Common variable immunodeficiency-gastrointestinal problems

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Gastrointestinal disease: three studies

1. Gastrointestinal symptoms and pathology
2. Gut microbial composition in fecal samples and their link to inflammatory phenotype
3. Liver transplantation in CVID

Gastrointestinal disease in CVID

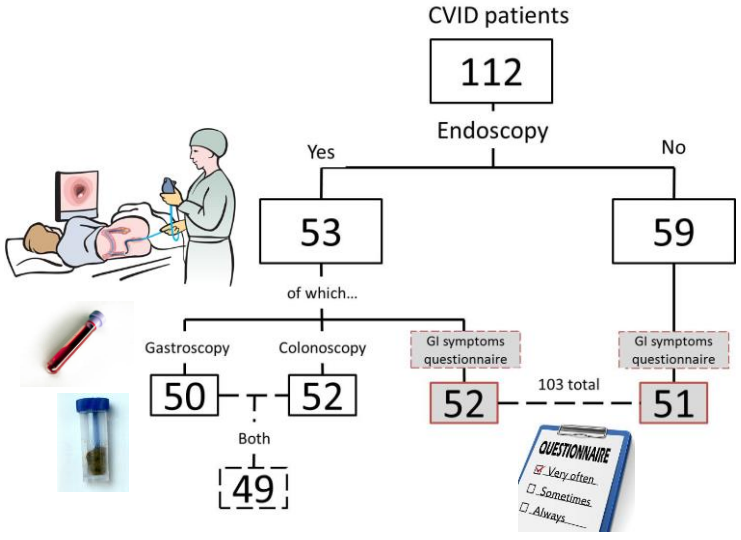
- The most common gastrointestinal symptom is intermittent or persistent diarrhoea reported in 20-60% of cases
- The prevalence of gastrointestinal disease varies: 20-60%
  - e.g. IBD-like, celiac-like diseasee and microscopic colitis
- No clear treatment guidelines

Paper 1

- Aim of the study
  - To characterize the true prevalence of GI symptoms and pathology in CVID patients by including patients irrespective of symptoms

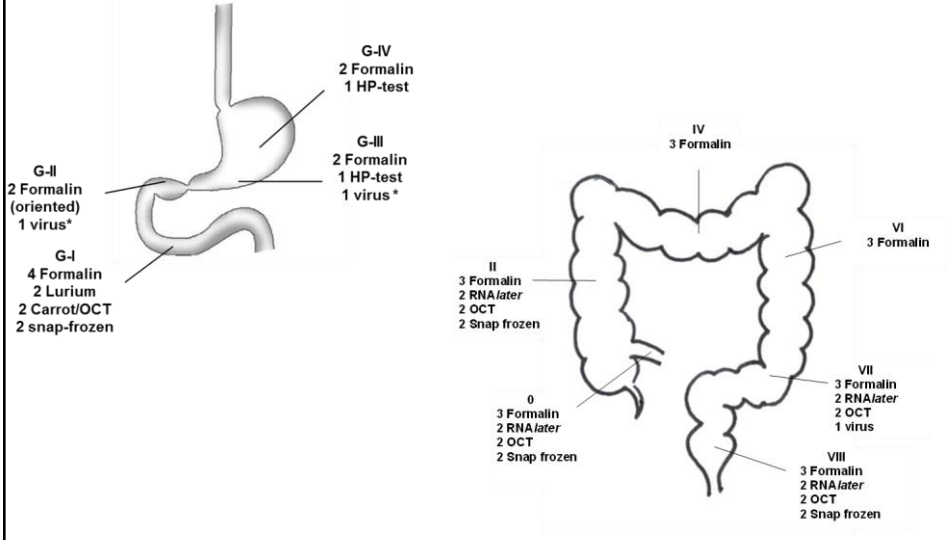
    ….as well as linking our findings to clinical, immunological and genetic features.

Revealing the true prevalence of GI pathology in CVID



Jørgensen et al, Am J Gastroenterol. 2016.

Overview of the biopsy protocol



Patient characteristics

	Total (n=104)
Male, n (%)	**53 (51)**
Age, mean years (range)	**47.5 (19-83)**
Splenomegaly, n (%)	**47 (45)**
Organ specific Autoimmunity, n (%)	**20 (19)**
Autoimmune Cytopenia, n (%)	**22 (21)**

Jørgensen SF, *Am J Gastroenterol*.,2016.

Symptoms from GI tract in the study group

Symptoms	CVID %, n (total)
Bloating	34%, 34 (99)
Diarrhoea	26%, 26 (102)
Constipation	13 % , 13 (102)
Pain	30% 31 (103)
Satiety	14% 14 (100)

Jørgensen SF, *Am J Gastroenterol*.,2016.

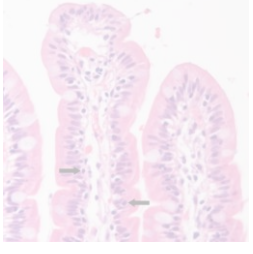
Histopathological finding	Number of patients, n (%)	
Increased intraepithelial lymphocytes **(IEL)** total	33 (62%)	
Descending part of duodenum	**24 (48%)**	**←*Celiac-like disease***
Reduced number of plasma cells	**33 (62 %)**	
Lymphoid hyperplasia	**20 (38 %)**	
Gastric metaplasia in duodenal bulb	13 (26 %)	
Fibrosis in the gastric mucosa	13 (26 %)	
Intestinal metaplasia in gastric mucosa	6 (12 %)	
Subacute inflammation	2 (4%)	
Chronic/Chronic active inflammation, total	24 (45%)	
Stomach	20 (40%)	
Colon	11 (22%)	
Atrophic gastritis	9 (18%)	
GVHD-like	1 (2%)	
Eosinophilic inflammation	4 (8%)	
Lymphocytic enteritis/colitis	4 (8%)	
Collagenous enteritis/colitis	3 (6%)	
Granulomatous inflammation	3 (6%)	

Jørgensen SF, *Am J Gastroenterol*.,2016.

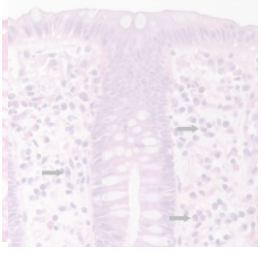
Main histopathological findings

- Chronic/Chronic active inflammation in 45%

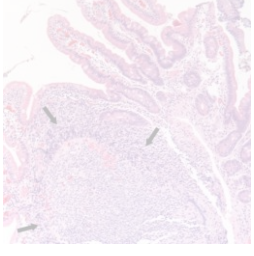
Celiac like disease 46 %



Reduced number of plasma cells 62%



Lymphoid hyperplasia 38 %



- No association with GI symptoms
- Reduced plasma cells in GI biopsies were associated with markers of systemic inflammation and immune activation in blood

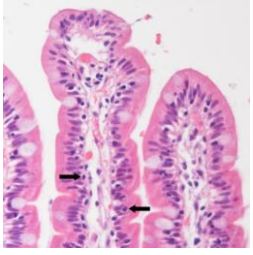
Jørgensen SF, *Am J Gastroenterol*.,2016.

Celiac like disease in CVID

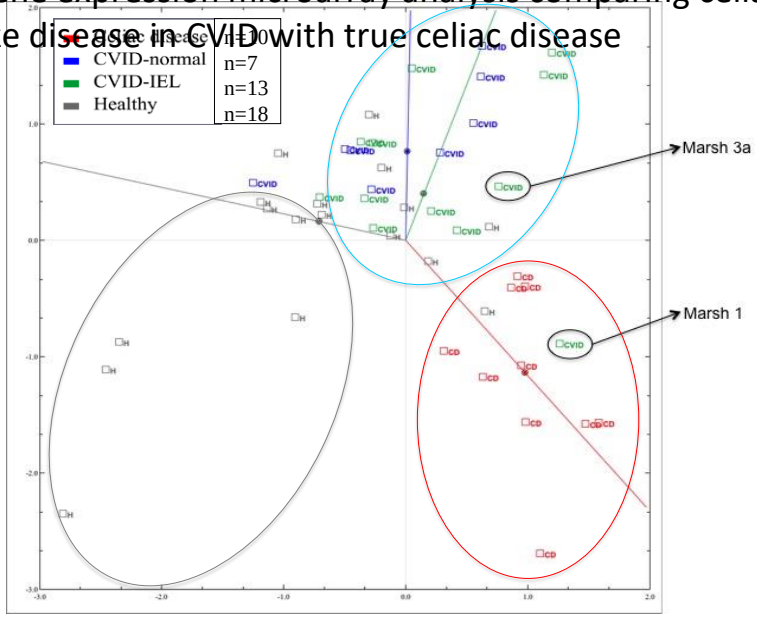
- Question:

  Are the findings of celiac like disease in CVID a result of gluten allergy or is there another mechanism in leading to these histopathological findings in CVID?

Celiac like disease 46 %



Gene expression microarray analysis comparing celiac-like disease in CVID with true celiac disease



Jørgensen SF, *Am J Gastroenterol*.,2016.

The HLA genotype HLA DQ2.5 and HLA DQ8 in our CVID cohort

- 42 patients (endoscopy group) had HLA DQ2.5 and HLA DQ8 data available
  - 13 patients carried the **HLA DQ2.5** phenotype (26%) and were not associated with increased IEL in duodenal pars descendens (Fisher exact test, P=1)
  - 14 patients carried the **HLA DQ8** phenotype (26%) and were not associated with increased IEL in duodenal pars descendens (Fisher exact test, P=0.75).

GI infections

- 1 *Clostridium difficile*
- 1 C*ryptosporidium*
- 1 *Campylobacter jejuni* infection (stool culture)
  - few pathological findings on endoscopy
  - only the patient with C*ryptosporidium* had significant symptoms
- *H. pylori*
  - Rapid test: 3 out of 50 patients positive
  - Immunohistochemical staining: 1 patient positive (also positive rapid test)

Jørgensen SF, *Am J Gastroenterol.*,2016.

GI infections: CMV, EBV

- CMV/EBV

  PCR: duodenum (n=41), ventricle (n=40) and colon (n=46)

  – Positive EBV: 12 biopsies - 10 patients - ; 6 stomach, 5 duodenum and 1 colon biopsy
  – Positive CMV: 6 biopsies - 4 patients -; 2 from each site

  None of these positive specimens were positive on immunohistochemistry (CMV) or in situ hybridization (EBV).

  There was no association between histopathological findings or symptoms with positive CMV and/or EBV.

Jørgensen SF, *Am J Gastroenterol*.,2016.

GI infections: norovirus

- A recent study suggested chronic norovirus infection as cause of severe CVID enteropathy in 8 CVID patients
  - Duodenal biopsies
  - Fecal screening
  - Villous atrophy
- We screened for norovirus,rotavirus and astrovirus by PCR in GI biopsies from 3 sites
- All biopsies were negative for norovirus and astrovirus
  – One biopsy was positive for rotavirus

Woodward et al, Am J Gastroenterol. 2015.

Summary

- Symptoms: bloating (34%), pain (30%) and diarrhoea (26%)
- The most frequent histopathological:
  - increased IEL in descending duodenum ~ *celiac-like disease*~ (48% of patients)
  - lymphoid hyperplasia (38%)
  - decreased plasma cells in GI tract mucosa (62%)
- GI infections including norovirus were rare

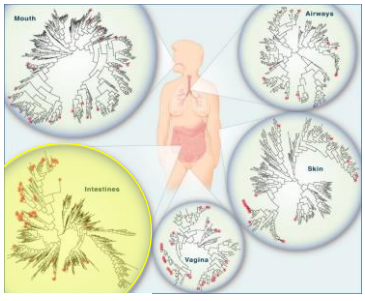
Summary Paper 1

- CVID patients with *celiac-like disease* and celiac disease are different disease entities as assessed by gene expression analysis
- A large proportion of CVID patients had inflammation in the gastrointestinal tract; a potential source of gut leakage

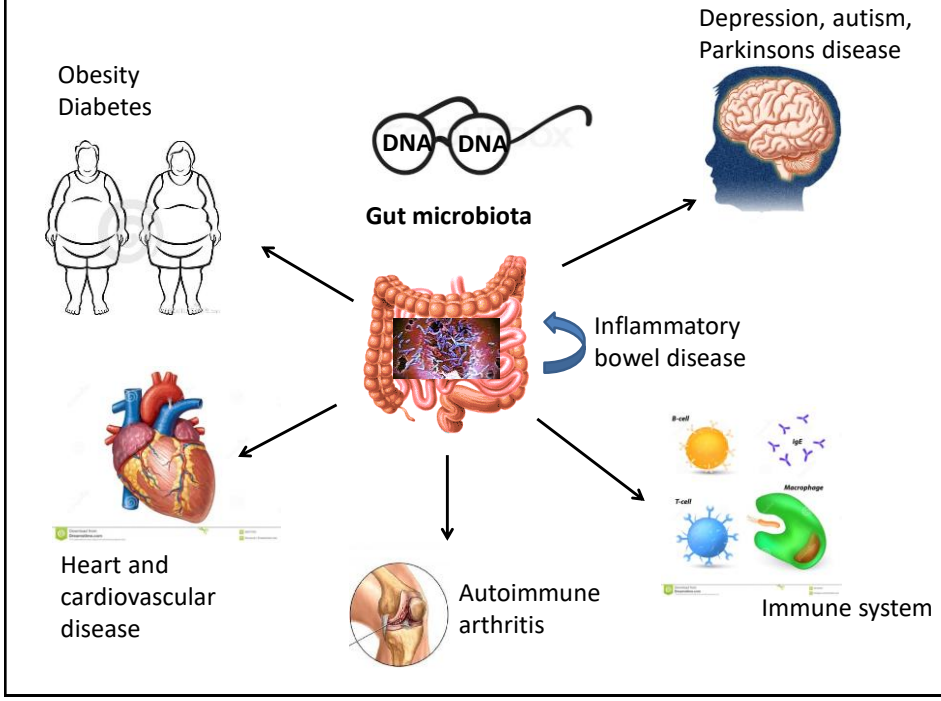
Paper 2, Gut microbiota in CVID

- Humans are colonized with 100 trillion bacteria

Gut microbiota
All microorganisms that reside in the gut of the host in question:
bacteria, viruses, archaea and some eukaryotes.



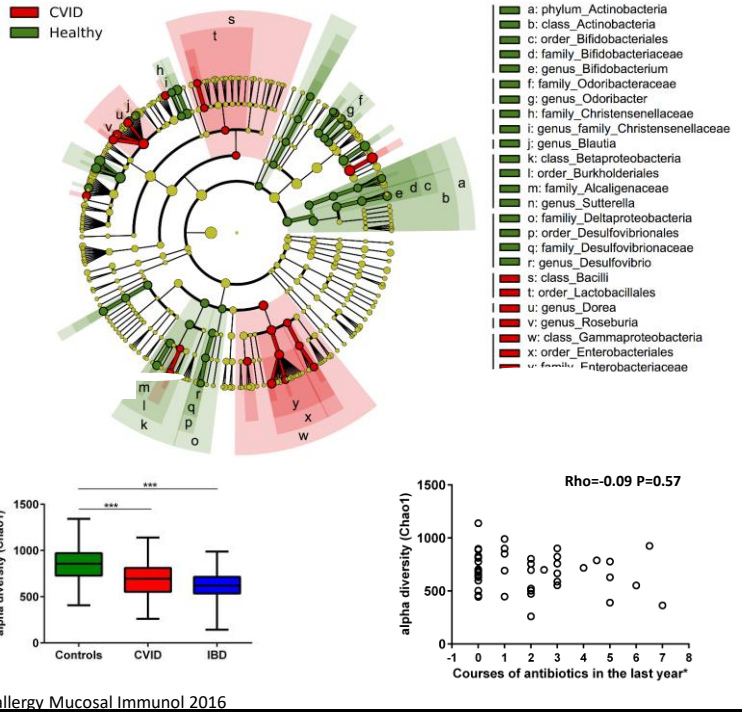
Lee KL, Science, 2010



Hypothesis and methods

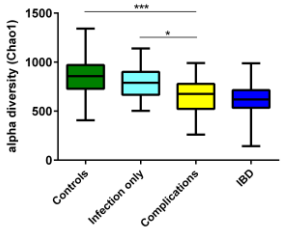
- There is a difference in the gut microbiota:
  - between healthy and CVID patients
  - clinical and immunological subgroups within CVID
- We performed a cross-sectional study of the gut microbiota in 44 CVID patients, 263 controls and 45 disease controls IBD

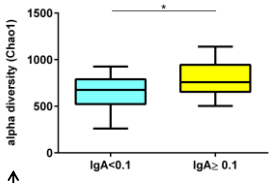
Gut microbiota in CVID



Jørgensen SF et al, J allergy Mucosal Immunol 2016

Altered gut microbiota associates with "Complications" subgroup and IgA levels





number of bacteria

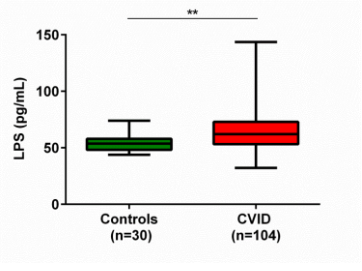
CVID subcategories:
1. **Infection only** → normal survival
2. **Complications** → reduced survival

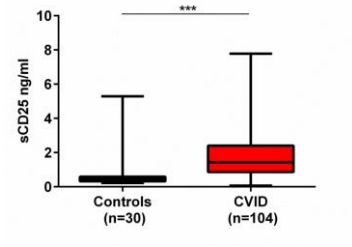
Inflammatory and autoimmune complications

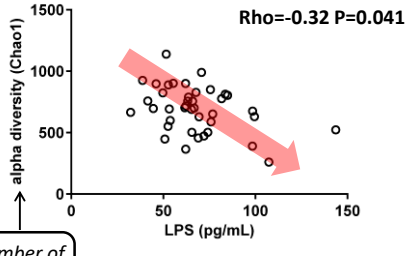
***P<0.001, **P<0.01, *P<0.05

Jørgensen SF et al, J allergy Mucosal Immunol 2016

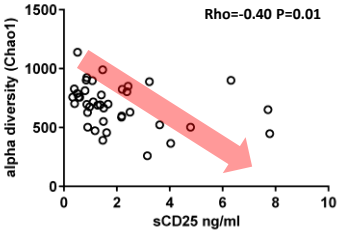
Increased lipopolysaccharide (LPS) in CVID patients correlates with altered gut microbiota







number of bacteria



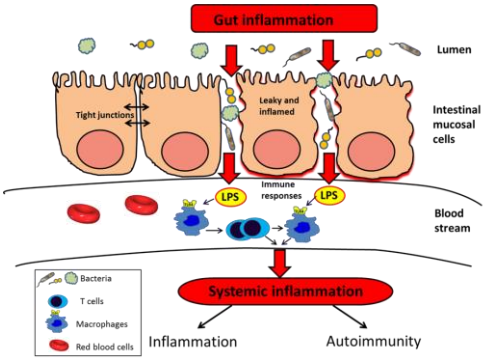
***P<0.001, **P<0.01, *P<0.05

Jørgensen SF et al, J allergy Mucosal Immunol 2016

Summary Paper 2

- Large differences in gut microbiota profile between CVID patients and controls
  - without obvious associations to the use of antibiotics

- Decreased gut microbial diversity in CVID patients was associated with markers of gut leakage and systemic inflammation



Livertransplantations (LTX) in patints with primary antibody deficiency (PAD)

- Patients with CVID may develop severe liver disease

- There has been a reluctance to perform LTX in these patients
  - lifelong immunosuppression
  - fear of severe infections

Aim of paper 3:

present our experiences of LTX in patients with PAD with an emphasis on complications and outcome.

Clinical characteristics and liver disease in 6 patients with primary antibody deficiency before liver transplantation

Patient	Age	Sex	Primary immunodeficiency	Cause of liver transplantation	Histology of native liver	MELD* score at time of tx**	Year of tx
1	19	M	CVID	Hepatitis C – liver failure	Cirrhosis with portal and lobular inflammation with interphase activity, consistent with end-stage HCV infection Loss of small intrahepatic bile ducts and lymphocyte-dominant cholangitis of larger bile ducts Chronic cholecystitis with pyloric metaplasia	16***	1993
2	47	M	XLA	Hepatitis C – liver failure	Cirrhosis with portal and lobular inflammation with interphase activity, consistent with end-stage HCV infection	11***	1998
3	57	F	CVID	Acute portal vein thrombosis and liver failure	Portal and septal fibrosis, nodular parenchyma suggestive of nodular regenerative hyperplasia Multifocal ischemic parenchymal necrosis and portal vein thrombosis	21	2009
4	54	M	CVID	Respiratory failure due to hepatopulmonary shunting	Nodular regenerative hyperplasia, portal, centrilobular and perisinusoidal fibrosis, lymphocyte-dominant portal and lobular inflammation Focal circulatory changes with sinusoidal dilatation and hepatocyte injury Chronic cholecystitis	8	2011
5	62	M	CVID	Respiratory failure due to hepatopulmonary shunting	Nodular regenerative hyperplasia Portal and lobular inflammation with parenchymal granulomas	15	2011
6	40	F	CVID	Liver failure	Nodular regenerative hyperplasia Portal and septal fibrosis, portal and lobular inflammation	14	2013

Jørgensen SF et al, J allergy Clin Immunol. 2017.

Patients characteristics Prior to LTX

- All patients had recurrent bacterial airway infections and bronchiectasis
- All CVID patients had splenomegaly and lymphadenopathy
- Other non-infectious complications included
  - granulomatous inflammation (2 CVID)
  - organ-specific autoimmune diseases (3 CVID)
  - autoimmune cytopenias (3 CVID)
  - enteropathy (3 CVID).

Patient	Complications							
	Rejection	Viral infection	Bacterial infection	Parasitic infection	Fungal infection	Malignant or premalignantlesions	Miscellaneous	Survival (years)
1*	No	No	No	No	Fatal A. fumigatus brain abscess	No	None	0,1
2*	Yes	CMV pneumonia	Sepsis*	Fatal C .parvum infection	No	No	Inflammation of upper GI-tractus. Autolytic liver with portal fibrosis and bile stasis	1,8
3**	No	No	Recurrent C. difficile** colitis Recurrent UTI S. enteritis and pyelonephritis***	No	No	No	Monoclonal B-cell of uncertain significance	7
4**	No	Ulcerative CMV disease of GI-tract#	S. aureus pneumonia C. difficile colitis	No	A. fumigatus pneumonia	Carcinoma in situ of the skin in head, leg and penis	Bilateral lung emboli. A-V malformations in lungs	5
5**	No	No	Bacterial pneumonia and sepsis*	No	PCP pneumonia Candida esophagitis	No	Moderate renal failure Respiratory failure	5
6**	No	No	Recurrent bacterial vaginosis	C. parvum intestinal infection	No	No	Colitis and cytopenia of all 3 lineages of unknown cause – glucocorticoids sensitive	3

Treatment
*glucocoricoids, cyclosporine A or tacrolimus
**glucocoricoids, tacrolimus and mycophenolate

Jørgensen SF et al, J allergy Clin Immunol. 2017.

Review of the literature on liver transplantations to primary immunodeficiency patients

Source	Patients: Age	Immunodeficiency	Hepatitis C	Rejection	Infection	Miscellaneous	Outcome
Smith et al.[3] 1995	1: 41 years	CVID*	Yes	Yes	Sepsis, HCV** recurrence	No	Dead 23 m post LTX#
	2: 30 years	CVID	No	Yes	Pneumonia	No	Dead 15 m post LTX
Hadzik et al.[2] 2000	3: 18 years	CD40L deficiency	No	Mild GVHD§ after HSCTX§§	No	HSCTX 34 d post LTX	Alive 14 m post LTX
Razvi et al.[3] 2001	4-9: 4 of 6> 21 years old	Various primary antibody-deficiencies	Yes	?	?	?	4 of 6 patients died
Gow et al.[4] 2002	10: 43 years	CVID	Yes	Yes	No	HCV recurrence, liver failure	Alive 5 y follow-up.
Rodrigues et al.[5] 2004	11: 13 years	CID§§§	No	Chronic GVHD	No	LTX 6 w after HSCTX	Alive 55 m post LTX
	12: (0.8-17.9)	CD40L deficiency	No	No	Fatal C. parvum	LTX 2 m after HSCTX	Dead
	13: (0.8-17.9)	CVID	No	No	Fatal C. parvum	No	Dead
	14: (0.8-17.9)	CD40L deficiency	No	No	Fatal C. parvum	LTX x 2	Dead 4 m post LTX
Murakawa et al.[6] 2012	15: 20 years	CVID	No	Yes	No	LTX x 2	Alive 2 y post LTX
	16: 9 years	CVID	No	x 5	No	No	Alive 5 y post LTX
Chen et al.[7] 2013	17: 17 years	CVID	No	No	Fatal aspergillosis	No	Dead 33 d post LTX
Montalti et al.[8] 2014	18: 21 years	CVID	Yes	No	HCV recurrence	Anastomotic biliary stricture, Roux-en-Y	Alive 3.5 y post LTX
	19: 53 years	CVID	No, HBV	Yes	CMV reactivation	No	Alive at 1 y post LTX

Jørgensen SF et al, J allergy Clin Immunol. 2017.

Discussion - increased survival PAD

- Changes in immunosuppressive drug regimens from the 1990s to 2009-2013 e.g. lower doses of glucocorticoid
- A general improvement of results after LTX, regardless of diagnosis
- The switch of the major indication for LTX from chronic progressive HCV infection to idiopathic liver disease like NRH

Conclusions

- The combination of PAD and LTX seemingly lead to uncommon opportunistic infections
  - (C. parvum, invasive aspergillosis)
  - We advise that anti-fungal prophylaxis include drugs active against filamentous fungi in PAD patients undergoing LTX.
- **Patients with primary antibody deficiency and liver failure should be considered for liver transplantation and not rejected because of their immunodeficiency alone**

Take home message

- GI inflammation is common in CVID, but does not necessarily correspond with symptoms
- Increased IEL in duodenal biopsies may represent inflammatory processes not induced by gluten
- A reduced gut microbial diversity is associated with inflammatory phenotype
- CVID patients should be considered for liver transplantation

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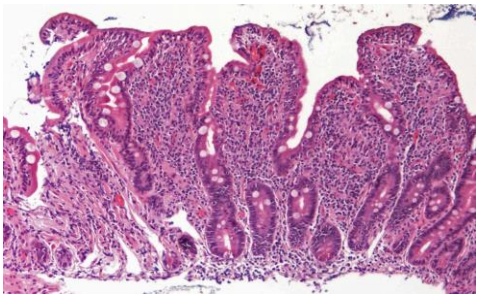
Case report 1

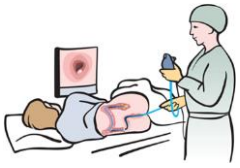
- Man, aged 56, referred in May 2016
- Sarcoidosis, 2008
- Pneumonia, February 2016
- 20 kg weight loss since September 2015
  - Weight: 61 kg, height 178 cm, BMI: 19
- Watery diarrhoea, 4x

Case report 1

- CT abdomen: no malignancy
- Upper endoscopy: athrophic mucosa?
- duodenal biopsy:
  - increased intraepithelial lymphocytes
  - Crypt hyperplasia and villous atrophy. Marsh grade 3b-3c: no plasma cells



Case report 1



- Lower endoscopy: described as normal.
  Biopsy: light focal inflammation and increased apoptosis in the cryptheepithelial tissue: extremely few plasma cells, resembles GVHD, CMV negative.
- Fecal screening for pathogenic gut bacteria: negative
- HLA DQ2 and HLA DQ8 are negative

Case report 1

- IgG: 1,2
- B cell subpopulations:
  - reduced number and % of B cells
  - Increased naïve and Cd21 low
  - reduced, transitional, class switched and plasmablasts
- Reduced vitamin B12, B9, vitamin C, D, E, K, zink, calsium, Pottasium

Case report 1

- Something we have forgotten?
- Positiv norovirus

What to do

- Immunoglobulins
- Nutriontal support
- Gluten free diet?
- Immunosuppressiva?
- Antiretorviral treatment?

What we did

- No gluten free diet
- Nutrional support
- High dose Immunoglobulins
- No Ribavarin

Outcome

- Stabilised weight
- Still norovirus positive
- No need for ribavirin (yet?)
- Intermittent diarrhoea

Case 2

- Female, 41 years old
- Recurrent respiratory tract infections
- Chronic sinusitis, bronchiectasis
- Enteropathy
- Joint pain
- Splenomegaly
- Lymphadenopathy
- Hypothyrosis

Case 2

- Progressive liver disease, cirrhosis
- Ascites
- Bacterial peritonitis
- Oesophageal varices
- Portal hypertension
- Very large spleen
- Pain/discomfort
- Low quality of life

Case 2

- ASAT 61, ALAT 44, ALP 250, bilirubin 56, INR normal
- CT abdomen: liver cirrhosis with portosystemic shunting

Case 2

- Liver transplantation, January 2013
- Treated routinely with immunosuppression according to protocol
- Some post operative complications
- After prednisolon were stopped: diarrhoea and joint pain returned
- Coloscopy: focal ulcerations of unknown origin
- Restarted steroids: the diarrhoea disappeared

Case 2

- 2016 worsening of diarrhoea. Still ulcerations in Colon (MB. Crohns?)
- Could not get below 15 mg prednisolone
- Started Humira (anti-TNF)
- Improved already after the first dose
- Reduced Prednisolon to 5 mg
- After this no diarrhoea, no joint pain
- Put on 15 kg of weight in 9 months

Thank you for your attention

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