but significantly decreased mean liver weight and the mean liver-to-body weight ratio compared to the vehicle group. Furthermore, treatment with SOLI improved glucose metabolism as evidenced by reduction of whole blood glucose levels. These changes were accompanied with a significant improvement in the histological score of NASH (NAFLD Activity Score [NAS]). There was no difference in triglycerides between the SOLI treated and vehicle treated mice. MCP-1 and MMP9 mRNA expression levels were significantly decreased in the liver. CONCLUSION: SOLI has demonstrated potential anti-NASH and anti-hyperglycemic effects in the present study. Because NAS is a clinical endpoint used to assess the treatment of NASH, these observed changes in the treatment group suggest potential for SOLI in the treatment of NASH.

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Systematic Association Study of Exonic Variants in Idiopathic Achalasia

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Idiopathic achalasia represents a severe disorder of the lower esophageal sphincter (LES) and esophageal body with a lifetime prevalence of 1:10,000. The disease is characterized by the degeneration of neurons in the myenteric plexus leading to the development of a megaesophagus with irreversible loss of LES function. On the etiological level, achalasia is a multifactorial disorder with environmental and genetic factors being risk-associated. By testing markers in immune-relevant loci using the Illumina's Immunochip, we already identified strong association signals reaching genome-wide significance within the HLA-DQ complex indicating that autoimmune processes contribute to the etiopathogenesis of achalasia. The aim of the present study was to determine the role of exonic variants in the development of achalasia. We performed an association study using Illumina's Exomechips, which have been developed based on the data of 12,000 exomes. The chip contains more than 240,000 - mainly functional-relevant - markers. We genotyped 674 patients with idiopathic achalasia and 2,316 population-based controls from Central Europe and after quality control (QC) steps 106,417 markers remained for association testing. Our analysis yielded a strong association signal within the HLA region ($P < 10\text{-}08$). We carried out a conditional analysis adjusting for the variants within the HLA-DQ complex identified before in the Immunochip study. This analysis revealed that the HLA signal on the Exomechip is not independent of the already known achalasia risk variants within this region. Next, we focused on variants outside the HLA region and identified 139 markers reaching a $P < 10\text{-}03$. In total, 31 of the 139 markers are common variants (MAF controls > 5%, best hit P = 1.55x10-05). In contrast, 49 are low-frequent markers (MAF controls < 5%) and the minor allele is more frequent in patients compared to controls (best hit P = 2.57x10-06). Furthermore we used the INTERSNP-RARE software to test if there is an enrichment of rare associated variants within specific genes. This analysis revealed an overload within the genes EDNRB and PLBD1 ($P < 8x10\text{-}05$). The present study provides evidence that low-frequent and common exonic variants play a role in the pathophysiology of achalasia. Currently, we genotype a subset of the associated variants identified in this study in an independent sample of approx. 400 achalasia patients and 1,000 controls in order to confirm the contribution of these variants to the development of achalasia.

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Achalasia As an Autoimmune Inflammatory Disease

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Introduction: Achalasia is a disease of unknown etiology. Several hypothesis exploring genetic, immune, and infectious disease mechanisms have been proposed. Degenerative alterations and the loss of myenteric plexus associated with an inflammatory infiltrate, support the hypothesis that achalasia is a chronic inflammatory process with a possible autoimmune mechanism. Aim: The purpose of this study was to analyze local and systemic inflammatory pattern in patients with primary achalasia. Methods: Specimens from LES muscle were harvested during laparoscopic myotomy of idiopathic achalasia patients diagnosed by high resolution manometry and compared with biopsies of esophagectomy cases due to squamous cell carcinoma of the upper third of the esophagus as controls. Histological characteristics were classified and immunohistochemical analysis was performed including proteins involved in extracellular matrix turnover: MMP9 and TIMP-1; proinflammatory cytokines: IL-22, IL-17 and IFNγ; profibrogenic cytokines: TGF-β1, IL-4 and IL-13; proteins involved in apoptosis: FAS; regulatory T cells (Tregs): CD25/Foxp3 and regulatory B cells (Bregs): CD20/IL-10. Peripheral blood T-cells of achalasia patients and samples of age-matched healthy donors were analyze by flow cytometric immunophenotyping (Th22: CD3+/CD4+/CD161-/IL-22+; Th17: CD3+/CD4+/CD161+/IL-17A+; Th2: CD3+/CD4+/CD14-/IL-4+; Th1: CD3+/CD4+/CD14-/IFN-γ+ and Tregs: CD3+/CD4+/CD25hi/Foxp3+). Erythrocyte sedimentation rate was measured in all acalasia patients before myotomy. Antimyenteric plexus antibodies directed against enteric neurons in sera were evaluated and compared with 10 healthy age-matched donors as controls. Results: 19 patients with primary achalasia and four controls were evaluated. The analysis with high-resolution manometry in the achalasia patients showed 47% type I, 37% type II and 16% type III. In the histopathology analysis of the myenteric plexus, 51% of the cases had capillaritis, 23% plexitis, 16% nerve hypertrophy, 7% venulitis and 3% fibrosis. The achalasia cases had a significant increase in the expression of proteins involved in extracellular matrix turnover, proinflammatory cytokines, profibrogenic cytokines, proteins related to apoptosis, Tregs and Bregs compared to controls ($p<0.001$). The peripheral blood T-cells analysis of the achalasia patients had a significant increase in the percentage of Th22 (6x); Th17 (6x); Th2 (4x) and Th1 (2x) compared with healthy controls ($P<0.01$). In 6/6 (100%) of the achalasia patients had positive antimyenteric plexus antibodies compared with none of the healthy controls. Erythrocyte sedimentation rate was elevated in 30% of the acalasia patients. Conclusion: Our results indicate that achalasia is an autoimmune mediated disease with important local inflammation that also produces secondary systemic inflammation.

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Hydraulic Dilation in Idiopathic Achalasia Using the EsoFLIP Dilation Balloon: A Prospective Cohort Study

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Background: Pneumatic dilation is often used in achalasia patients. Fluoroscopy is used during dilation to position the balloon at the esophagogastric junction (EGJ) and to visualize the effect of dilation but has the disadvantage of radiation exposure. Distensibility of the esophagus is the compliance of the luminal wall at a certain point and can be used to assess the effect of dilation and possibly the risk of perforation. Unfortunately, distensibility cannot be measured during pneumatic dilation. A new hydraulic dilation balloon, the EsoFLIP, is able to visualize the shape of the balloon in vivo and measures diameter, pressure and distensibility during the dilation procedure. Aim: To evaluate technical feasibility and safety of the 30mm EsoFLIP hydraulic dilation balloon in patients with a new diagnosis of achalasia. Methods: Consecutive patients with newly diagnosed achalasia were dilated on two separate days using the EsoFLIP balloon under endoscopic visualization. Patients were contacted one week, one month and three months after dilation. Technical success (placement at the EGJ and successful dilation while measuring diameter, pressure and distensibility), clinical success and major complications were evaluated. Results: Nine patients (4 male [44%], median age 40 years, range 28-62) were included in the period August-December 2013. Patients were subjectively symptomatic for a median of 9 months (range 3-23) prior to dilation. Technical success was achieved in all cases. Gradual inflation showed that the balloon had a strong tendency to move proximally or distally but in vivo imaging enabled precise placement at the EGJ. On day one, the median minimal diameter (mm) of the GEJ before and after dilation were 9.5 (range 7.2-12.9) and 16.3 (range 13.4-21.4), respectively. On day two, these diameters were 13.1 (range 8-15.2) and 16.7 (range 14.5-18.6), respectively. Median difference in diameter before the first and after the second dilation was 7.3 (range 3.2-9.2). Median pressures (mmHg) used during the first and second dilation were 551 (range 310-1130) and 603 (range 390-815), respectively. Median esophageal distensibility (mm2/mmHg) on the first day before and after dilation were 1.2 (range 0.2-2.2) and 10.4 (range 0.8-20.1), respectively, while on the second day this was 1.7 (range 1-4.3) and 7.3 (range 3.3-29.3). Median difference in distensibility before the first and after the second dilation was 6 (range 2-28). No major complications were seen. Two patients (22%) reported recurrent dysphagia and laparoscopic Heller myotomy was performed. Conclusion: Dilation with the EsoFLIP balloon in achalasia is feasible and safe. In vivo imaging of the balloon shape facilitates placement of the balloon at the EGJ and esophageal distensibility measurements allow for a personalized dilation regimen, thereby possibly improving effectiveness and safety.

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Novel Impedance Measurements to Assess Bolus Retention in Achalasia

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Background: The aim of this study was to develop new techniques to assess bolus retention in achalasia using high-resolution impedance manometry (HRIM). In addition, we also sought to determine whether these metrics were associated with symptom severity. Methods: 20 achalasia patients [10 males, ages 21-79] were prospectively evaluated with HRIM utilizing a 200 ml saline challenge protocol in upright position. These patients also underwent a timed barium esophagram (TBE) within 1 month using 200 ml of barium. A metric to simulate bolus retention on TBE was created by determining the impedance bolus height (IBH) at 30 second time intervals along the 5 minute protocol. IBH was evaluated using 2 methods (Figure): 1) color impedance topography using nadir impedance in the distal esophagus as the threshold for the liquid interface with mucosa/air and manually measuring the impedance bolus height with the smart-mouse tool and 2) the spatial impedance variation plot that depicts the change in impedance along the axial plane of the HRIM catheter with the deflection point of the nadir impedance being used as the liquid interface with mucosa/air. The IBH data was utilized to develop 3 different outcome measures that focused on bolus retention and rate of emptying: 1) IBH at 5 minutes [presented as height in cm], 2) Impedance Bolus Area over 5 minutes [presented as area by cm-sec] and 3) time to ½ IBH over the 5 minutes [presented as time in seconds]. The correlation between these parameters and symptom severity was assessed using the Impaction Dysphagia Questionnaire (IDQ; 10 questions with 6 point likert scale (range 0-50)). Each measurement was made by two blinded reviewers and the agreement between the two techniques for determining IBH was assessed. Results: The correlation between the color impedance topography method and the spatial impedance variation plot approach for measuring IBH was excellent at both the 1 minute (R=0.99) and the 5 minute (R=0.99) time point. The range of discrepancy at 1 minute was 0 to 1.9 cm and at 5 minutes was 0 to 1.5 cm. The correlation between IDQ score and the three metrics developed using impedance as an outcome metric to assess bolus retention in achalasia were similar to barium column at 5 minutes on TBE (IBH at 5 minutes- IDQ, R=0.40; IBA-IDQ, R=0.48; ½ time IBH-IDQ, R=0.40; TBE at 5 minutes-IDQ, R=0.35). Conclusions: HRIM can be leveraged to visualize and assess bolus retention dynamics in achalasia in a fashion that is similar to the standard TBE protocol. Additionally, these metrics have a fair correlation with symptom severity and future studies should focus on whether or not these tools can be modified and validated to predict outcome in achalasia.