Dr. Sevcan İMAM

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Çocuk Gastroenteroloji, Hepatoloji ve Beslenme

2018

OLGU

- K.E. 
- 11 yaş, erkek hasta
- Yakınma:
  - Uzamış ishal
  - Kakada kan görme

ÖYKÜ

- Son 2 aydır aralıklı ishal geçirme öyküsü mevcut olan hasta gaytası üzerinde kan görmesi nedeni ile DEUTF çocuk acil servise getirilmiş.
- Bu şikayetlerle acil serviste değerlendirilen hastanın ishalinin haftada 3 gün sıvı dışkılama şeklinde olup sonrasında normale döndüğü, ishalinin açık sarı renkli mukussuz, günde 1-2 kez, bol miktarda olduğu ateşin eşlik etmediği ancak yeni başlayan gayta üzerinde kan görme şikayeti olduğu öğrenildi.

ÖYKÜ

- Hastanın acil servis değerlendirmesinde karaciğer fonksiyon testlerinde bozukluk saptanmış olup hasta tanı, ileri tetkik ve tedavi amacıyla çocuk gastroenteroloji departman polikliniğe yönlendirilmiş.
- Hastanın şikayetlerine eşlik eden son iki ayda kilo kaybı öyküsü mevcut. Hastanın kronik hastalık, ilaç kullanımı ve hastaneye yatış öyküsü yok.

ÖZGEÇMİŞ

- **Prenatal :**
  - 30 yaşında G2P2A0K0 gestasyonel diyabeti olan anne
  - Annenin gebelikte ilaç kullanım öyküsü yok.
  - Gebelik düzenli takip edilmiş.
- **Natal :**
  - Miad NSVY ile 3180 gr
- **Postnatal:**
  - Doğar doğmaz ağlamış. Oksijen ihtiyacı olmamış.
  - Motor – Mental gelişme: Yaşına uygun.
  - Aşıları Sağlık Bakanlığı takvimine göre tam.
  - Bilinen alerjisi yok.
  - Beslenme: 2 yaşına kadar anne sütü almış, 6. ayda tamamlayıcı beslenmeye geçilmiş.

SOYGEÇMİŞ

- Anne; 40 yaşında, sağ sağlıklı
- Baba; 40 yaşında, sağ sağlıklı
- Anne baba arasında akrabalık yok
- Kız kardeş; 8 yaşında, sağ ve sağlıklı

Ağırlık:	27,5 kg (5,8p -1,57 SDS)
Boy:	142 cm (45,2p -0,12 SDS)
VKİ:	15,09(9,3p -1,32 SDS)
Boya göre vücut ağırlığı(Waterlow)	%71(o)
Yaşa göre ağırlık(Gomez)	%73(o)
Yaşa göre boy	%97
Ateş:	36,3°C (timpanik)
Nabız:	78/dk (ritmik)
Solunum sayısı:	16/dk (düzenli)
Kan basıncı:	100/60 mmHg

FİZİK MUAYENE

- Genel durumu iyi, bilinci açık, **soluk ve halsiz** görünümde
- **Cilt:** Olağan, döküntü yok
- **Baş – boyun:** Orofarinks doğal. Timpanik membran ve dış kulak yolu bilateral olağan. Trakea orta hatta, venöz dolgunluk yok. Patolojik lenf nodu büyüklüğü saptanmadı.
- **Kardiyovasküler Sistem:** Kalp sesleri ritmik. Ek ses ve üfürüm duyulmadı.
- **Solunum Sistemi:** Her iki hemitoraks solunuma eşit katılıyor. Ral ve ronküs duyulmadı.
- **GİS:** Batın rahat, defans ve rebound yok. Bağırsak sesleri normoaktif. Karaciğer nonpalpabl, traube açık, dalak nonpalpabl.**Anal bakı ve rektal muayene olağan**
- **GÜS:** Haricen erkek görünümde, fenotipik anomali yok, olağan görünümde.
- **Nörolojik muayene:** Kraniyal sinir muayenesi olağan, kas gücü tam, DTR normoaktif, patolojik refleks yok, lateralize nörolojik defisit yok .

LABORATUVAR

WBC	8,9	10^3/µl	4-10,3
NEU	5,9	10^3/µl	2,1-6,1
LYM	2,3	10^3/µl	1,3-3,5
MONO	0,4	10^3/µl	0,3-0,9
EOS	0,2	10^3/µl	0-0,5
BASO	0,0	10^3/µl	0-0,2
RBC	5,05	10^6/µl	4-5,77
HGB	11,6	g/dl	12-16
HCT	36,6	%	36-46
MCV	72,5	fl	80,7-95,5
MCHC	31,8	g/dl	32,7-35,6
RDW	14,7	%	11,8-14,3
PLT	414	10^3/µl	156-373

INR	1,0		0,8-1,2
PT	11,2	sn	11,2-14,4
APTT	27,9	sn	28,1-39,1

BUN	15,2	mg/dL	5-18
Kreatinin	0,44	mg/dL	0,26-0,77
Ürik asit	5,41	mg/dL	2,6-6
AST	183	U/L	0-35
ALT	222	U/L	0-35
ALP	347	U/L	69-325
GGT	187	g/dL	3-22
Albümin	3,86	g/dL	3,8-5,4
Total Bilirubin	0,48	mg/dL	0,3-1,2
Direkt Bilirubin	0,12	mg/dL	
Sodyum	137	mmol/L	138-145
Potasyum	4,71	mmol/L	3,4-4,7
Klor	106	mmol/L	98-107
Kalsiyum	9,70	mg/dL	8,8-10,8
Fosfor	4,766	mg/dL	4,5-5,5
CRP	3,6	mg/L	0,2-5
ESH	20	mm/h	0-15

BOYASIZ DİREK MIK.INC. (DIŞKI)	LÖKOSİT VE ERİTROSİT GÖRÜLMEDİ
AEROP DIŞKI DÜLTÜR	Salmonella,Shigella ve EHEC üremesi saptanmadı.
ENTERİK ADENOVİRUS ANTİJENİ	NEGATİF
DIŞKIDA ROTAVİRUS ANTİJENİ	NEGATİF
YAĞIN MİKROSKOBİK İNCELENMESİ(SUDAN BLACK)	2 POZİTİF
GİZLİ KAN (DIŞKI)	POZİTİF

Anti-HAV IGM	Negatif
Anti-HAV TOTAL	Negatif
HBsAg	Negatif
Anti-HBC IGM	Negatif
Anti-HBC TOTAL	Negatif
Anti-HBS	26,54 mIU/ml
Anti HCV	Negatif
Anti-CMV IGM	Negatif
Anti-CMV IGG	Negatif
Anti-TOXOPLASMA IGM	Negatif
Anti-TOXOPLASMA IGG	Negatif
Anti-RUBELLA IGM	Negatif
Anti-RUBELLA IGG	34,40 IU/ml
EBV VCA IGM	Negatif
EBV VCA IGG	Negatif
Anti-EBV EBNA IGG	Negatif

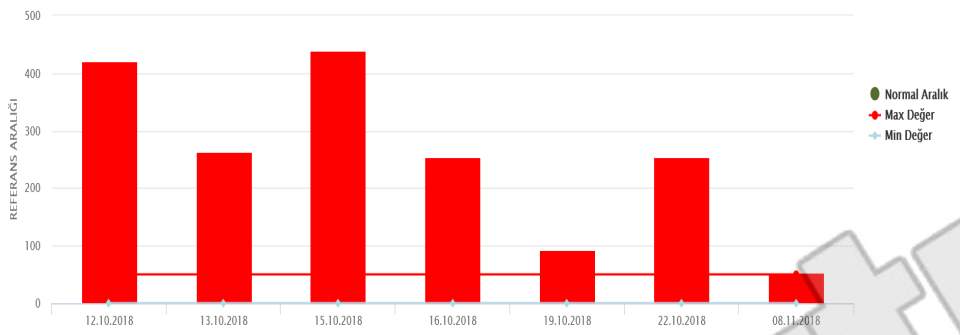
Anti Nükleer Antikor(ANA)	+2 (1/320-1/1000) Dilüsyonda sitoplazmik benekli peroksisom benzeri floresan tutulum
Anti Düz Kas Antikoru (ASMA)	NEGATİF (<1/100 titre)
Anti Mitokondrial Antikor (AMA)	NEGATİF (<1/100 titre)
Liver Kidney Mikrozomal Antikor (LKM)	NEGATİF (<1/100 titre)
Anti-Soluble Liver Antijen (SLA)	NEGATİF
Anti-Liver Sitosol (LC)	NEGATİF

Anti Endomisyum IGA	+3 POZİTİF (1/100-1/320 titre)
Anti Gliadin IGA,IGG	+3 POZİTİF (1/100-1/320 titre)
Anti Doku Transglutaminaz IgA	POZİTİF (90,42 RU/ml)
IgA	192,4 mg/dl (70-400 mg/dl)

Seruloplazmin	0,340 g/L(0,2-0,6)
Bakır	149 mg/dL (80-160mg/dL)

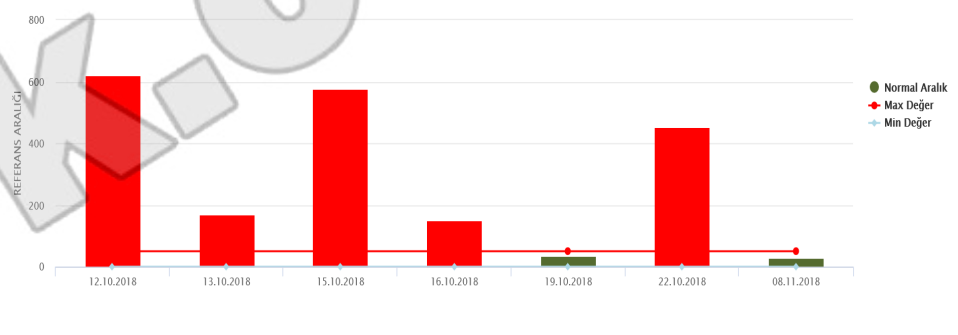
ALT/* Alanin aminotransferaz (ALT) SONUÇ GRAFİĞİ

Başlangıç Tarihi:08.10.2018
Bitiş Tarihi:08.11.2018
Hasta No:4589714
Parametre Id:706419
Parametre Adı:ALT/* Alanin aminotransferaz (ALT)



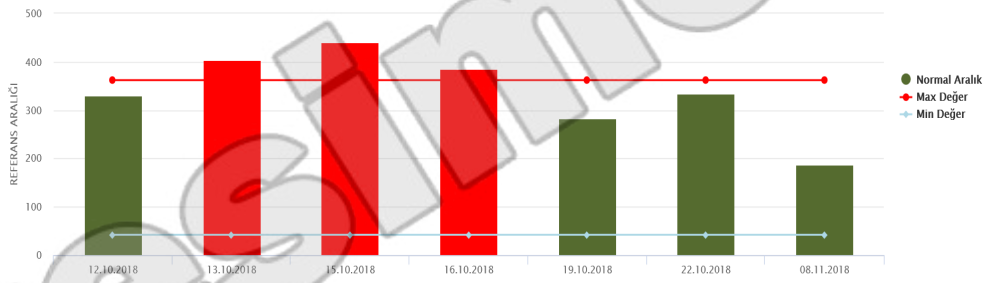
AST/* Aspartat aminotransferaz (AST) SONUÇ GRAFİĞİ

Başlangıç Tarihi:08.10.2018
Bitiş Tarihi:08.11.2018
Hasta No:4589714
Parametre Id:706386
Parametre Adı:AST/* Aspartat aminotransferaz (AST)



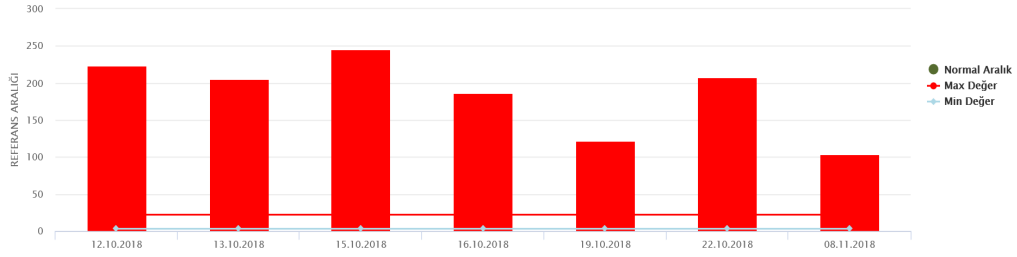
ALP/* Alkalen fosfataz (ALP) SONUÇ GRAFİĞİ

Başlangıç Tarihi:08.10.2018
Bitiş Tarihi:08.11.2018
Hasta No:4589714
Parametre Id:706424
Parametre Adı:ALP/* Alkalen fosfataz (ALP)



GGT/* Gamma glutamil transferaz (GGT) SONUÇ GRAFİĞİ

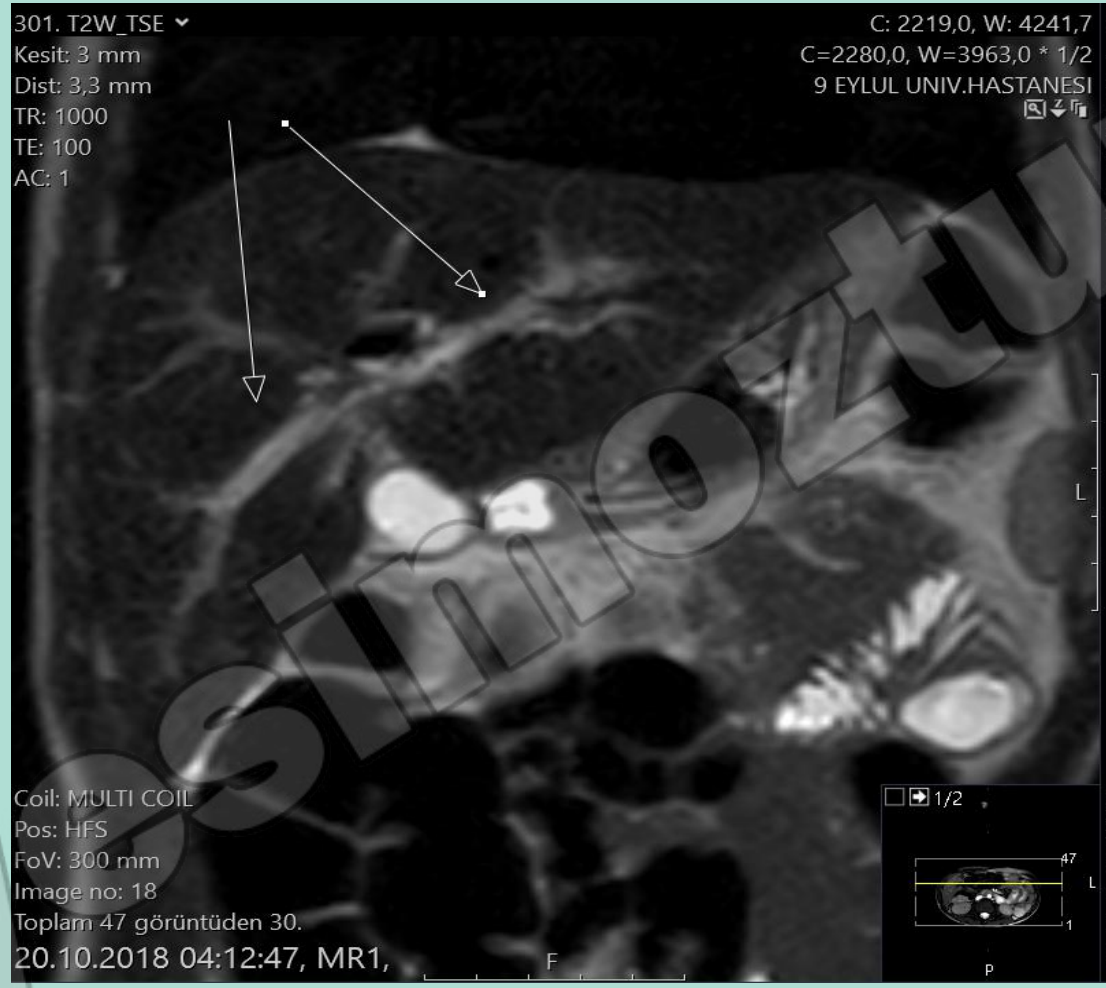
Başlangıç Tarihi:08.10.2018
Bitiş Tarihi:08.11.2018
Hasta No:4589714
Parametre Id:706739
Parametre Adı:GGT/* Gamma glutamil transferaz (GGT)

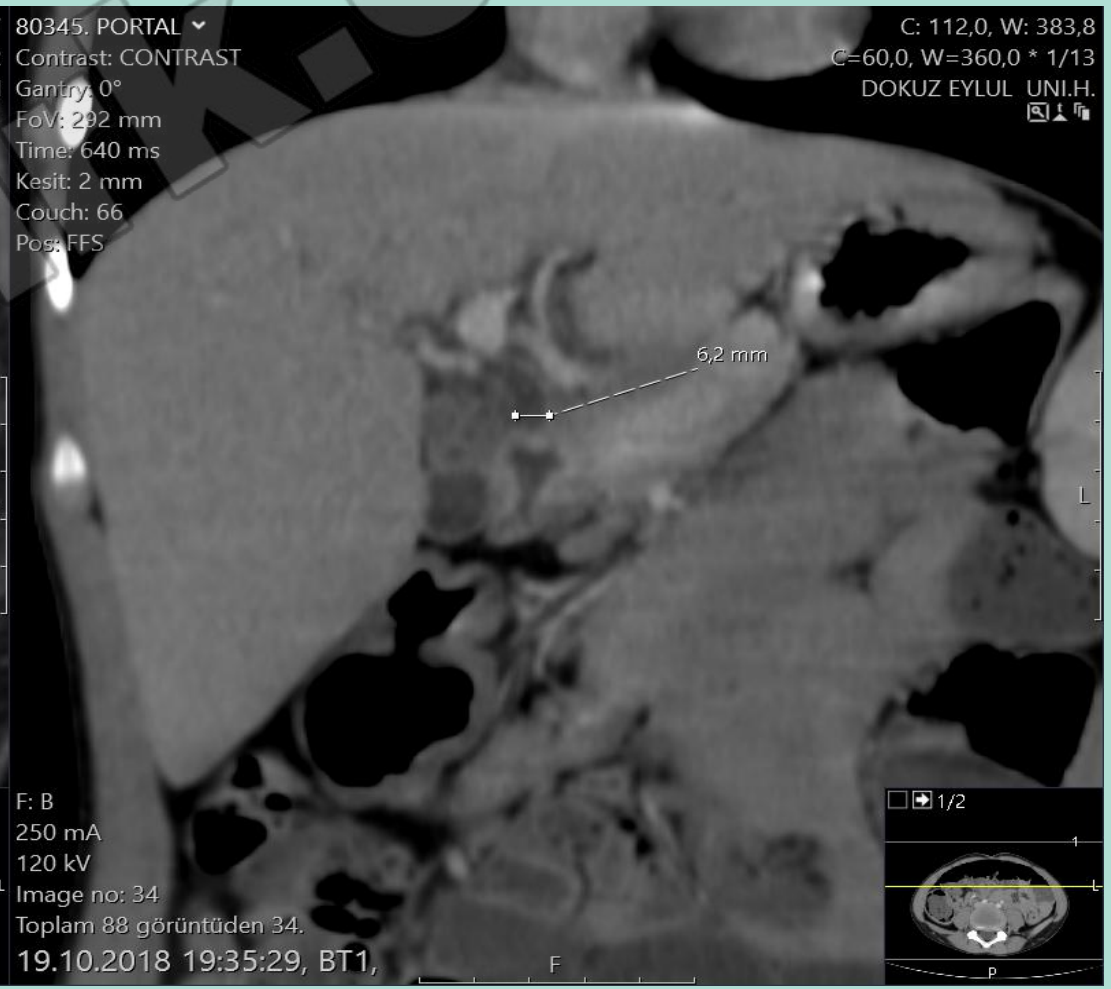


GÖRÜNTÜLEME

- **Batın USG:** Koledokta ılımlı genişleme,**intrahepatik safra yollarında ılımlı genişleme ve yer yer darlık** ;MRCP önerilir.
- **MRCP:**Safra kesesi normaldir **intrahepatik ve ekstrahepatik safra yollarında ılımlı dilatasyon** vardır,pankreatik kanalda dilatasyon saptanmamıştır.

MRCP





KLİNİK GİDİŞ

- Klinik ve laboratuvar olarak → **ÇÖLYAK HASTALIĞI** düşünüldü.
- Endoskopi (24/09/2019) → Bulbus ve duodenum 2. kısım ödemli görünümde, endoskopik eritamatöz pangastrit ile uyumlu bulgular saptandı.
- Sitopatoloji çölyak ile uyumlu

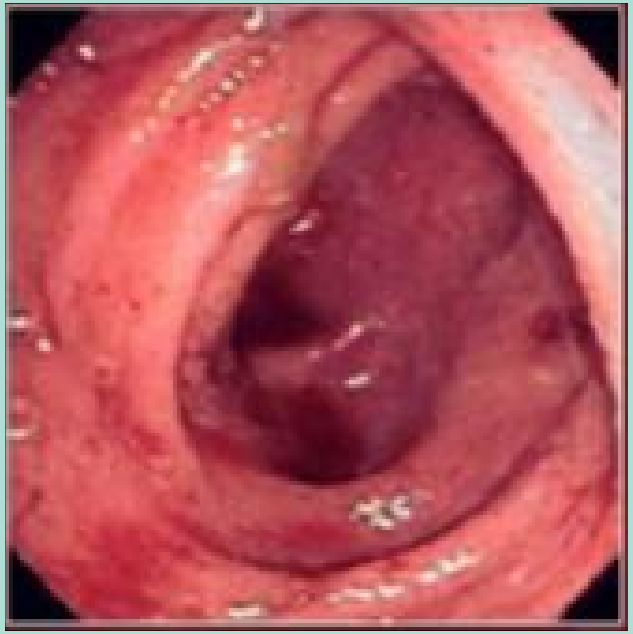
KLİNİK GİDİŞ

- Glutensiz diyet başlandı.
- Hastanın izleminde glutensiz diyete uymasına rağmen aralıklı karın ağrısı,kanlı dışkılama ve ishal şikayetlerinin devam etmesi nedeni ile ileri tetkik amaçlı çocuk servisine yatışı yapıldı.

KLİNİK GİDİŞ

- **İBH** ayrıcı tanısı açısından (18/10/2018) →**Kolonoskopi**
- Sağ kolon,transvers kolon,sol kolon ve sigmoid kolon mukozası hiperemik ödemli, frajil damarlanmasını kaybetmiş
- Yer yer üzeri eksudalı lineer ülsere alanlar
- Rektum mukozası hiperemik,frajil,ödemli
- Retroversiyonda anal kanal olağan

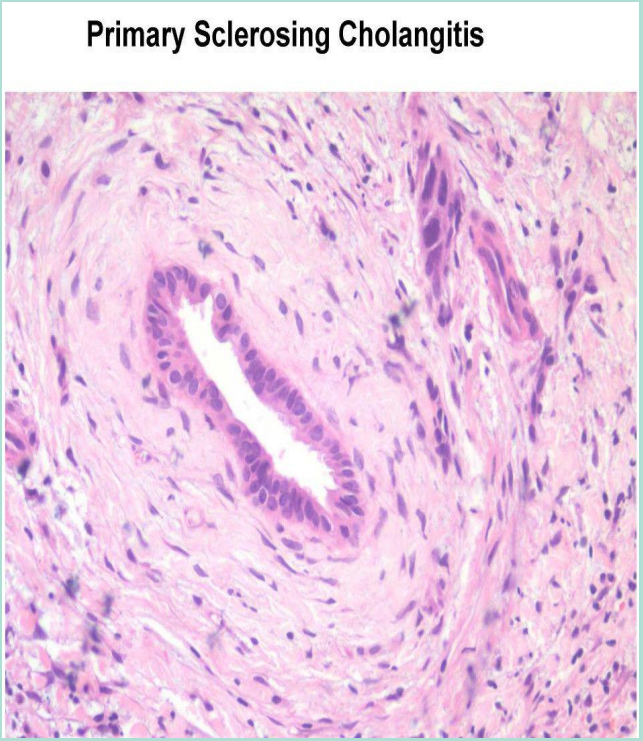
Patoloji →Aktif kolit



KLİNİK GİDİŞ

Otoimmun hepatit ,sklerozan kolanjit ön tanıları ile → **Karaciğer biyopsisi** (26.10.2018)

- Portal inflamasyon: orta şiddetli
- İnterfaz hepatit: yaygın
- Safra yolu hasarı: lenfositik kolanjit ile uyumlu bulgular
- Kolonjiol profilerasyonu: var
- Biliyer interfaz aktivitesi: var
- Portal fibrozis +
- Fe birikimi: sinüzoidal
- Morfolojik incelemede **hemosideroz ve portal enflamasyon** ve **lenfositik kolanjit** ile uyumlu tablo izlenmiştir.



ÖNEMLİ BULGULAR:

- Kronik ishal
- Karın ağrısı
- Malnutrisyon
- Demir eksikliği anemisi
- Transaminaz yüksekliği
- D-vitamin eksikliği
- Çölyak otoantikor pozitifliği
- Çölyak hastalığı ile uyumlu endoskopik ve histolojik bulgular
- Ülseratif kolit ile uyumlu kolonoskopi ve histolojik bulgular
- Lenfositik kolanjit, interfaz hepatiti ile uyumlu karaciğer biyopsi bulguları

TANILAR:

- Çölyak hastalığı
- Ülseratif kolit
- İBH ile ilişkili karaciğer hastalıkları
  - Otoimmun sklerozan kolanjit

TARTIŞMA

KRONİK İSHAL

KRONİK İSHAL

- İshal, tüm dünyada çocuklarda önemli bir morbidite ve mortalite nedenidir.
- Normal dışkılama, çocuk ve yetişkinlerde günde üç ile haftada üç arası iken; süt çocuklarında genellikle daha sık ve kıvamlı olmaktadır.
- Bebek ve çocuklarda dışkı miktarı >10 gr/kg/gün, adölesanlarda >200 gr/gün olduğunda ishal olarak tanımlanır.

TANIM

- Akut bir ishal 7-10 gün sürer, **ishalin 14 günden uzun sürmesi kronik veya persistan ishal** olarak adlandırılır.
- Gelişmiş ve gelişmekte olan ülkelerde kronik ishal nedenleri farklılık gösterir.
- Gelişmekte olan ülkelerde bağırsak enfeksiyonları en önemli nedendir.

KRONİK İSHALLİ HASTAYA YAKLAŞIM

ÖYKÜ VE FİZİK MUAYENE

- Yaş grubuna göre değişen nedenler
- Beslenme öyküsü
- Dışkılama sıklığı, volümü, kan ve mukus içeriği
- Laksatif vb. ilaç kullanımı
- Antropometrik değerlendirme
- Anal muayene ve rektal tuşe

LABORATUVAR

- Gaita direkt bakısı ve serolojik testler
- Bağırsak emilim testleri
- Hemogram
- BFT, KCFT, Fe ve diğer eser elementler
- Çölyak antikorları
- Besin alerjisi açısından spesifik Ig'ler
- Radyolojik tetkikler
- Endoskopik tetkikler
- Patolojik tetkikler

Tablo-2 Kronik ishalin yaşlara göre nedenleri

0-30 gün	1-24 ay	2-18yaş
Konjenital ishalli hastalıklar*	Aşırı meyve suyu/sorbitol/ karbonat içeren gıdaların alımı	Aşırı meyve suyu/sorbitol/ karbonat içeren gıdaların alımı
Gıda alerjisi	Enfeksiyöz kolitler	Enfeksiyöz kolitler
Hirschprung hastalığı	Kronik nonspesifik ishal	Çölyak hastalığı
	Kistik fibrozis	İrritabl bağırsak hastalığı
Konjenital kısa bağırsak sendromu	Çölyak hastalığı	İnflamatuar bağırsak hastalığı
	Gıda alerjisi	
Neonatal lenfienjiektazi	Postgastroenterit sendromu	Laktoz intoleransı
	Sükroz-izomaltaz eksikliği	
Konjenital heparan sülfat eksikliği	Otoimmün enteropati	Postgastroenterit sendromu

*Sükroz-izomaltaz eksikliği dışında

ÇÖLYAK HASTALIĞI

GENEL BİLGİLER

- Çölyak hastalığı (ÇH) genetik yatkınlığı olan kişilerde gluten içeren yiyeceklerin yenmesi sonucu ortaya çıkan otoimmün bir enteropatidir.
- Otoimmün mekanizmalar ile gelişir.

PATOGENEZ

- Glutenin sindirim sistemine alınmasıyla ince bağırsak mukozasında bulunan gliadin peptidleri ile (HLA) sınıf II moleküllerinin birleşmesi sonucunda klinik bulguların oluştuğu immünolojik olaylar zinciri başlamaktadır.
- Bu reaksiyonu en fazla gösteren doku grupları HLA-DQ2 ve DQ8'dir.

TANI

- Tanı koymada hastalığı düşünmemek en önemli engeldir; tanı koymak için önce ÇH tanısının akla gelmesi gerekir.

Tablo III: Çölyak hastalığı tanısında kullanılan serolojik testler.

Serolojik testler		Yöntem
Antigliadin Antikor (AGA)	IgA/IgG	ELİSA
Anti Endomisyum Antikor (EMA)	IgA/IgG	IFA, ELİSA
Antiretikülin Antikor (ARA)	IgA/IgG	IFA
Doku Transglutaminaz Antikor (dTG)	IgA/IgG	ELİSA, IKY
Deamide gliadin peptid (DGP) antikor	IgA, IgG	ELISA

ELİSA: *Enzyme Linked Immuno Sorbent Assay,* ***IFA:*** *Immuno Fluorescense Assay,* ***IKY:*** *İmmuno Kromatografik Yöntem.*

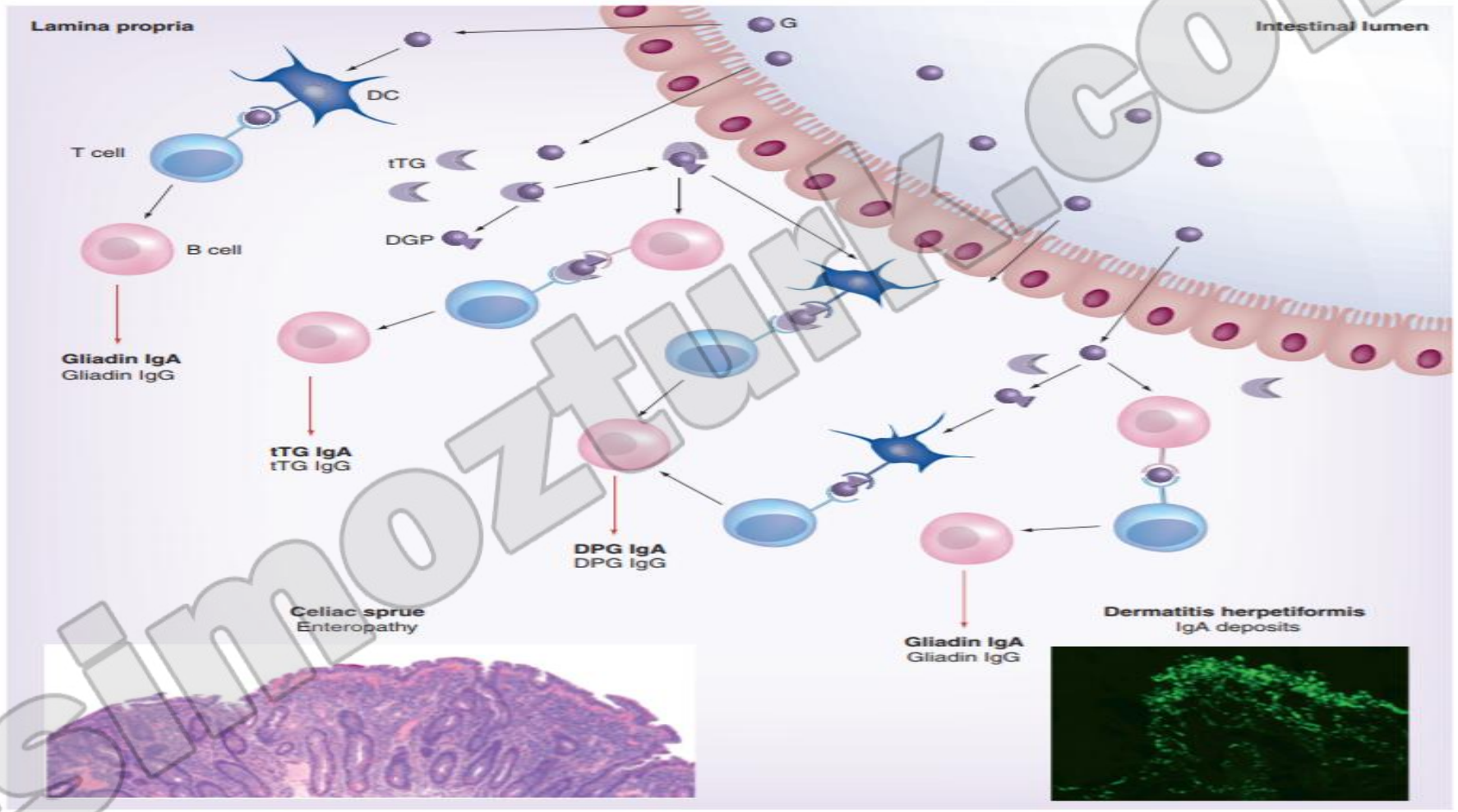


Figure 1. Pathogenesis of gluten-sensitive disorders. The two gluten-sensitive disorders, celiac sprue and dermatitis herpetiformis, are the consequences of an abnormal autoimmune response that occurs in the intestine in genetically susceptible individuals (HLA-DQ2 or -DQ8 positive). tTG forms a complex with G and deamidates specific glutamine residues of these peptides. DGPs are then presented to T cells by DCs or B cells. The T cells then provide help to the B cells, resulting in the production of antibodies (mainly IgA but also IgG) against gliadin and DGP, as well as antibodies specific for tTG. These abnormal responses triggered by gliadin can result in either celiac sprue (with mucosal inflammation and loss of villi) or dermatitis herpetiformis (with IgA deposits in the dermal papillae), or even both.

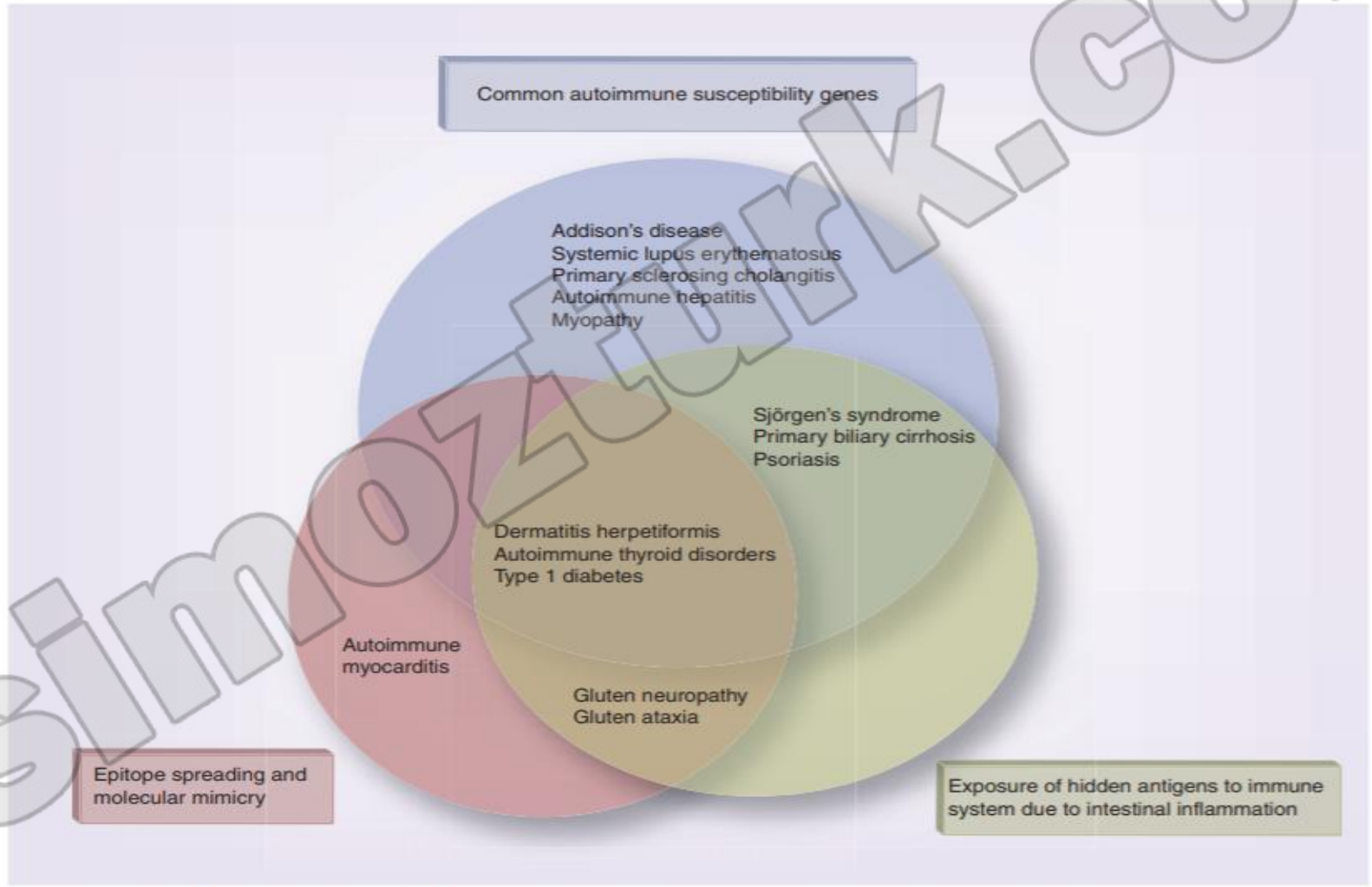


Figure 2. Potential mechanisms behind the association of celiac sprue and other autoimmune disorders.

Link Between Celiac Disease and Inflammatory Bowel Disease

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*and Gerald J. Holtmann, MD, PhD, MBA, FRACP, FRCP**

Goal: The aim of this analysis was to assess in patients with inflammatory bowel disease (IBD) the risk of celiac disease and in celiac disease patients the risk of IBD.

Background: Previous studies report a possible association between IBD and celiac disease; however, this link is controversial.

Study: Using the search terms "inflammatory bowel disease" and "celiac disease," we identified initially 1525 publications. In total 27 studies met inclusion criteria. Proportions and 95% confidence intervals (CIs) for the prevalence of IBD in celiac disease and vice versa were compared with published prevalence rates for the respective geographic regions.

Results: We included 41,482 adult IBD patients (20,357 with Crohn's disease; 19,791 with ulcerative colitis; and 459 patients with celiac disease). Overall, in IBD patients the prevalence of celiac disease was 1110/100,000 (95% CI, 1010-1210/100,000) as compared with a prevalence of 620/100,000 (95% CI, 610-630/100,000) in the respective populations (odds ratio, 2.23; 95% CI, 1.99-2.50). In contrast, in patients with celiac disease, 2130/100,000 had IBD (95% CI, 1590-2670/100,000) as compared with 260/100,000 (95% CI, 250/100,000-270/100,000) in the respective populations (odds ratio, 11.10; 95% CI, 8.55-14.40). This effect was not different for ulcerative colitis and Crohn's disease. Although there was no evidence for publication bias for celiac disease in IBD, the funnel plot suggested that the association between IBD in celiac disease might be influenced by publication bias.

Conclusions: The data are consistent with the notion that celiac disease is a risk factor for IBD and to lesser degree patients with IBD have an increased risk of celiac disease.

Key Words: celiac disease, inflammatory bowel disease, Crohn's disease, incidence and prevalence, developed countries

(*J Clin Gastroenterol* 2018;00:000–000)

The etiology of immune-mediated diseases such as ulcerative colitis (UC), Crohn's disease (CD), and celiac disease is incompletely understood but likely multifactorial involving a complex interplay between genetic and environmental factors. Ultimately a dysregulation of the innate and adaptive immune system and activation of inflammatory cascade leads to chronic gut inflammation and disease manifestation.[1–6]

The clinical manifestations of celiac disease and inflammatory bowel disease (IBD) can be similar[7,8] and often patients with celiac disease, particularly those that have no response to a gluten-free diet (GFD), are investigated for possible IBD as the 2 conditions may coexist. The first description of a link between celiac disease and IBD dates back to 1965 when Salem and Truelove[9] described 14 patients with duodenal mucosal villous atrophy among 60 patients with UC. Habior et al[10] reported a case of an association of primary sclerosing cholangitis, UC, and celiac disease in 2 sisters. Thereafter, several case reports and case series have reported a possible association between IBD and celiac disease[9–27]; however, this link is controversial.

We aimed to determine the prevalence of celiac disease (CeD) in IBD and the prevalence of IBD in CeD. We hypothesized that celiac disease is a risk factor for IBD.

Çölyak hastalığında İBH gelişme riski 11 kez artarken , İBH hastalarında çölyak gelişme riski 2 kat artmakta

Çölyak gelişiminde rol oynayan patofizyolojik süreç mukozal inflamasyona neden olarak İBH gelişmesi ile sonuçlanmakta

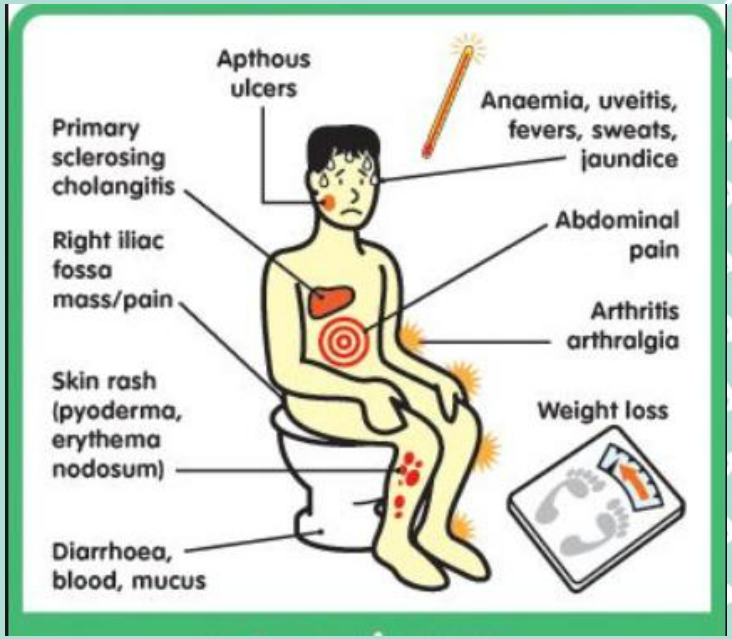
ÜLSERATIF KOLIT

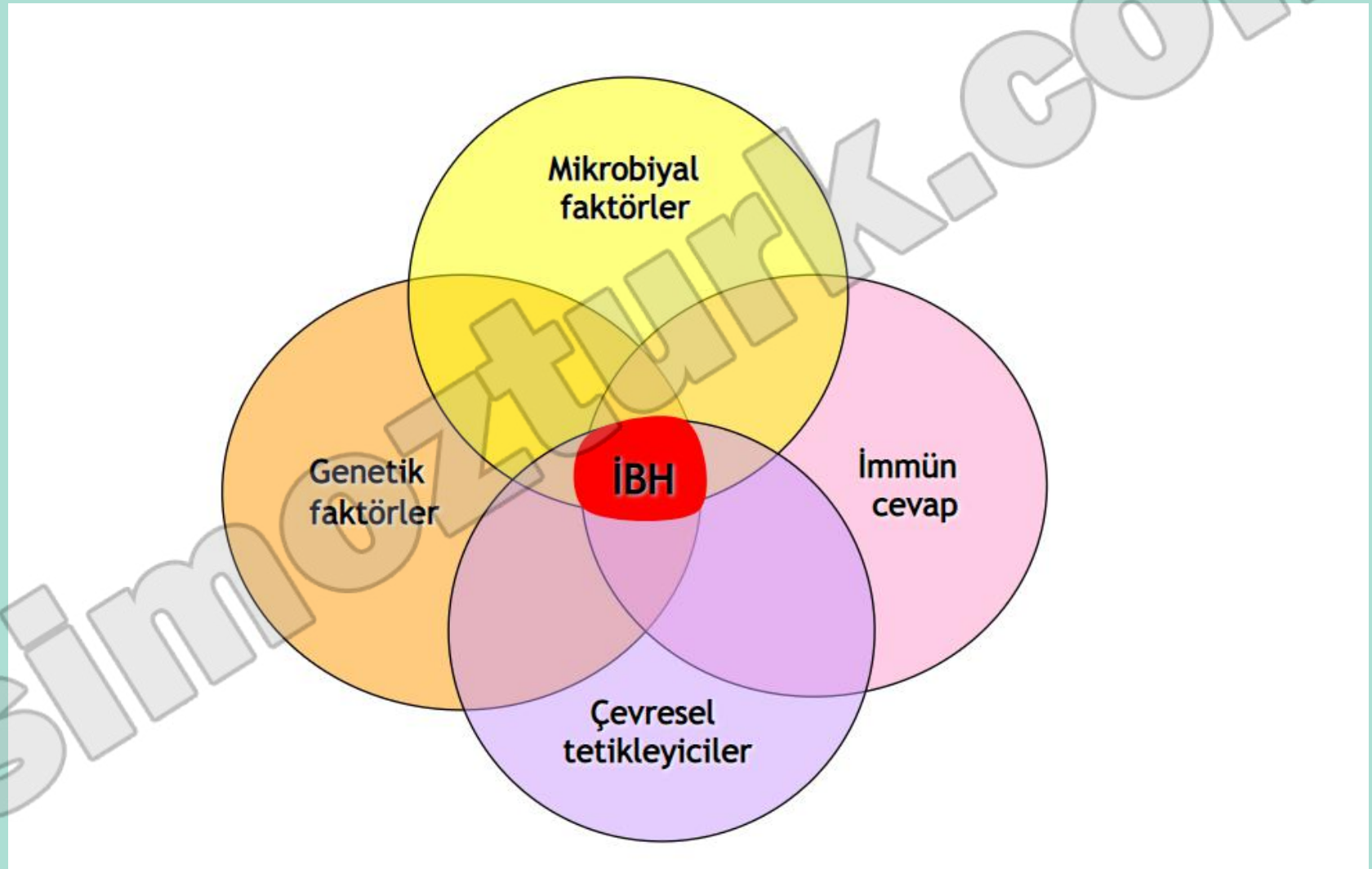
ÜLSERATİF KOLİT

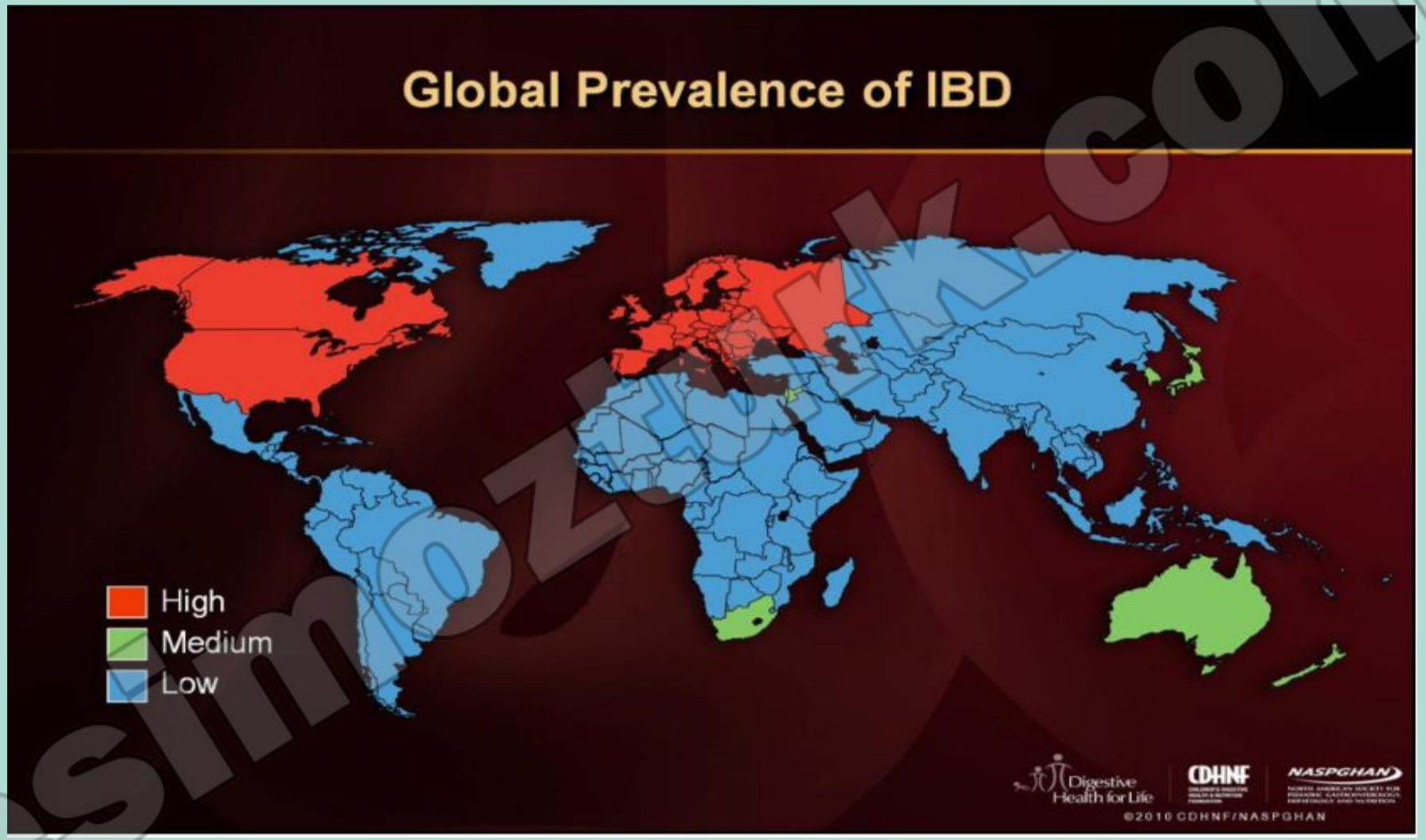
- İnflamatuvar barsak hastalıkları,ÜK ve Crohn hastalığı ,immun aracılı bozukluklar olup gastrointestinal sistemde kronik tekrarlayıcı inflamasyona neden olurlar.
- İBH tanısı alan hastaların yaklaşık %25'lik kısmı 25 yaş altındadır.

ÜLSERATİF KOLİT

- Ülseratif kolit,rektum proksimale kadar değişik derecelerde ilerleyen kolonun kronik relapslarla giden inflamatuar sürecidir.
- Hastalarda kanlı ishal, tenesmus, karın ağrısı şikayetleri olup hastalık daha şiddetli hale geldiğinde kilo kaybı, halsizlik kusma gibi semptomlar eklenmektedir.
- Çocuk yaş grubunda şikayet sadece rektal kanama şeklinde olup ayırıcı tanıyı daha güç hale getirmekte
- Genç yaşta başlayan ÜK yine yetişkine oranla daha çok akut alevlenme dönemiyle gitmekte 10 yılda kolektomiye gitme oranları yetişkine göre daha fazladır







Kuzey Amerika, İngiltere ve İskandinav ülkelerinde Güney Avrupa, Asya ve Afrika'ya göre daha sıktır

EPIDEMIYOLOJI

- Yapılan çalışmalarda ÜK insidansında belirgin artış saptanmış olup on yaş altı grupta Kanada'da yapılan bir çalışmada insidansı en sık artan hastalık olduğu saptanmış.
- Anne ve babasında İBH olan çocukta hastalık gelişme riski %35'den fazladır.

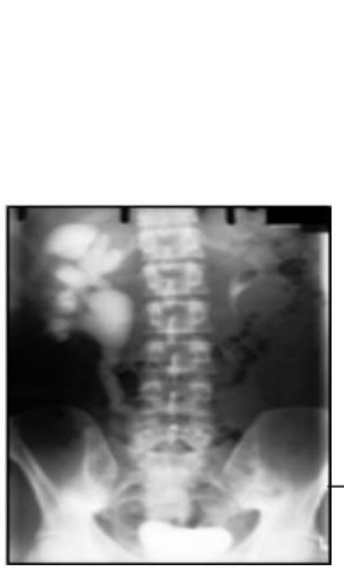
ETYOLOJİ

- Etyolojide beslenme, enfeksiyoz süreçler,genetik ve immunite önemli yer oynamakta
- İBH tanısı alanlar almayanlarla kıyaslandığında yine daha çok anne sütü aldığı saptanmış.
- Pek çok çalışmada mono ya da poliansature yağların IBH riskini artırırken lifli beslenmenin ya da vitamin D alımının azalmış riskle birlikte olduğu gösterilmiş

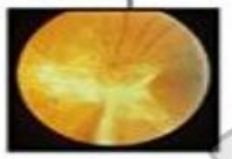
İMMUNİTE

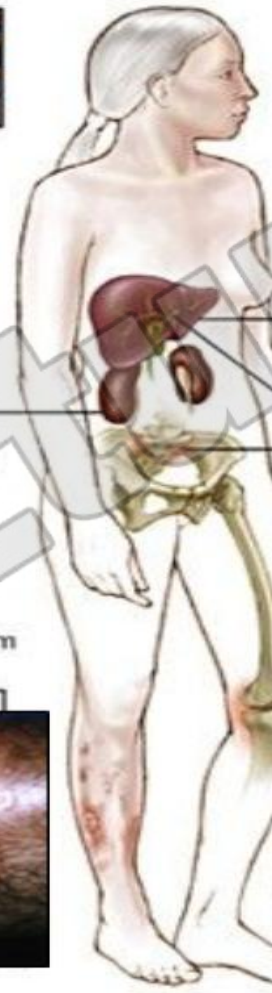
- **Doğal immun yolaklar: NOD2**
- **Mikrobial immun yolaklar:** Defects in autophagy Related 16-Like 1 (ATG16L1) and immunity-related GTPase M (IRGM)
- **Sitokin yolakları**
- **Adaptif immune yolaklar :***PTPN2* and *PTPN22*
- **Epitelyal yolaklar:** X-box binding protein 1 (XBP1) and ORMDL3

Ekstaraintestinel tutulum



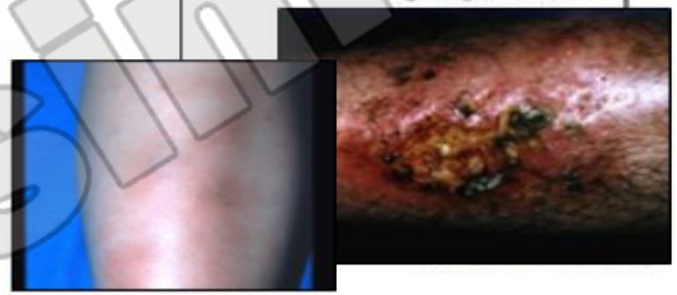
Eyes
Episcleritis
Uveitis



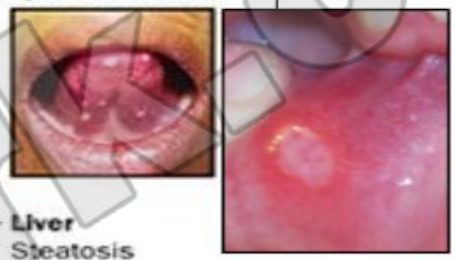


Kidneys
Stones
(nephrolithiasis)
Hydronephrosis
Fistulae
Urinary tract
infection

Skin
Erythema nodosum
Pyoderma
gangrenosum

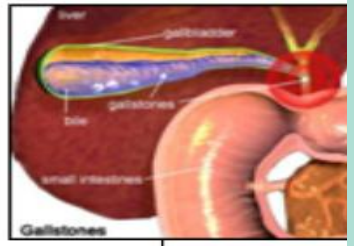


Mouth
Stomatitis
Aphthous ulcers

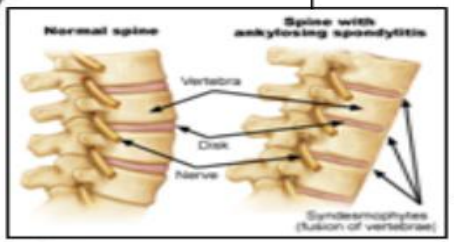


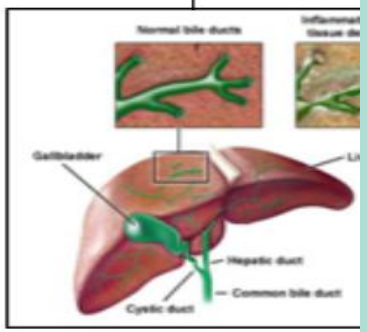
Liver
Steatosis

Biliary tract
Gallstones
Sclerosing cholangitis



Joints
Spondylitis
Sacroiliitis
Peripheral arthritis





Circulation
Phlebitis

TANI

- Tanı için klinik şüphenin olduğu durumlarda fizik muayene, laboratuar ve tipik kolonoskopi ve histolojik bulguların varlığı ile konur.
- Laboratuar incelemeleri; tam kan sayımı, karaciğer enzimleri, albümin, eritrosit sedimentasyon hızı, demir parametleri ve c-reaktif proteini içermeli
- Dışkı kültürü,dışkı parazit incelemeri ve Clostridium difficile toxin bakılması gerekir.
- 2 yaş altı çocuklarda immun yetmezlik ve alerjik durumların dışlanması gerekir

İBH BENZERİ ENFEKSİYOZ DURUMLAR

Shigella species

Enterohemorrhagic *Escherichia coli*

Enteroinvasive *E. coli*

Campylobacter jejuni

Salmonella species (gastroenteritis and typhoid fever)

Yersinia enterocolitica

Mycobacterium tuberculosis

Clostridioides (formerly *Clostridium*) *difficile*

Vibrio parahaemolyticus

Chlamydia trachomatis (lymphogranuloma venereum serotypes)

Entamoeba histolytica

Schistosoma species

Balantidium coli

Trichinella spiralis

Neisseria gonorrhoeae

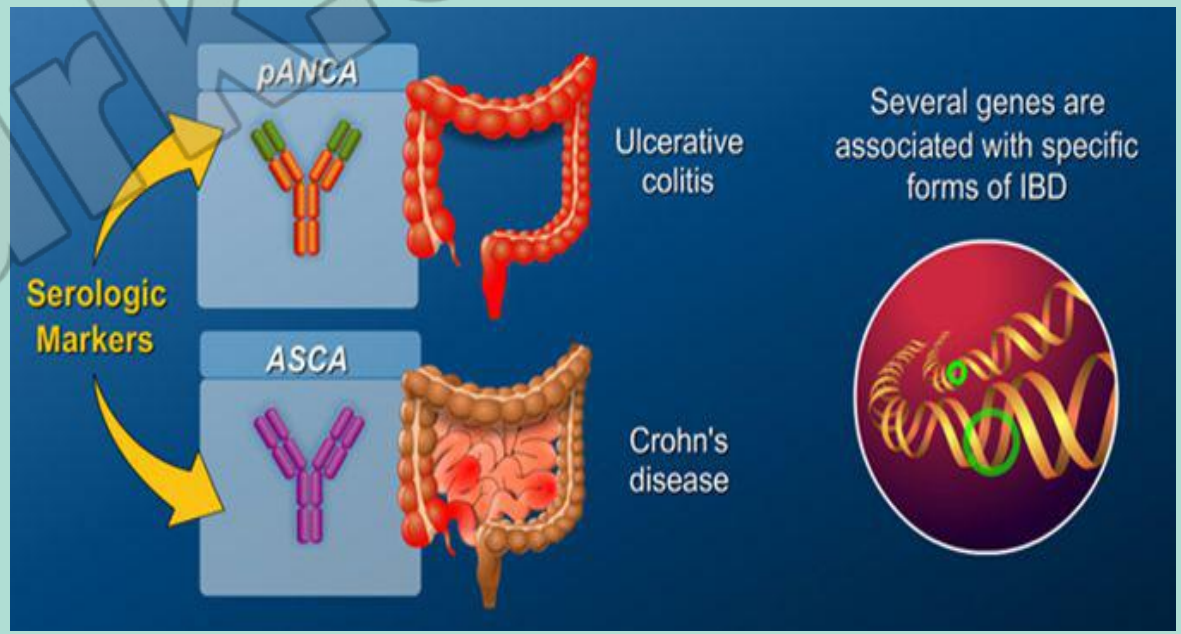
Herpes simplex virus

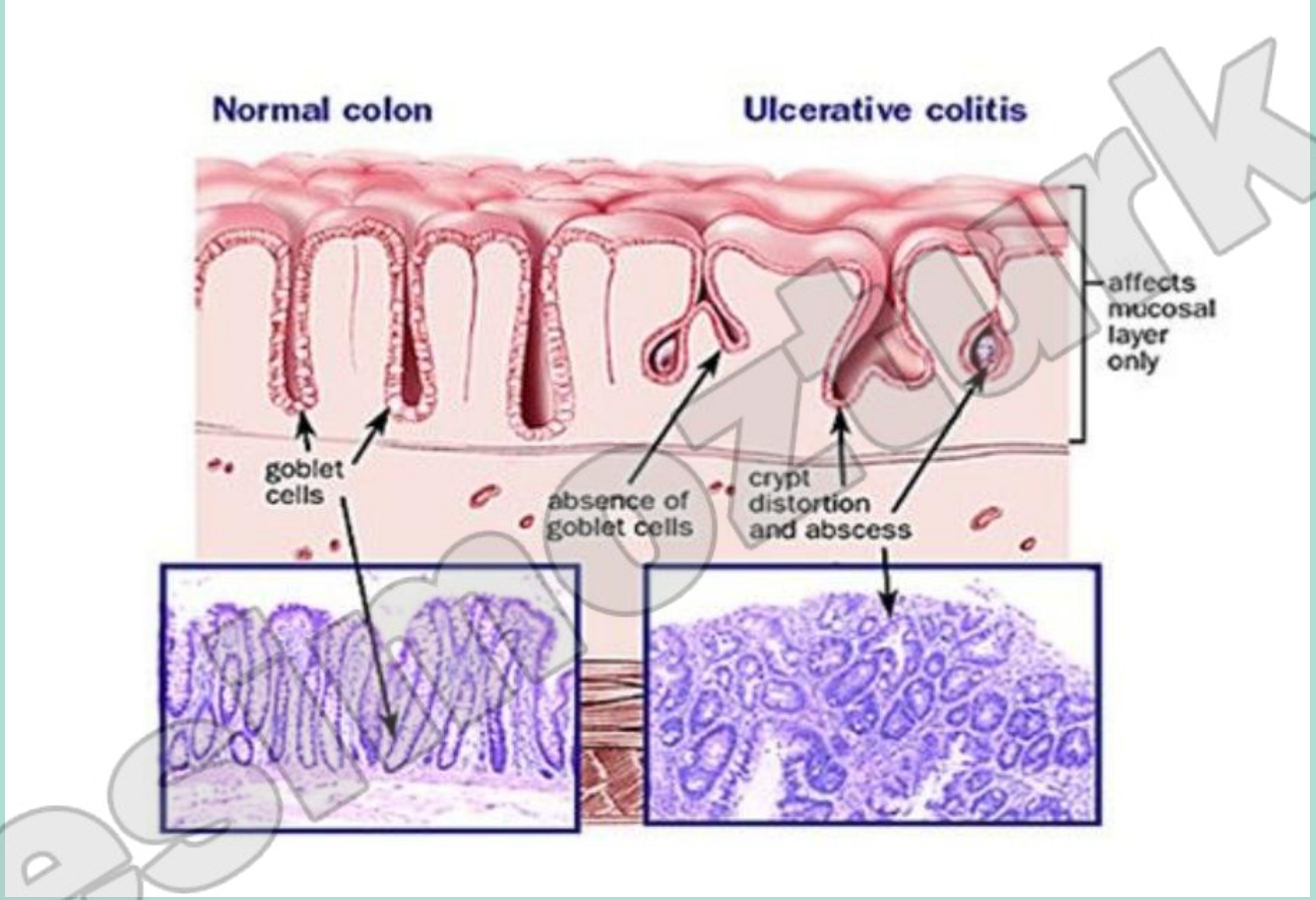
C. trachomatis

Treponema pallidum

Cytomegalovirus

- ASCA (anti-saccharomyces cerevisiae antibodies) Crohn ‘da %30-40 oranında,
- P-ANCA (perinuclear antineutrophil cytoplasmic antibodies), Cronh'li erişkinlerin yüzde 10 ila 27'sine kıyasla ülseratif kolitli çocukların ve yetişkinlerin yüzde 60 ila 80'inde tespit edilebilir





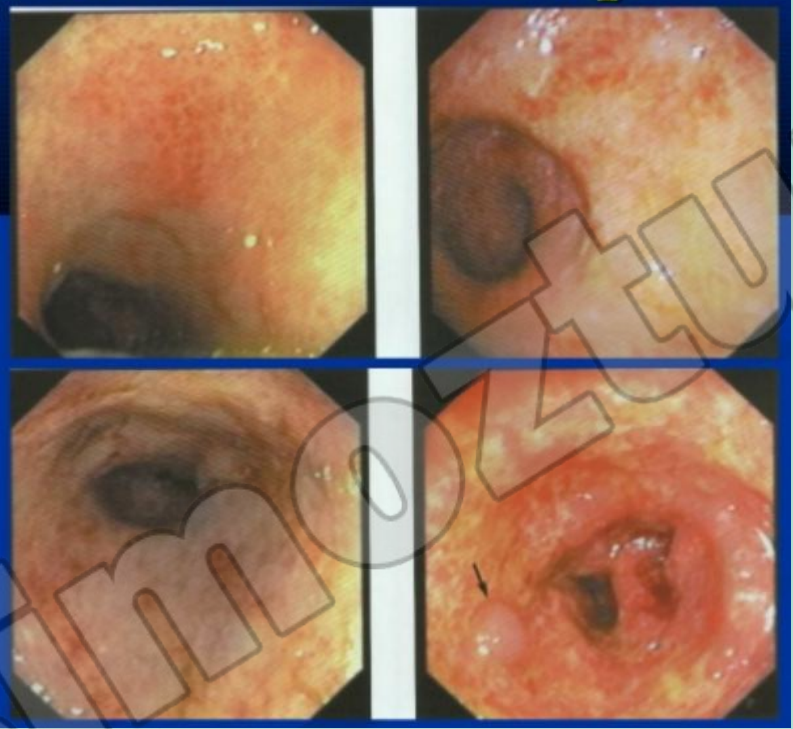
PATOLOJI

- Kript
- Kript abseleri
- Pseudopolip
- Mukozal ve submukozal inflamasyon
- Sol kolonda Paneth hücreleri

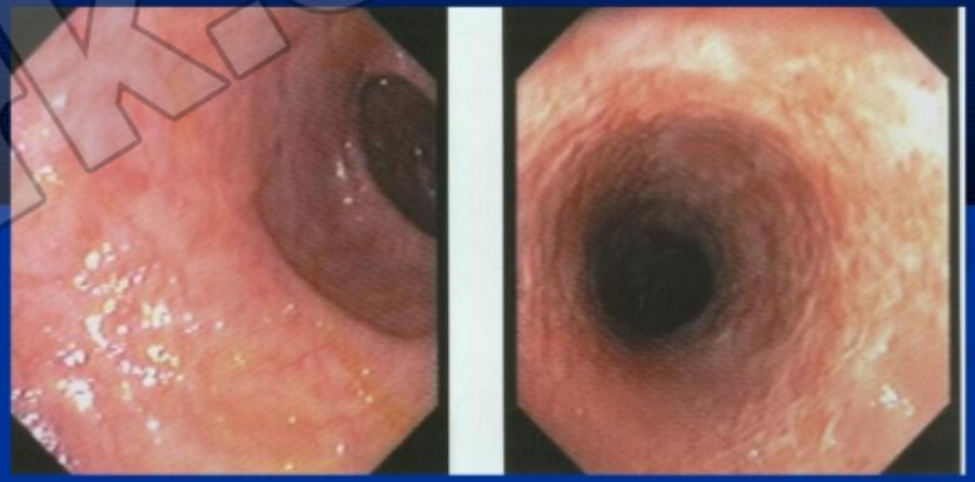
Ülseratif Kolit : Endoskopi

Hafif derecede mukozal kanama odakları

İleri derecede mukozal kanama odakları (ok: psödopolip)

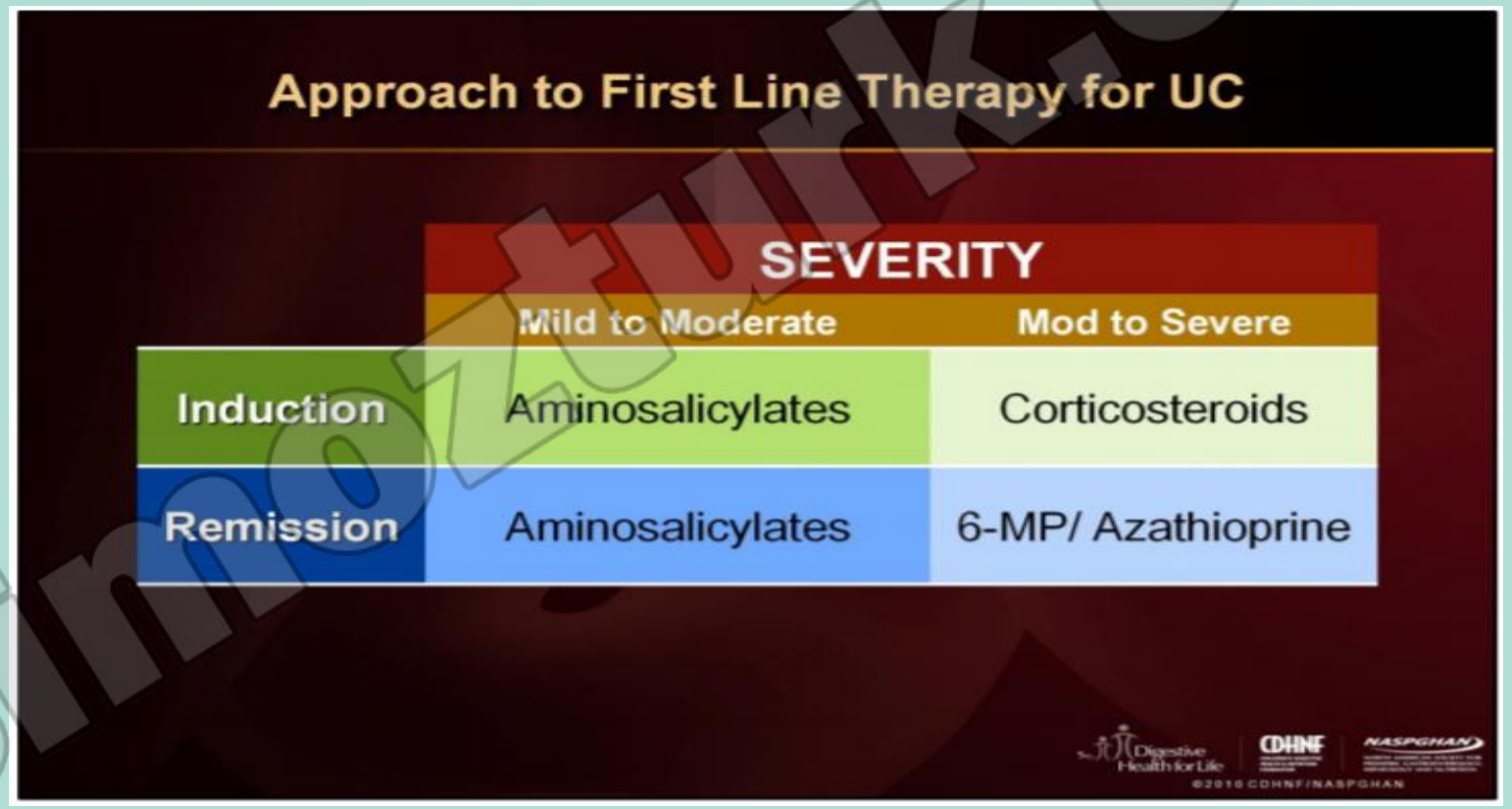


Ülseratif Kolit : Endoskopi



Remisyonda Ülseratif Kolit:
Belirgin damarlanma yok
Işık yansıması belirgin

Kronik ülseratif kolit:
Haustrasyon kaybı dikkat çeker



Tiopurin (Azotiopurin/Merkaptopurin)

Anti-TNF ajanlar
(Infliksimab/adalimumab/golimumab)

Kolektomi

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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Inflammatory bowel disease and celiac disease: Overlaps and differences

Virginia Pascual, Romina Dieli-Crimi, Natalia López-Palacios, Andrés Bodas, Luz María Medrano, Concepción Núñez

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Author contributions: Pascual V contributed to the extensive literature search and preparation of the first manuscript draft; Dieli-Crimi R contributed to the literature search and preparation of the first manuscript draft; López-Palacios N contributed to the literature search and preparation of the first manuscript draft; Bodas A contributed to the literature search and preparation of the first manuscript draft; Medrano LM contributed to the literature search and preparation of the first manuscript draft; Núñez C contributed to the study idea, literature search, manuscript writing and final revision of the article; all authors approved the manuscript.

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the bowel. The etiology and immunopathogenesis of both conditions characterized by chronic intestinal inflammation, inflammatory bowel disease (IBD) and celiac disease (CeD), are not completely understood. Both are complex diseases with genetics and environment contributing to dysregulation of innate and adaptive immune responses, leading to chronic inflammation and disease. CeD constitutes a particular disease because the main environmental and genetic triggers are largely known. IBD comprises two main clinical forms, Crohn's disease and ulcerative colitis, which most likely involve a complex interplay between some components of the commensal microbiota and other environmental factors in their origin. These multifactorial diseases encompass a broad spectrum of clinical phenotypes and ages of onset, although the clinical presentation often differs depending on childhood or adult onset, with greater heterogeneity commonly observed in adults.

Key words: Disease susceptibility; Gene-environment interaction; Immune system; Inflammation; Microbiota; Inflammatory bowel disease

Core tip: Inflammatory bowel disease and celiac disease

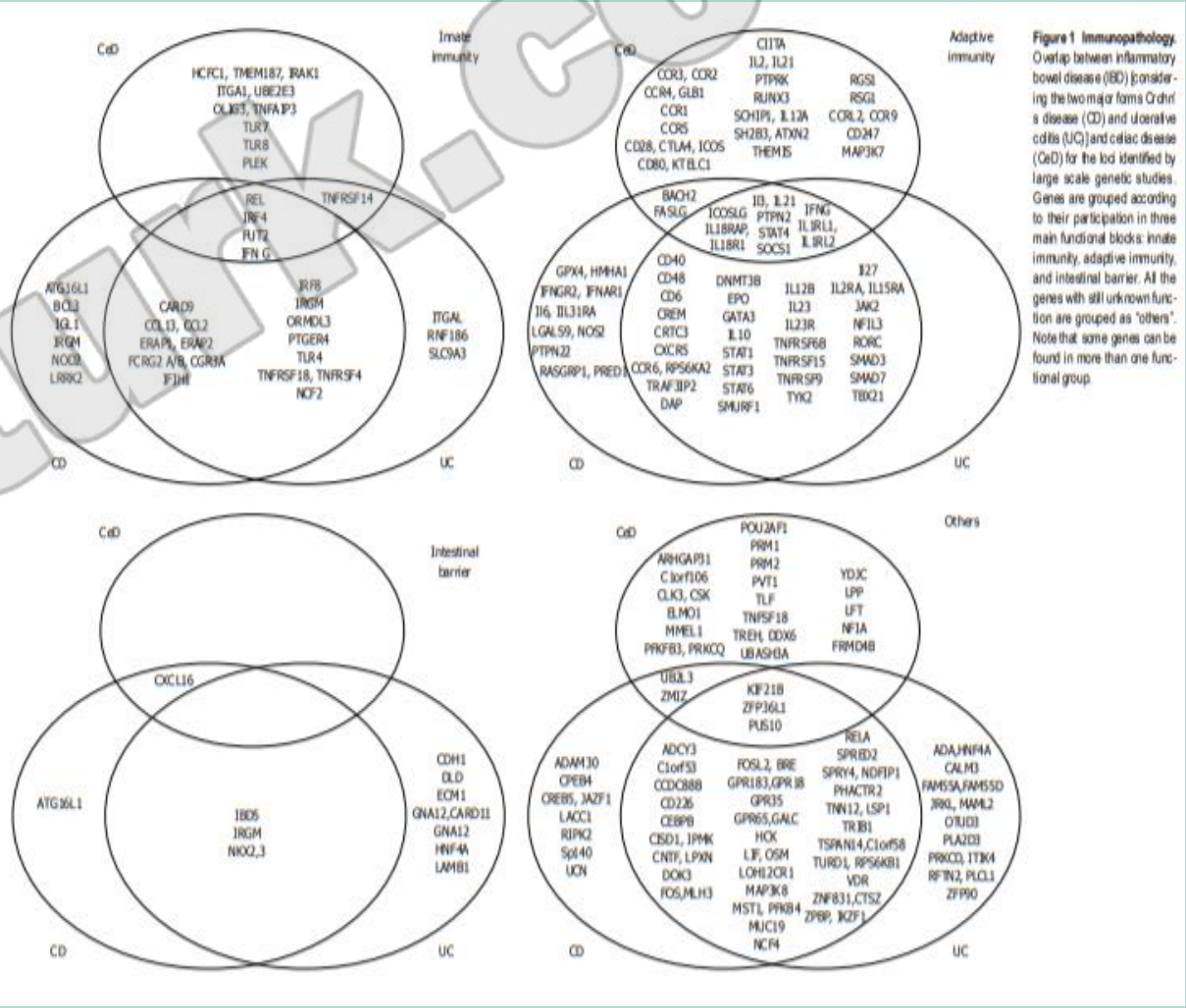

Figure 1 Immunopathology. Overlap between inflammatory bowel disease (IBD) [considering the two major forms Crohn's disease (CD) and ulcerative colitis (UC)] and celiac disease (CeD) for the loci identified by large scale genetic studies. Genes are grouped according to their participation in three main functional blocks: innate immunity, adaptive immunity, and intestinal barrier. All the genes with still unknown function are grouped as "others". Note that some genes can be found in more than one functional group.

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ORIGINAL ARTICLE

Retrospective Study

Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases

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Author contributions: Halling ML, Kjeldsen J, Knudsen T and Koch Hansen L designed the study; Koch Hansen L performed data collection; Nielsen J performed statistical analyses; Halling ML and Koch Hansen L drafted the manuscript and obtained funding; all authors revised and accepted the final manuscript.

Institutional review board statement: This study was approved by the Danish Data Protection Agency (approval # 2013-41-1596).

Conflict-of-interest statement: The authors report no conflict of interest.

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Accepted: July 12, 2017
Article in press: July 12, 2017
Published online: September 7, 2017

Abstract

AIM

To investigate whether immune mediated diseases (IMD) are more frequent in patients with inflammatory bowel disease (IBD).

METHODS

In this population based registry study, a total of 47325 patients with IBD were alive and registered in the Danish National Patient Registry on December 16, 2013.

Çölyak hastalığının risk genleri ile Crohn hastalığında olan aynı genlerin adaptif immuniteyi bozduğu, Ülseratif kolit'de ise bariyer fonksiyonlarında bozukluğa sebep olduğu saptanmış.

TABLE 1. Hepatobiliary issues to consider in patients with inflammatory bowel disease

Extraintestinal manifestations:
Immune-related:
Primary sclerosing cholangitis
Autoimmune hepatitis
Autoimmune sclerosing cholangitis
Thrombotic disorders:
Portal vein thrombosis
Venous thromboembolism
Hepatic vein thrombosis
Medication Toxicity:
Glucocorticoids
Sulfasalazine
Thiopurines
Methotrexate
Anti-TNFs
Underlying disorder:
Cholelithiasis
Viral Hepatitis
Transplant issues
IgG4 cholangiopathy
Granulomatous hepatitis
Primary biliary cirrhosis
Hepatic amyloidosis
Nonalcoholic fatty liver disease/steatohepatitis

İBH tanısından sonraki 3 aylık dönemde **ALT ve GGT** yüksekliği saptanan hastalarda karaciğer hastalığı gelişme oranı 3 kat artmakta

OTOIMMUN HEPATIT

- Otoimmün hepatit (OİH) nedeni bilinmeyen, kronik, ilerleyici, inflamatuar bir karaciğer hastalığı
- Serumda çeşitli otoantikorların varlığı, gamaglobülin yüksekliği ve histolojik olarak periportal veya portal alanda mononükleer hücre infiltrasyonu ile tanımlanmaktadır .
- Otoimmün hepatit görece olarak genel pediatrik populasyonda yaygın olmakla birlikte İBH'da **%0,6 ile %1,6** oranında görülmekte

OİH TİP 1

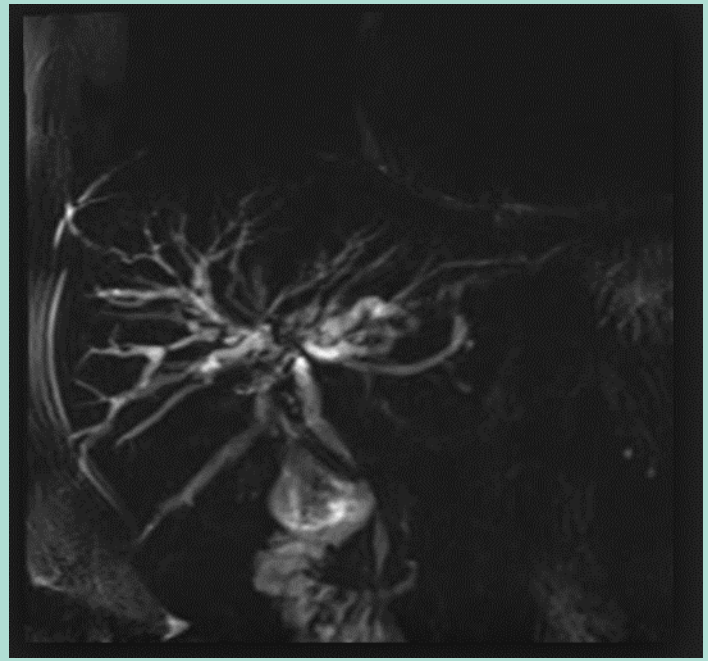
- ANA/SMA
- P-ANCA
- PUBERTE

OİH TİP 2

- Anti-LKM1/Anti-LC1
- ÇOCUKLUK YAŞ GRUBU

OTOİMMUN SKLEROZAN KOLANJİT

- OİH ve PSK'in overlap olmasına otoimmun sklerozan kolanjit olarak adlandırılmakta
- İBH hastalarında **%1,5** oranında saptanmakta
- Otoimmun hepatit ve sklerozan kolanjit overlap durumu yetişkine göre çocuklarda daha fazla görülmekte
- ALP ve GGT düzeyleri kolestatik hastalıklarda artmakta iken otoimmun sklerozan kolanjitin başlangıcında normal olabilir ancak ALP/AST oranı OSK'de OİH göre belirgin artmıştır.



OTOIMMÜN SKLEROZAN KOLANJIT

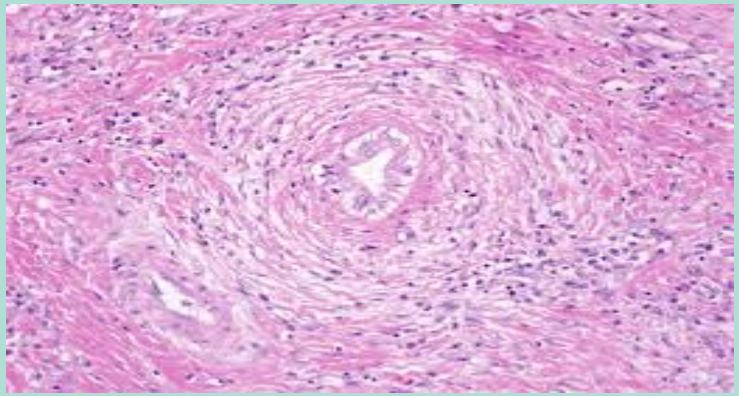
1.Hastaların %50 si erkek

2. Karın ağrısı, kilo kaybı,halsizlik

3. ANA ve SMA pozitifliği

4. %90 oranında serum IgG güzeyi artmış saptanır

5. pANCA %75 oranında OSK pozitif iken %45 oranında OIH tip1 ve %10 oranında OİH tip 2'de pozitif

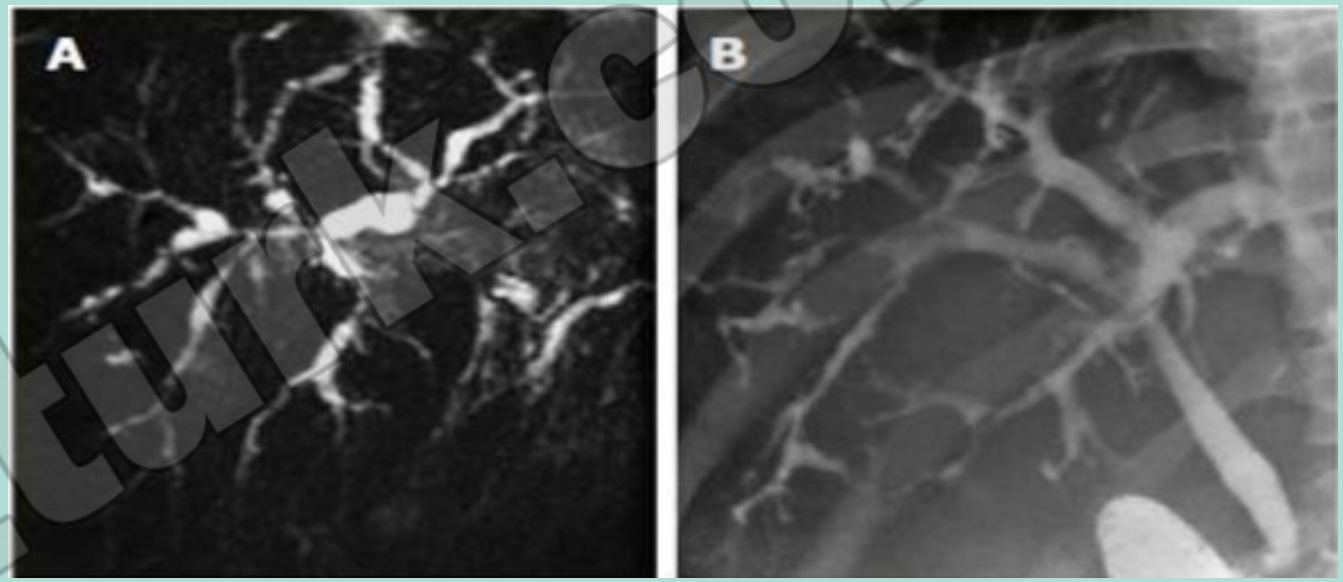


TANI

1. Otoimmun hepatit ve otoimmun sklerozan kolanjit ayırcı tanısı ancak kolonjiografik görüntüleme ile münküm

- USG
- MRCP
- ERCP

2. Karaciğer biyopsi



A→İntrahepatik striktür ve dilate safra yolları (MRCP)
B →Aynı hastanın ERCP görüntüsü

TEDAVİ

- Tedavi palyatif ve destekleyici
- Progresif seyirli olanlarda tek çözüm karaciğer transplantasyonu
- Ursodeoksikolik asitin kullanımı ile ilgili sadece biyokimyasal düzelme sağladığı ile ilgili çalışmalar mevcut
- İmmun modulator ajanların kullanımı ile ilgili kesin kanıtlar olmamakla birlikte çoğu hasta İBH tedavisine yönelik yine bu ajanları kullanmakta

TABLE 3. Comparison between AIH-1, AIH-2, and ASC

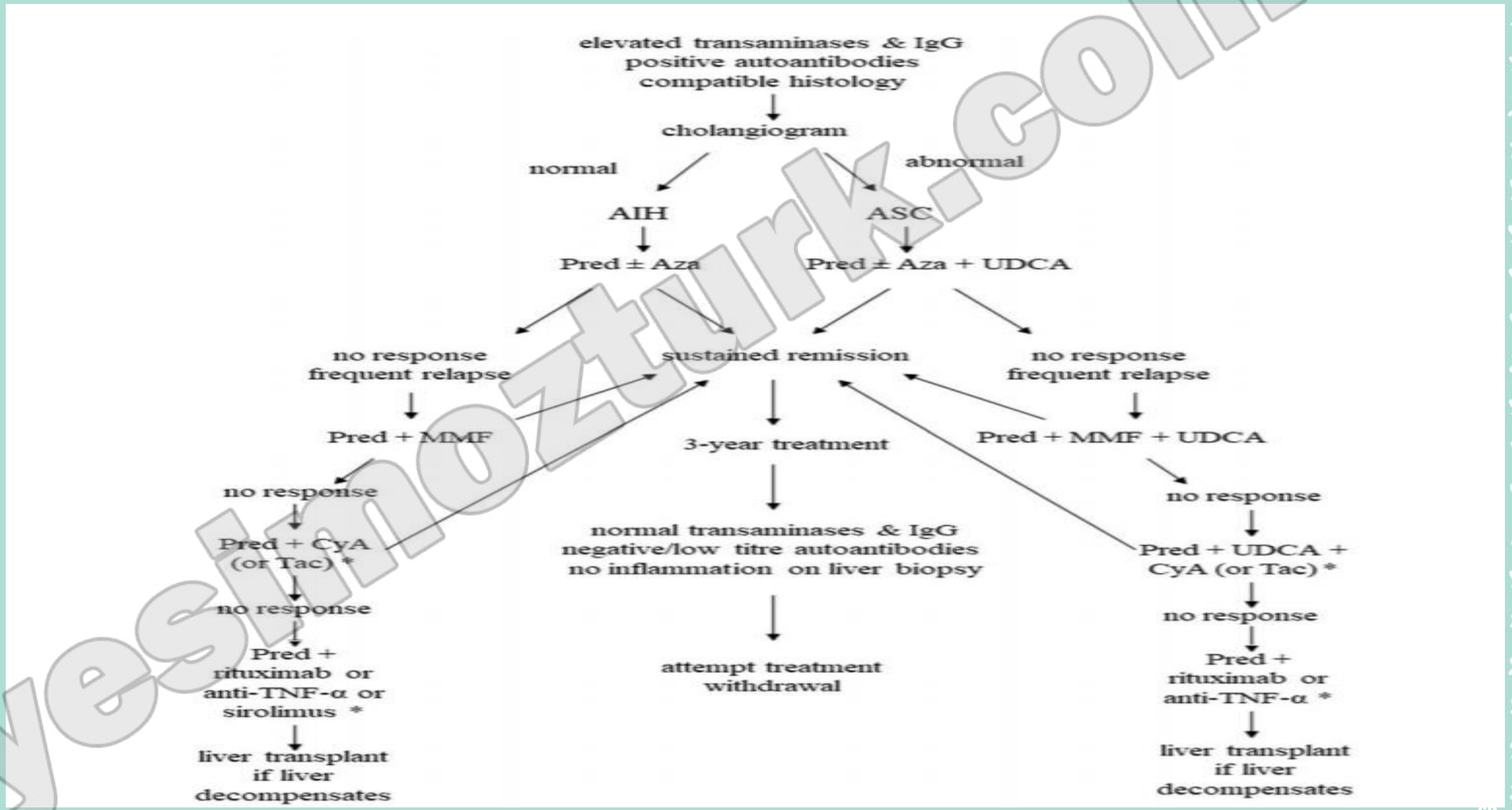
Variable	AIH-1	AIH-2	ASC
Female sex	80%	80%	50%
Male sex	20%	20%	50%
ANA or SMA*			
≥1:20	++	+/−	++
Anti-LKM-1*			
≥1:10	−	++	+/−
Anti-LC-1			
Positive	−	++	−
Anti-SLA			
Positive	+	+	+
pANNA			
Positive	+	-	++
IgG			
>Upper limit of normal	++	+	++
>1.20 Times upper limit of normal	++	+	++
Liver histology			
Compatible with AIH	+	+	+
Typical of AIH	+	+	+
Viral hepatitis (A, B, C, E, EBV), NASH, Wilson disease, and drug exposure	−	−	−
Presence of extrahepatic autoimmunity	+	+	+
Family history of autoimmune disease	+	+	+
Cholangiography			
Normal	+	+	−
Abnormal	−	−	+
Biochemical and immunological response to steroid treatment			
Yes	+	+	+
No	−	−	−

TEDAVİ

TABLE 1. Immunosuppressive treatment regimens for juvenile autoimmune liver disease

	Initial regimen		Maintenance				
AIH	Predni(so)lone	Azathioprine	Prednis(ol)one	Azathioprine	Azathioprine mono-therapy (in AIH-1)	Definition of remission	Treatment length
	2 mg · kg^{-1} · day^{-1} (up to 60 mg/daily) decreased weekly in parallel to transaminase levels decrease to a minimum maintenance dose of 2.5 to 5 mg daily	1–2 mg · kg^{-1} · day^{-1} added gradually if transaminase levels plateau or increase. Alternatively, added in all patients after 2 weeks of predniso(lo)ne treatment	0.1–0.2 mg · kg^{-1} · day^{-1} or 5 mg/day	1–2 mg/kg/day if required	1.2–1.6 mg/kg/day	Normal transaminase and IgG levels; - Negative or low titer (< 1:20) ANA/ SMA -negative anti-LKM-1/anti-LC-1	3 y Before considering suspension
ASC	Predniso(lo)ne ± azathioprine as above, plus ursodeoxycholic acid 15 mg/Kg/day		Predniso(lo)ne ± azathioprine as above, plus ursodeoxycholic acid 15 mg · kg^{-1} · day^{-1}			As above	As above

AIH = autoimmune hepatitis; ANA = anti-nuclear antibody; ASC = autoimmune sclerosing cholangitis; SMA = anti-smooth muscle antibody.



Karaciğer Transplantasyonu

- Otoimmun hepatit tanısı alan çocukların **%10'u,**
- Otoimmun sklerozan kolanjit tanısı alanların ise **%20'si**

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Alimentary Tract

Systematic screening for primary sclerosing cholangitis with magnetic resonance cholangiography in inflammatory bowel disease

Arthur Belle[a], Valérie Laurent[b,1], Lieven Pouillon[a,c,1], Cédric Baumann[d], Xavier Orry[b], Anthony Lopez[a], Hélène Rousseau[d], Jean-Pierre Bronowicki[a], Laurent Peyrin-Biroulet[a,*]

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ABSTRACT

Background: Primary sclerosing cholangitis (PSC) is a major concern in inflammatory bowel disease (IBD).
Aims: Evaluating the use of magnetic resonance cholangiography (MRC) as a screening tool for PSC in IBD patients.
Methods: A single-center cohort study investigating systematic MRC to assess PSC in IBD patients with (cohort 1) and without (cohort 2) liver function tests (LFTs) abnormality, combined with a retrospective analysis of MRCs in a control group of non-IBD patients with abnormal LFTs (cohort 3).
Results: In total, 420 patients (cohort 1: n = 203, cohort 2: n = 30, cohort 3: n = 187) underwent imaging. MRC was classified 'abnormal' in 49/203 (24.1%) patients in cohort 1, in 1/30 (3.3%) patients in cohort 2, and in 66/187 (35.3%) patients in cohort 3 ($p < 0.004$ for all comparisons). PSC was diagnosed in 20/203 (9.9%) patients in cohort 1, in 1/30 (3.3%) patients in cohort 2, and in 13/187 (7.0%) patients in cohort 3 ($p = 0.44$). Gamma-glutamyl transpeptidase was the only independent factor predicting the diagnosis of PSC in IBD (OR 1.8, 95% CI 1.3–2.5, $p = 0.001$).
Conclusions: MRC revealed PSC in one tenth of IBD patients with abnormal LFTs and should be systematically performed in IBD patients with abnormal LFTs, especially if gamma-glutamyl transpeptidase level is elevated.

Bozulmuş karaciğer fonksiyon testleri varlığında İBH hastalarında yapılan MRCP taramasında %10 oranında PSK saptanmış

Liver Enzyme Elevations Within 3 Months of Diagnosis of Inflammatory Bowel Disease and Likelihood of Liver Disease

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ABSTRACT

Background: Inflammatory bowel disease–associated liver diseases (IBD-LDs) include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and an overlap syndrome. Prospective unbiased multicenter data regarding the frequency of IBD-LD in patients with pediatric inflammatory bowel disease (IBD) are lacking. We examined early alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) elevations in children diagnosed as having IBD and assessed the likelihood of IBD-LD.

Methods: Data collected from the prospective observational Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry enrolling children of age <16 years within 30 days of diagnosis. AIH, IU/L compared with 21 of 42 (50%) of patients with both ALT and GGT > 50 (odds ratio 660, $P < 0.0001$). Of the 29 patients with IBD-LD, 21 had PSC, 2 had AIH, and 6 had overlap syndrome. IBD-LD was more common in patients with ulcerative colitis and IBD-unclassified (indeterminate colitis) than in those with Crohn disease (4% vs 0.8%, respectively, $P < 0.001$).

Conclusions: Elevation of both ALT and GGT within 90 days after the diagnosis of IBD is associated with a markedly increased likelihood of IBD-LD. Both ALT and GGT levels should be measured in all of the pediatric patients newly diagnosed as having IBD.

- Pediatrik inflamatuar barsak hastalığında karaciğer hastalığı eşlik etme oranı %1.8 ile %15.1 aralığında değişmekte
- Bu çalışmada IBH tanısı alan hastalarda anormal ALT ve GGT değerlerindeki yüksekliğin bizi IBH ilişkili karaciğer hastalığı konusunda uyarması gerektiği vurgulanmış.

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Liver, Pancreas and Biliary Tract

Pediatric autoimmune liver disease and extra-hepatic immune-mediated comorbidities

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ABSTRACT

Background: Autoimmune liver disease (AILD) includes autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC). AILD is often associated with other extra-hepatic immune-mediated disorders (EDs), but there are few pediatric studies available to date. In this study we evaluated the association between AILD and EDs in our pediatric series.
Methods: In this single centre retrospective study 48 patients (39 AIH and 9 ASC children) were evaluated. Thirty-six children were primarily referred to our Centre for liver disease suspicion, while the remaining twelve had a previous diagnosis of EDs. All the patients were screened for various EDs at AILD diagnosis and yearly during the follow-up.
Results: Mean duration of follow-up was 9 years and 1 month. Twenty-two (46%) patients had a diagnosis of EDs. Ulcerative colitis (UC) was the most frequent EDs (9 patients), followed by autoimmune thyroid disease (5 patients) and celiac disease (5 patients). In 7 out of 9 UC patients, ASC was present.
Conclusions: Our study showed a high association (46%) between AILD and EDs. In particular, in 8 out of 9 ASC patients UC was diagnosed (p-value 0.007). It is important to look for EDs in AILD children and, conversely, AILD in EDs children with abnormal liver function tests.

Pediatrik otoimmun karaciğer hastalığı olan hastalar tarandığında otoimmun extraintestinal hastalığın %46 oranında eşlik ettiği sapanmış.

Bu çalışmada özellikle %10 oranında otoimmun tiroidit ve çölyak hastalığı ile ilişkili saptanmış

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Clinical course and prognosis of pediatric-onset primary sclerosing cholangitis

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Abstract

Background: The natural history of pediatric-onset primary sclerosing cholangitis (PSC) and overlap with autoimmune hepatitis (PSC/AIH) is poorly known.

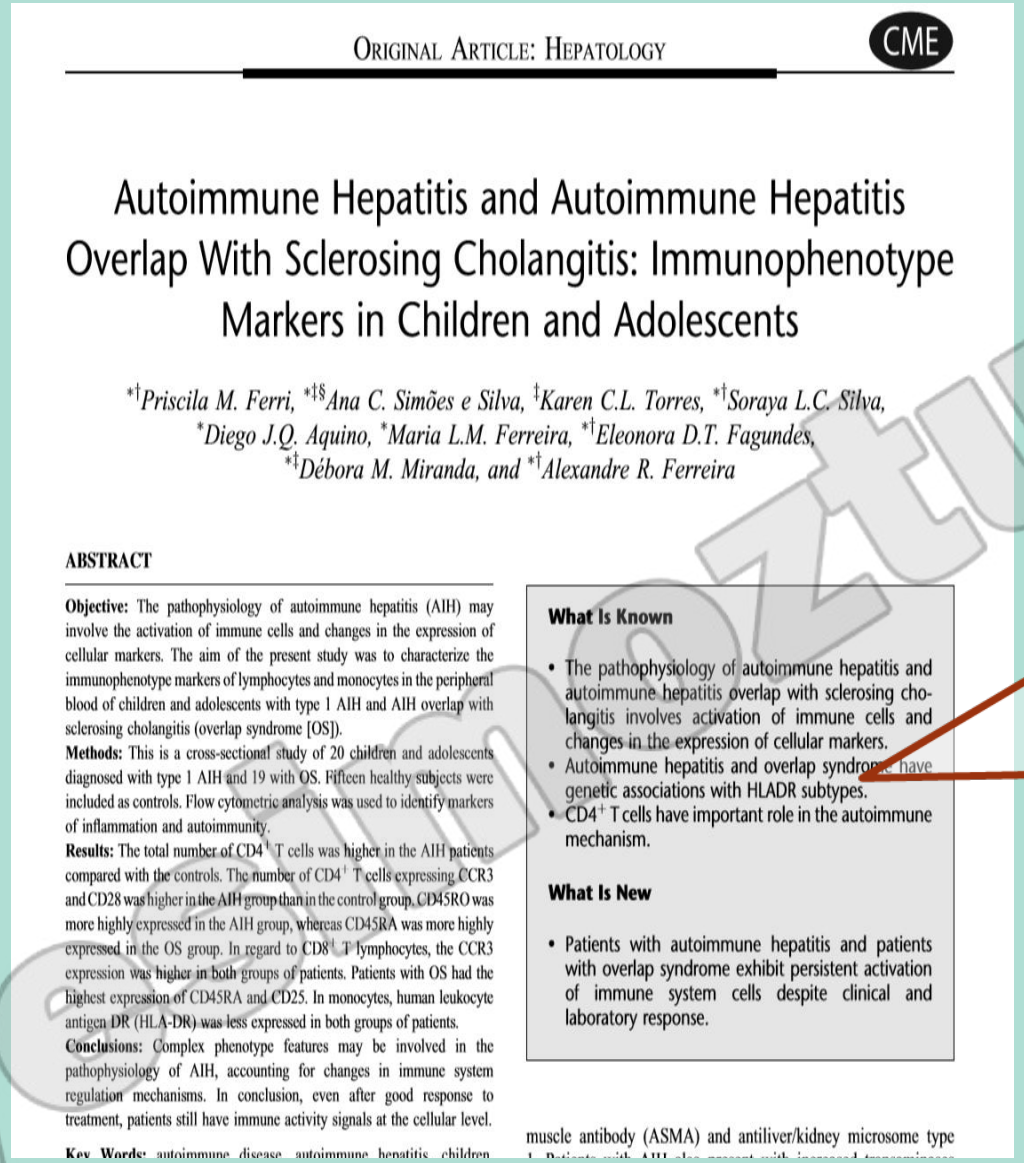
Objective: The aim of this study was to evaluate the clinical outcome of patients with pediatric-onset disease in a tertiary referral center.

Methods: We traced 33 patients (median age at diagnosis 16 years), with PSC or PSC/AIH in cholangiography and liver histology diagnosed between December 1993 and 2011, at Helsinki University Hospital. Diagnostic procedures and long-term follow-up were reassessed until the end of December 2013.

Results: PSC was confirmed in all 33 patients; 19 of them had an overlap with AIH. At diagnosis, three of 33 had cirrhosis. Inflammatory bowel disease (IBD) was associated in 76% of the patients, mostly ulcerative colitis (70%); treatment of IBD being a minor determinant of the clinical outcome of liver disease. In the last follow-up (median nine years), all patients were alive, and no malignancy occurred. Most patients (91%) were on ursodeoxycholic acid and 12 PSC/AIH patients on immunosuppression. Endoscopic retrograde cholangiography during follow-up showed a progression of intra-hepatic disease in 12 patients (36%). Four patients (12%) had undergone liver transplantation, and one was listed; no recurrence of the disease in the graft was seen.

Conclusion: The clinical course and outcome of pediatric-onset PSC and PSC/AIH seem to be favourable in the majority of patients until early adulthood. In about one-third of patients, however, PSC is progressive, challenging the current treatment guidelines and warranting further studies on disease pathogenesis.

PSK ve PSK/OİH overlap durumunun çocukluk yaş grubunda karaciğer yetmezliğine kadar giden klinik tablo oluşturabileceği
Genelde İBH ile olsa da bozulmuş karaciğer fonksiyon testleri varlığında ayırıcı tanıda aklımızda olması gerektiğini unutmamalıyız



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CME

Autoimmune Hepatitis and Autoimmune Hepatitis Overlap With Sclerosing Cholangitis: Immunophenotype Markers in Children and Adolescents

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ABSTRACT

Objective: The pathophysiology of autoimmune hepatitis (AIH) may involve the activation of immune cells and changes in the expression of cellular markers. The aim of the present study was to characterize the immunophenotype markers of lymphocytes and monocytes in the peripheral blood of children and adolescents with type 1 AIH and AIH overlap with sclerosing cholangitis (overlap syndrome [OS]).

Methods: This is a cross-sectional study of 20 children and adolescents diagnosed with type 1 AIH and 19 with OS. Fifteen healthy subjects were included as controls. Flow cytometric analysis was used to identify markers of inflammation and autoimmunity.

Results: The total number of $CD4^+$ T cells was higher in the AIH patients compared with the controls. The number of $CD4^+$ T cells expressing CCR3 and CD28 was higher in the AIH group than in the control group. CD45RO was more highly expressed in the AIH group, whereas CD45RA was more highly expressed in the OS group. In regard to $CD8^+$ T lymphocytes, the CCR3 expression was higher in both groups of patients. Patients with OS had the highest expression of CD45RA and CD25. In monocytes, human leukocyte antigen DR (HLA-DR) was less expressed in both groups of patients.

Conclusions: Complex phenotype features may be involved in the pathophysiology of AIH, accounting for changes in immune system regulation mechanisms. In conclusion, even after good response to treatment, patients still have immune activity signals at the cellular level.

What Is Known

- The pathophysiology of autoimmune hepatitis and autoimmune hepatitis overlap with sclerosing cholangitis involves activation of immune cells and changes in the expression of cellular markers.
- Autoimmune hepatitis and overlap syndrome have genetic associations with HLADR subtypes.
- $CD4^+$ T cells have important role in the autoimmune mechanism.

What Is New

- Patients with autoimmune hepatitis and patients with overlap syndrome exhibit persistent activation of immune system cells despite clinical and laboratory response.

muscle antibody (ASMA) and antiliver/kidney microsome type

- Otoimmün hepatit ve sklerozan kolanjitin HLADR subtipleri ile birlikteliği
- CD4+ T hüclerin otoimmünitede rol oynadığı
- Tedavi ile klinik ve labaratuar olarak iyileşen hastalarda hücresel düzeyde immun yanıtın devam ettiği gösterilmiş

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Case report

Acute-on-chronic hepatitis. A case report of autoimmune hepatitis/primary sclerosing cholangitis/ulcerative colitis overlap syndrome in a 15-year-old patient

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Abstract

Acute-on-chronic liver failure (ACLF) is a disease in which a rapid deterioration of liver function occurs in patients with chronic liver disease, and is usually associated with a precipitating event. We present the case of a boy with autoimmune hepatitis/primary sclerosing cholangitis/ulcerative colitis (AIH/PSC/UC) overlap syndrome, in whom liver function was stable for 4.5 years of treatment. At 15 years of age the patient was hospitalized due to a deterioration of his general condition, severe abdominal pain, diarrhoea, vomiting and weight loss. There was also a rapid deterioration of liver function and a deterioration of renal function. Despite a wide spectrum of diagnostic examinations, no precipitating agent was found. After two episodes of massive bleeding from the gastrointestinal tract, the patient was transferred to the intensive care unit. The patient underwent a successful liver transplantation. ACLF can cause irreversible liver failure with a high mortality rate, which calls for liver transplantation.