Su2062

Current Symptoms and Quality of Life in Patients Diagnosed With Achalasia at a Pediatric Age (0-18yr)

Marije J. Smits, Remy Vrijlandt, Marinde V. Lennep, Marc A. Benninga, Michiel P. van Wijk

Objectives and study Achalasia is a rare chronic motility disorder with a big impact on Quality of Life (QoL), even in patients treated successfully. We aimed to prospectively assess current symptoms and QoL in patients diagnosed with achalasia in childhood (0-18yr). **Methods:** Dutch children diagnosed with achalasia between 1990-2013 were contacted either by telephone or by mail and were asked complete 4 questionnaires. Severity of achalasia symptoms was assessed using the Eckardt score (suggestive for achalasia when >3) and the Reflux Disease Questionnaire (RDQ, suggestive for gastro esophageal reflux disease (GERD) when ≥mild heartburn/regurgitation occurred ≥2 days a week). Disease specific QoL was assessed with the Achalasia DS-QoL (when <18yr at time of study, 0= worst 100=best) or HRQoL (≥18yr, 0= worst 100=best). General QoL was measured with the KIDSCREEN-52 (<18yr, T-values over 10 domains relative to healthy norm, higher value suggests better QoL) or the SF-36 (≥18yr, 8 domains, 0= worst 100=best QoL per domain) and compared to healthy population norms. **Results** Seventy-two of 87 (83%) patients were prospectively reached. Median (inter quartile range, IQR) time since last clinical follow up was 1.7 years (0.5-6.9 years). Twenty (32%) patients were <18yr. Median Eckardt score was 3 (IQR 2-5) with 32 patients (44.5%) having a positive score. Median RDQ score was 0.92 (0.10-1.65). GERD was reported relatively more frequent after initial treatment with Heller's myotomy compared to pneumodilation (PD, P=0.04) and median RDQ scores were higher when initially treated with HM(F) (1.58 (0.96 - 2.71)) compared to ≥1x PD (0.58 (0 - 1.58)), P=0.005. Eckardt and RDQ scores were similar for adult and paediatric patients (P=0.980 and P=0.454, respectively). Overall HR-QoL score was 61.3 (48.3-71.0). General QoL (SF-36) in adults (n=52) was lower compared to healthy population norms for 7/8 domains, with scores on 'bodily pain' and 'general health perceptions' domains (18-25 yr) significantly lower compared to age adjusted norm (P=0.018 and P<0.0001). SF-36 scores were similar for patients initially treated with PD or HM. Paediatric achalasia DS-QoL score was 17.5 (8-29). Self-reported QoL (KIDSCREEN-52, n=20) was similar to population norms. On 2 domains (School Environment, Financial Resources) achalasia patients even scored better (P=0.038 and P=0.049). **Conclusion** Almost half of patients with achalasia diagnosed <18yr still have symptoms suggestive of active disease. This observation stresses the need for regular clinical follow-up and good transition to the adult gastroenterologist. Disease specific and general quality of life is lower for adult patients compared to paediatric patients. This suggests that the impact of achalasia increases with duration of disease.

Su2063

Pediatric Achalasia: Diagnosis, Management and Follow-Up in the Netherlands

Marije J. Smits, Marinde V. Lennep, Marc A. Benninga, Roderick Houwen, Fredericus T. Kokke, David C. van der Zee, F.A.J.A. Bodewes, Anita Van den Neucker, Tim de Meij, J.J. Schweizer, Johanna C. Escher, Gerard Damen, Michiel P. van Wijk

Introduction: Pediatric achalasia is a rare esophageal motility disorder. Data on prevalence, incidence, presenting symptoms, treatment success and follow up are scarce. **Methods:** Medical charts of registered Dutch pediatric achalasia patients (<18yrs) diagnosed between January 1990 and December 2013, were retrospectively reviewed for data on presenting symptoms, treatment, relapses and follow up. **Results:** In total, 87 Dutch pediatric achalasia patients (mean age at diagnosis 11.44 +/- 3.43 years, 60% male) were included. Mean incidence was 0.10/100,000 per year (range, 0.03 and 0.21). No significant increase in incidence was observed over the study period. The prevalence of pediatric achalasia in The Netherlands in 2012 was 0.90/100,000. Presenting symptoms included dysphagia (83%), regurgitation (69%), weight loss (44%) and chest pain (37%). Manometry was incorporated in diagnostic evaluation in 86%. Eleven (14%) of patients were diagnosed based on barium swallow and/or upper endoscopy without a documented manometry recording. Initial treatment was pneumatic balloon dilation (PD) in 68 (79%) patients and laparoscopic Heller's Myotomy (HM) in 18 (21%) patients. In 4 patients, achalasia was diagnosed as part of Triple A syndrome. Complications of initital treatment occurred more after HM compared to PD (10/18 vs 1/68 P<0.0001, n=4 perforations). Similarly, complication rate was higher for HM after relapse treatments (20/22 vs 3/135, P<0.0001, n=7 perforations). However, the cumulative amount of complications of re-treatment(s) after initial PD is higher compared to initial HM (n=21/229 vs n=13/24). Re-treatment was required more often after initial PD (n=59, 88%) compared to initial HM (n=4, 22%), P<0.0001. First re-treatment after initial PD was re-PD in 90% and HM in 10% of patients. After initial HM, first relapse treatment was PD in 50% and re-HM in 50%. Median (interquartile range) follow-up after initial treatment was 3.9 years (1.4 - 10.2). Four years after initial treatment, 46% of patients <18 years were lost to follow up. **Conclusion:** Incidence of pediatric achalasia in the Netherlands is 0.10/100.000/year. Pneumatic balloon dilation is the predominant initial treatment of choice, however high relapse rates indicate the need for prospective studies comparing laparoscopic Heller's Myotomy and pneumatic balloon dilation for pediatric achalasia. Many patients are lost to follow up. Considering the long term risks of uncontrolled achalasia, there is a need for a standardized follow up regime to improve clinical outcome and transfer to adult care.

Su2064

Brain Processing of Rectal Sensation in Children With Functional Defecation Disorders

Ilan J. Koppen, Suzanne M. Mugie, Maartje M. van den Berg, Paul Groot, Michiel B. de Ruiter, Liesbeth Reneman, Aart Nederveen, Marc A. Benninga

Objectives and Study: The pathophysiology underlying functional defecation disorders (FDD) such as functional constipation (FC) and functional nonretentive fecal incontinence (FNRFI) is poorly understood. Both groups often report fecal incontinence (FI) and a lack of sensation of urge to defecate, although only FC is characterized by low defecation frequency, hard stools and fecal impaction. Impaired brain processing of visceral sensory stimuli might play a role in the loss of rectal sensation in both disorders. The aim of this study was to investigate the cerebral activity in response to rectal distension in children with FNRFI and FC. **Methods:** 10 patients with FNRFI (8 boys, mean age 13.7 years, range 12-17 years) and 15 patients with FC (8 boys, mean age 14.3 years, range 12-18 years) participated. Rectal barostat was performed prior to the fMRI scan. A stepwise pressure-controlled distension protocol was used to determine the pressure threshold for urge sensation. During acquisition of blood oxygenation level-dependent (BOLD) fMRI, subjects received 2 sessions of 5 stimulations consisting of repetitions of 30 seconds of rectal stimulation with previous defined threshold pressures, followed by 30 seconds of rest. Images were acquired on a 3Tesla MRI scanner with an 8-channel SENSE head receive coil. A T2*-weighted echo planar imaging sequence was acquired with: TR/TE=3000/30 ms, slice thickness=3.0 mm, voxel size=1.72 x 1.72 x 3 mm, with 40 axial slices covering the whole brain. Analyses were performed using SPM8 in Matlab, thresholded at p<0.001. Cerebral activation was defined as BOLD increase during rectal distension and cerebral deactivation as BOLD decrease during rectal distension. **Results:** Defecation frequency per week was 5.2 for FNRFI patients and 1.8 for FC patients. The mean number of FI episodes per week was 4.5 for FNRFI patients and 3.3 for FC patients. FC patients required a mean pressure of 18 mmHg above minimal distension pressure (MDP) to provoke urge sensation, for FNRFI patients this was 16 mmHg above MDP. During rectal distension, FC patients showed activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, inferior parietal lobule and putamen. In contrast, FNRFI patients showed no activation of brain areas during rectal distension. FNRFI patients showed significant deactivation in the hippocampus, parahippocampal gyrus, fusiform gyrus, lingual gyrus, posterior parietal cortex and precentral gyrus. While no significant deactivation was detected in FC patients. **Conclusion:** Children with FNRFI differ significantly from children with FC with respect to neural processing of rectal urge sensation in several brain regions. This confirms that FNRFI is a different clinical entity compared to FC.

Su2065

Antimicrobial Peptide Cathelicidin Inhibits Obesity in Diabetic Mice Via Inhibition of CD36 Fat Receptor Expression

Deanna H. Tran, Diana Hoang-Ngoc Tran, S Anjani Mattai, Samantha Ho, Aristea Sideri, Kyriaki Bakirtzi, Iordanis Karagiannidis, David Q. Shih, Simon W. Beaven, Hon Wai Koon

Background: Obesity is a global epidemic. It increases an individual's risk of developing diabetes, which is associated with debilitating complications. Despite medical advances, a new molecular target that can reflect the severity of obesity and diabetes in diagnosis or act as therapeutic agent is actively sought after. Cathelicidin is an antimicrobial peptide that possesses anti-inflammatory properties. Its expression is reduced in the skin of diabetic patients, but the overall metabolic role of cathelicidin in obesity and diabetes is not understood. We hypothesize that cathelicidin expression correlates to obesity and modulates fat mass and hepatic steatosis. **Materials and Methods:** (Human study) Human serum samples from non-diabetic and type II diabetic male and female patients of ages 18-70 were collected from UCLA. Cathelicidin levels in the serum samples were measured by ELISA. (Animal study) c57BL6 male mice were fed with a high fat diet for 8 weeks. After a streptozotocin injection to induce diabetes, the mice were fed with the high fat diet for 3 more weeks. Some groups were injected with cathelicidin and CD36 overexpressing lentiviruses. Fat and lean mass were measured by an EchoMRI machine. Liver steatosis was observed through Masson Trichrome staining. (In vitro study) Human mesenteric fat adipocytes were isolated from patients undergoing gastrointestinal procedures. Mouse 3T3-L1 differentiated adipocytes were used. **Results:** (Human study) Serum cathelicidin protein levels are significantly increased in obese, (BMI >30) non-diabetic patients, compared to non-diabetic patients with normal BMI values. Meanwhile serum cathelicidin protein levels are significantly lower in obese (BMI >30) type II diabetic patients than those of overweight (BMI 25-29.9) type II diabetic patients. (Animal study) Lentiviral overexpression of cathelicidin did not change the body weight but did reduce hepatic steatosis and decrease fat mass with corresponding increased lean mass of high fat diet-treated obese and streptozotocin-induced diabetic mice. Cathelicidin overexpression reduced mesenteric fat CD36 receptor mRNA expression and hepatic CD36 protein expression. Such changes were reversed by lentiviral CD36 overexpression. (*In vitro* study) Exposure of human mesenteric fat adipocytes, mouse 3T3-L1 adipocytes, and human HepG2 hepatocytes to cathelicidin significantly inhibited CD36 mRNA expression with reduced fat accumulation. Overexpression of CD36 reversed cathelicidin dependent inhibition of fat accumulation. **Summary:** Altering levels of circulating cathelicidin may indicate the development of obesity and diabetes. Cathelicidin inhibits the CD36 fat receptor and fat accumulation in adipocytes and hepatocytes, leading to reduction of fat mass and hepatic steatosis *in vivo*. Cathelicidin may be a novel therapeutic target against obesity in diabetic conditions.

Su2066

Immunoneutralization of Gastric Inhibitory Polypeptide (GIP) Attenuates Weight Gain in Mice

Michael O. Boylan, Patricia A. Glazebrook, Milos Tatalovic, M. M. Wolfe

Background: Past studies have indicated that GIP functions as an efficiency factor by enhancing both nutrient uptake and storage. Thus, a reduction in GIP signaling should prevent the development of obesity in mice fed a high-fat diet (HFD). **AIM:** To develop a safe and effective biological agent with the capacity to neutralize circulating GIP. **Methods:** A hybridoma library was created by fusing splenic B cells isolated from mice immunized with a GIP fragment to mouse myeloma SP2/0 cells. Supernates from hybridomas were screened for GIP-specific monoclonal antibodies (mAbs) using a specific ELISA. To identify GIP-neutralizing mAbs, positive supernates were analyzed with a cell-based reporter assay. The mAbs were then purified using protein A agarose, and their effects on intraperitoneal (*i.p.*) glucose tolerance, oral glucose tolerance (OGT), and diet-induced weight gain were evaluated. For *i.p.* glucose tolerance tests (IPGTTs), mAbs (30 mg/kg body weight [BW]) were administered *i.p.* 60 min before *i.p.* administration of glucose (18 mmol/kg BW) and human GIP (2.5 nmol/kg BW). For OGT tests, mAbs (30 mg/kg BW) were injected *i.p.*