (Pharmacia CAP) testing were performed at 18 months, 5, 10 and 15 years of age against a panel of inhalant allergens (birch, grass, mugwort, dog, cat, horse, Dermatophagoidespteronyssinus, Dermatophagoides farinae, alternaria and cladosporium herbarum). Furthermore, lung function measurements were performed in children when 10 and 15 years of age. Based on controlled milk elimination and challenge procedures, the diagnosis of CMPA/I was confirmed in 39 out of 117 infants, with symptoms suggestive of CMPA/I, thus resulting in a 1-year incidence of CMPA/I of 2.2%. The overall prognosis of CMPA/I was good, with a total recovery of 56% at 1 year, 77% at 2 years, 87% at 3 years, 92% at 5 and 10 years and 97% at 15 years of age. In children younger than 10 years of age, 41% developed asthma and 31% rhinoconjunctivitis. Children with non-IgE-mediated CMPI had a good prognosis, whereas children with IgE-mediated CMPA in early childhood had a significantly increased risk for persistent CMPA, development of other food allergies, asthma and rhinoconjunctivitis. During early infancy, recurrent wheezing was the most prevalent disease (20%), followed by atopic dermatitis (14%) and food allergy (7%) at 18 months of age. Physician diagnosed asthma increased from 2% at 1.5 years of age to 9% at 10 years of age. Rhinoconjunctivitis increased from <1% at 1.5 years of age to 9% at 10 years of age. Overall, the current prevalence of any atopic disease was 20% at 1.5 years of age, declining to 14% at 5 years of age and followed by an increase to 25% at 10 years of age. Sensitization to inhalant and/or food allergens (specific IgE of > or = class 2; CAP RAST) showed a low rate of sensitization among asymptomatics (3%, 10% and 12%) compared with higher rates of sensitization of 8%, 39% and 30% among symptomatic atopics at 1.5, 5 and 10 years of age respectively. The highest rate of sensitization (53%) was found among children with current asthma at 10 years of age.

Kokkonen J, Tikkanen S, Karttunen TJ, Savilahti E. A similar high level of immunoglobulin A and immunoglobulin G class milk antibodies and increment of local lymphoid tissue on the duodenal mucosa in subjects with cow's milk allergy and recurrent abdominal pains. Pediatr Allergy Immunol. 2002 Apr;13(2):129-36. **Sarnane kõrge piima IgA ja IgG tase ja lokaalse lümfikoe kasv duodenumi limaskestal lehmapiima allergiaga ja taastekkivate kõhuvaludega isikutel.**

Varasemates uuringutes on kirjeldatud endoskoopilisi ja histoloogilisi muutusi gastrointestinaal(GI) traktis gastrointestinaalset tüüpi lehmapiima allergia (CMA) korral. Meie hüpotees oli, et seletamatute ja korduvate kõhuvalude puhul võib sama asjaga tegemist olla. Uurisime igakülgselt 22 mitteravitud ja 14 ravitud last lehmapiima allergiaga ja 44 kõhuvaludega last. Immunoloogilisi tulemusi võrreldi 54 terve lapse tulemustega.

Lümfonodulaarne hüperplaasia (LNH) duodeenumis oli peamine endoskoopiline leid 11-l (50%) mitteravitud ja 5-l (36%) ravitud CMA-ga lapsel. 6 last 40-st omasid (*recurrent abdominal pains RAP)* taastekkivat/pidevat kõhuvalu. Kontrollgrupi isikutega võrreldes omasid CMA lapsed märkimisväärselt kõrgemaid IgA klassi antikehi täispiimale ja betaLG-le (laktoglobuliinile), IgG klassi antikehi betaLG-le, BSA ja alphaCAS-le (kaseiinile) olid märkimisväärselt kõrgemad. Patsiendid LNH-ga duodenaalses bulbuses omasid märkimisväärselt kõrgemaid IgG klassi antikehi betaLG –le ja alphaCAS-le. Patsiendid, keda uuriti kõhuvalu (RAP) suhtes, omasid samasugust reaktsiooni täispiimale ja spetsiifilisi piimavalgu antigeene nagu CMA-ga lapsed. Uuring näitas, et gastrointestinaalne CMA väljaspool imikuiga on märkimisväärselt seotud kõrgete IgG ja IgA klassi antikehadega piimale ja piima fraktsioonidele. Kuna nende antikehade kõrge tase ja LNH duodenaal-bulbuses leiti ka RAP-iga laste puhul, arvatakse et selle üheks peamiseks põhjuseks võib olla **gastrointestinaalne CMA.**

In previous studies, we have reported endoscopic and histological alterations locally on the gastrointestinal (GI) tract associated with a gastrointestinal type of cow's milk allergy. In this study, we sought to further characterize endoscopic, and immunological findings in these children. We also hypothesized that the same type of immune responses might also be found in children with unexplained and recurrent abdominal pains. We did a gastroduodenoscopy for persistent GI symptoms, examined the mucosal histology of the small intestine and measured the antibodies to whole cow's milk and its fractions with an enzyme-linked immunosorbent assay (ELISA) in a consecutive series of 22 subjects with untreated and 14 with treated cow's milk allergy (CMA) and 44 with recurrent abdominal pains (RAP). The immunological findings of the study subjects were compared with 54 controls. Lymphonodular hyperplasia (LNH) of the duodenum was the main endoscopic finding in 11 subjects (50%) with untreated and 5 (36%) with treated CMA. It was also found in 6 of 44 subjects with RAP. Compared with the controls, the patients with CMA showed significantly higher levels of IgA class antibodies to whole milk ($p = 0.003$) and betaLG ($p < 0.0001$). Of the IgG class antibodies to betaLG ($p = 0.032$), BSA ($p < 0.0001$) and alphaCAS ($p < 0.0001$) were significantly higher. The patients with LNH of the duodenal bulb as the main endoscopic finding showed significantly higher values of IgG class antibodies to betaLG ($p = 0.01$) and alphaCAS ($p = 0.005$). Interestingly, the patients examined for RAP showed a similar increment in the pattern of whole milk and specific milk protein antibodies as the CMA children. In conclusion this study showed that gastrointestinal CMA beyond infancy is significantly associated with high levels of IgG and IgA class antibodies to milk and its fractions. As high levels of these antibodies and LNH of the duodenal bulb were also found in subjects with RAP, the study further suggests that gastrointestinal CMA might be one major reason for RAP.

Magazzù G, Scoglio R. Gastrointestinal manifestations of cow's milk allergy. Ann Allergy Asthma Immunol. 2002 Dec;89(6 Suppl 1):65-8. **Lehmapiima allergia mao-sooletrakti väljendused**

Arutleme ja anname ülevaate seostest lehmapiima allergia *(cow's milk allergy*) CMA ja GI (gastrointestinaalsete ehk mao-sooletrakti sümptoomide vahel: gastroösofageaalne refluks, kõhukinnisus, FPIES *(food protein-induced enterocolitis)* ja toidust tingitud eosinofiilne proktokoliit *(food-induced eosinophilic proctocolitis)*, eesmärgiga näidata, et pole vajadust kaksikpimeda, platseebokontrollitud suukaudse provokatsiuoonitest (*double-blind, placebo-controlled oral food challenge DBPCFC*) uuringu järele.

Antakse ülevaade 10 a jooksul publitseeritud uuringutest PubMedis, kus on analüüsitud võrdlevalt haigeid ja kontrollgrupi isikuid.

Gastroösofageaalne reflukstõbi - tüüpiline 24-tunnine söögitoru pH jälgimine võib ära hoida DBPCFC (CMAst tingitud refluksi korral).

Seos CMA ja kõhukinnisuse vahel on raporteeritud vaid ühes prospektiivses kontrollitud uuringus. Kliinilised ja laboratoorsed näitajad on: pärakuümbruse kahjustused/lesioonid, histoloogilised ebanormaalsused ning ülitundlikkuse märgid.

Teatud väljaheite teste soovitatakse FPIEC korral: rooja tuumori nekroosi-faktori-alfa ja alpha1-antitrüpsiini määramine. Imikutel näitab eosinofiilse proktokoliidi puhul rektaalne biopsia eosinofiilset infiltratsiooni, mis teeb DBPCFC mittevajalikuks.

Kuigi praegune diagnoos nõuab GI sümptoomide olemasolul DBPCFC, otsitakse uusi võimalusi diagnoosimiseks.

To review and discuss the relationship between cow's milk allergy (CMA) and some gastrointestinal manifestations, such as gastroesophageal reflux, constipation, food protein-induced enterocolitis, and food-induced eosinophilic proctocolitis, with respect to diagnostic strategies that might eliminate the need for a double-blind, placebo-controlled oral food challenge (DBPCFC). A review of pertinent PubMed articles, published during the past 10 years, was performed. To obtain positive and negative predictive values known as posterior probabilities and to calculate the likelihood ratio, only those studies including both patients and control subjects were selected for analysis. With respect to gastroesophageal reflux, a typical 24-hour esophageal pH monitoring pattern might obviate the performance of a DBPCFC in patients with symptoms of reflux suspected of having CMA, provided this pH pattern is confirmed in other studies. A relationship between CMA and constipation has been reported in only one prospective controlled study; the clinical and laboratory variables of perianal lesions, histologic abnormalities, and signs of hypersensitivity had likelihood ratios of 2.2, 2.4, and 3.7, respectively, and posttest probabilities of 83, 84, and 88%, respectively. Therefore, a DBPCFC is warranted. In reference to food protein-induced enterocolitis, clinical and laboratory criteria suggested in the literature for defining a food challenge as positive have not been prospectively evaluated in the untreated state. Some simple stool tests, such as fecal tumor necrosis factor-alpha and alpha1-antitrypsin determination, might be candidates for diagnostic studies in patients with food protein-induced enterocolitis, if prospectively evaluated. In infants with food-induced eosinophilic proctocolitis, rectal biopsy invariably shows eosinophilic infiltration and thus makes performance of a DBPCFC unnecessary. Although the current diagnosis of gastrointestinal

manifestations of CMA usually depends on a DBPCFC, investigators continue to study other options for confirming the diagnosis.

Sicherer SH. Food protein-induced enterocolitis syndrome: clinical perspectives. J Pediatr Gastroenterol Nutr. 2000;30 Suppl:S45-9. **Food Protein-Induced Enterocolitis Syndrome (FPIES): kliinilised perspektiivid**

FPIES on sümptoomide kompleks, mis hõlmab tõsist oksendamist ja diarröad/kõhulahtisust, mis on põhjustatud mitte-IgE-vahendatud allergiast lehmapiimale ja sojale imikutel. Sümptoomid algavad tüüpiliselt esimestel elukuudel *failure to thrive´*ga seoses ja progresseeruvad atsideemiaks ja methemoglobineemiaks. Kui põhjuslik valk eemaldatakse, siis sümptoomid kaovad ja taastuvad 2 tundi pärast toidu uuesti andmist koos samaaegse **polümorfonukleaarsete leukotsüütide hulga tõusuga perifeerses veres**. Tundlikkus tavaliselt kaob 3 eluaastaks.

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a symptom complex of severe vomiting and diarrhea caused by non-IgE-mediated allergy to cow's milk and/or soy in infants. Symptoms typically begin in the first month of life in association with failure to thrive and may progress to acidemia and methemoglobinemia. Symptoms resolve after the causal protein (usually sensitivity to both cow's milk and soy) is removed from the diet. Symptoms recur approximately 2 hours after reintroduction of the protein along with a coincident elevation of the peripheral blood polymorphonuclear leukocyte count. The sensitivity is usually outgrown by 3 years of age. The purpose of this review is to delineate the characteristic clinical features, diagnosis and management of FPIES. Furthermore, infantile FPIES will be discussed in relation to clinical syndromes that share features with it ("atypical FPIES") and other food-allergic disorders affecting the gastrointestinal tract.

Høst A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. Pediatr Allergy Immunol. 1994;5(5 Suppl):1-36. **Lehmapiima allergia ja talumatus imikutel. Mõned kliinilised, epidemioloogilised ja immunoloogilised aspektid**

Reprodutseeritavad kliiniliselt ebanormaalsed reaktsioonid lehmapiima valgule võivad olla tingitud ühe või rohkema piimavalgu ja ühe või rohkema immuunmehhanismi interaktsioonist, võimalik, et ühena neljast baasilisest ülitundlikkuse reaktsiooni tüübist. Praeguseks ajaks on I, III ja IV tüüpi reaktsioonid lehmapiima valgule tõendatud.

Immunoloogiliselt vahendatud reaktsioonid, peamiselt IgE vahendatud reaktsioonid defineeritakse **piimavalgu allergiana (CMPA**), mitteimmunoloogilised reaktsioonid piimavalgule aga **piimavalgu talumatusena (CMPI**). **Ei ole olemas ühtegi üksikut laboratoorset testi, mis neid seisundeid diagnoosiks ja neid ei ole sümptomite alusel võimalik eristada**. Paljudes nn „lehmapiima allergia“uurimustes ei ole uurinud kliiniliste reaktsioonide immunoloogilist alust. Diagnoos pannakse range eliminatsiooni ja väljakutsetestide alusel. Enne 1950.ndaid diagnoositi neid seisundeid harva. 1970.ndatel aga juba 1,8-7,5%-l isikutest. Korralike diagnostiliste kriteeriumite alusel arvatakse, et seda esineb 2-5%-l imikutest arenenud maades. Sümptomeid on 5-15%-l imikutest, mis nõuab testimist eliminatsiooni/provokatsiooni testiga. Rinnapiimal imikutel on leitud reaktsiooni lehmapiimavalgule emapiimas 0,5%-l. Enamusel CMPA/CMPI tekivad sümptoomid enne esimest elukuud, sagedamini 1 nd pärast lehmapiimal baseeruvate segude manustamist. Enamusel on 2 või rohkem sümptoomi 2 või rohkema organi poolt. 50-70% omavad nahasümptoome, 50%-60% gastrointestinaalseid ja 20-30% respiratoorseid sümptoome. Rinnapiimal olevatel on eranditult

CMPA/CMPI domineeriv sümptoom atoopiline ekseem. CMPA/CMPI esmatekkimine pärast 12 kuud on väga harv. Baasiline ravi on täielik lehmapiima eemaldamine menüüst. Imikutel on vajalik kasutada kindlaid lehmapiimavabu hüpoallergeenseid segusid. Tänu kliiniliselt tähtsale residuaalsele allergeensusele mõningate kliinilistes uuringutes kontrollitud hüpoallergiliste segude puhul on vajalik individuaalne testimine enne kasutamist. **Kitsepiimavalgud on identsed toore lehmapiima valguga ja mittehomogeniseeritud lehmapiim on sama allergeene kui pastöriseeritud ja homogeniseeritud piim.** CMPA/CMPI prognoos on hea koos remissiooni sagedusega 45-50% ühe aastaga, 60-75% kahe aastaga ja 85-90% kolme aastaga. **Kõrvalreaktsioonid teistele toitudele arenevad 50%-l ja allergia sissehingatavate ainete peale areneb 50-80%l enne puberteeti.**

Reproducible clinically abnormal reactions to cow's milk protein (CMP) may be due to the interaction between one or more milk proteins and one or more immune mechanisms, possibly any of the four basic types of hypersensitivity reactions. At present, evidence for type I, III and IV reactions against CMP has been demonstrated. Immunologically mediated reactions, mainly immediate IgE-mediated reactions are defined as cow's milk protein allergy (CMPA). Non immunologically reactions against CMP are defined as cow's milk protein intolerance (CMPI). Many studies on "cow's milk allergy'" have not investigated the immunological basis of the clinical reactions. It is not possible to differentiate between CMPA and CMPI solely on clinical symptoms. No single laboratory test is diagnostic of CMPA/CMPI. Therefore, the diagnosis still has to be based on strict well-defined elimination and milk challenge procedures. Before 1950 CMPA/CMPI was rarely diagnosed. Since 1970 widely varying estimates of the incidence from 1.8% to 7.5% have been reported, mainly reflecting differences in diagnostic criteria and study design. Based on strict diagnostic criteria the incidence of confirmed CMPA/CMPI in infancy seems to be about 2-5% in developed countries. Symptoms suggestive of CMPA/CMPI may be encountered in about 5-15% of infants emphasizing the importance of controlled elimination/milk challenge. In breastfed infants reproducible clinical reactions to CMP in human milk have been reported in about 0.5%. Most infants with CMPA/CMPI develop symptoms before one month of age, often within one week after introduction of cow's milk based formula. The majority have > or = 2 symptoms and symptoms from > or = 2 organ systems. About 50%-70% have cutaneous symptoms, 50-60% gastrointestinal symptoms, and about 20-30% respiratory symptoms. In exclusively breast-fed infants with CMPA/CMPI severe atopic eczema is a predominant symptom. Debut of CMPA/CMPI after 12 months is extremely rare. The basic treatment is complete avoidance of CMP. In infancy a proven hypoallergenic CM substitute is needed. Due to clinically important residual allergenicity in some hypoallergenic formulae controlled clinical testing is necessary in each case before use. Goat's milk proteins share identity with CMP Raw untreated cow's milk and unhomogenized cow's milk is as allergenic as normal pasteurized and homogenized milk products. The prognosis of CMPA/CMPI is good with a remission rate about 45-50% at one year, 60-75% at two years, and 85-90% at three years. Associated adverse reactions to other foods develop in about 50%, and allergy against inhalants in 50-80% before puberty.

Kaczmarski M, Lisiecka M, Kurpatkowska B, Jastrzebska J. Quantitative estimation of cellular infiltration of the small intestinal mucosa in children with cow's milk and gluten intolerance. Acta Med Pol. 1989;30(3-4):129-39**. Peensoole limaskesta rakulise infiltratsiooni hindamine lastel lehmapiima ja gluteeni talumatuse korral**

Piima- ja gluteenitalumatutel lastel määrati epiteelisiseselt lümfotsüütide ja eosinofiilide hulk. Enne dieediravi oli see mõlemal juhul kõrge, erinedes märkimisväärselt kontrollgrupi näitajatest. Eliminatsioonidieediga paranesid näitajad mõlemas grupis 8-24 kuuga.

Quantitative estimation of the infiltration by intraepithelial lymphocytes and eosinophils of the mucosa was carried out in 21 children with cow's milk and 35 children with gluten intolerance. Before dietary treatment, a statistically significant increase in the infiltration by LIE in children with milk intolerance to the mean value of 34.1 cells and in children with gluten intolerance to 39.0 cells was found, what statistically significantly differed from the mean value of LIE for the control group (19.0 cells/100 epithelial cells). The eosinophilic infiltration in this phase of the disease was noted in 38% of children with cow's milk intolerance (16.9 cells/mm2) and in 27% of children with gluten intolerance (28.6 cells/mm2). After 8-24 months of elimination diets--a decrease in the mean value of the LIE infiltration in the mucosa was revealed in both treated groups.

Balli F, Giberti G, Bertolani P, Amarri S, Palmieri R, Olivi O. Atrophy of the duodeno-jejunal mucosa in cow's milk protein intolerance. Importance of cell-mediated immunologic factors. Pediatr Med Chir. 1986 Sep-Oct;8(5):611-4. **Duodenumi ja peensoole ülemise osa limaskesta atroofia lehmapiima valgu talumatuse korral. Rakuliselt vahendatud immunoloogiliste faktorite olulisus.** [Article in Italian]

Lehmapiimale tundlikku enteropaatiat *(cow's milk sensitive enteropathy*) on kirjeldatud korduvalt, kuid patogeenees on teadmata. Meie uuringus olid lapsed, 1974 -1984 hospitaliseeritud Modena Ülikooli pediaatriakliinikusse. Patsiendid kannatasid **kroonilise kõhulahtisuse ja malabsorptsiooni käes.** Kõikidel lastel esines peensoole limaskesta biopsial **atroofia** ja kõik need lapsed said toiduga gluteeni. Me järgisime tsöliaakiahaiguse diagnoosi protokolli ja leidsime selle 85%-l juhtumitel, kuid **15% jäid välja**. **Viimased võivad olla lehmapiimatundliku enteropaatiaga lapsed**. Katamnestiliselt võeti arvesse kõiki kliinilisi andmeid ja parameetreid diferentsiaaldiagnoosi jaoks. Andmed olid nendes kahes grupis märkimisväärselt erinevad: peres esinev allergia, taastekkivad infektsioonid, varjatud veri väljaheites, eosinofiilid veres kõrgemad kui 400/mm3, seerumi IgE väärtus üle 97 kraadi/degrees P X (p less than 0.01). **Viimatiste uuringute alusel arvatakse, et tegemist on rakuliselt vahendatud immuunsusega lehmapiimale tundliku enterpopaatia korral.**

Cow's milk sensitive enteropathy has been described several times but in spite of that, it is still a problem concerning the pathogenesis. Our study involves the children hospitalized from 1974 to 1984 in the First Department of Pediatrics, University of Modena. Patients were suffering from chronic diarrhea and malabsorption. At the first biopsy each child showed atrophy of the small intestinal mucosa. All patients had been fed fed with gluten. We have followed the protocol for Celiac Disease's diagnosis; we found proved 85% of cases, excluded 15%. These last cases may be considered as cow's milk sensitive enteropathy. We catamnestically considered all the clinical and laboratory data of the two groups in the purpose of selecting significative parameters for a differential diagnosis. The data meaning fully different between the two groups resulted: family history of allergy, recurrent infections, positive occult blood in the stools, eosinophils in blood greater than 400/mm3 serum IgE value greater than 97 degrees P X (p less than 0.01). On the ground of recent studies the involvement of the cell-mediated immunity in cow's milk sensitive enteropathy is supposed.

Maluenda C, Phillips AD, Briddon A, Walker-Smith JA. Quantitative analysis of small intestinal mucosa in cow's milk-sensitive enteropathy. J Pediatr Gastroenterol Nutr. 1984 Jun;3(3):349-56. **Peensoole limaskesta kvantitatiivne analüüs lehmapiimatundliku enteropaatia korral.**

Lehmapiima talumatusega (CMPI) isikute peensoole limaskesta uuriti, täpsemalt eosinofiile *lamina proprias* ja epiteelis, hattude kõrguse/krüptitsooni sügavuse suhet, üldist limaskesta paksust. Ning

leiti, et intraepiteliaalste eosinofiilide hulk oli pärast lehmapiima provokatsiooni tõusnud. Seda nim **lehmapiima tundlikuks enteropaatiaks** – õhem limaskest haiguse aktiivsuse ajal, kuid see ei muutunud haiguse lahenedes. Tsöliaakiahaiguse puhul oli limaskest paksem kui CMPI korral. Ravimata tsöliaakiahaiguse korral korral ei olnud see paksem kui ravimata CMPI lastel. **CMPI korral esineb krüpti rakkude piiratud võimekus kompenseerida hattude epiteeli kaotust.**

The appearance of the small intestinal mucosa in cow's milk protein intolerance (CMPI) was studied using quantitative morphometry. The parameters under study were the numbers of eosinophil cells in the lamina propria and epithelium, villous height, crypt zone depth, villous height/crypt zone depth ratio, and total mucosal thickness. Tracings of whole sections were analysed using a suitably programmed minicomputer linked to a digitising table. Small bowel biopsy specimens from children with untreated CMPI, from children before and after clinical relapse on cow's milk challenges, and from children with resolved CMPI were compared to each other, to those from control infants, and to those from children with coeliac disease. No change of diagnostic significance could be found in the number of lamina propria eosinophil cells, but levels of intraepithelial eosinophils were significantly increased following cow's milk challenge. Quantification of mucosal dimensions confirmed the presence of a cow's milk-sensitive enteropathy and established the finding of a thin mucosa in CMPI regardless of clinical disease activity. Mucosal thickness was not different from control values following resolution of the disease. In coeliac disease mucosal thickness was significantly greater than in CMPI (apart from young children with untreated coeliac disease whose mucosa was not thicker than that of children with untreated CMPI) but not different from control values. It is suggested that in CMPI there is a limitation in the capacity of crypt cells to compensate for the loss of villous epithelium.