Kocaeli Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı

Çocuk İmmünolojisi ve Alerji Bilim Dalı

Olgu Sunumu

24 Aralık 2020

Dr. Yasemin Özgen

OLGU 1

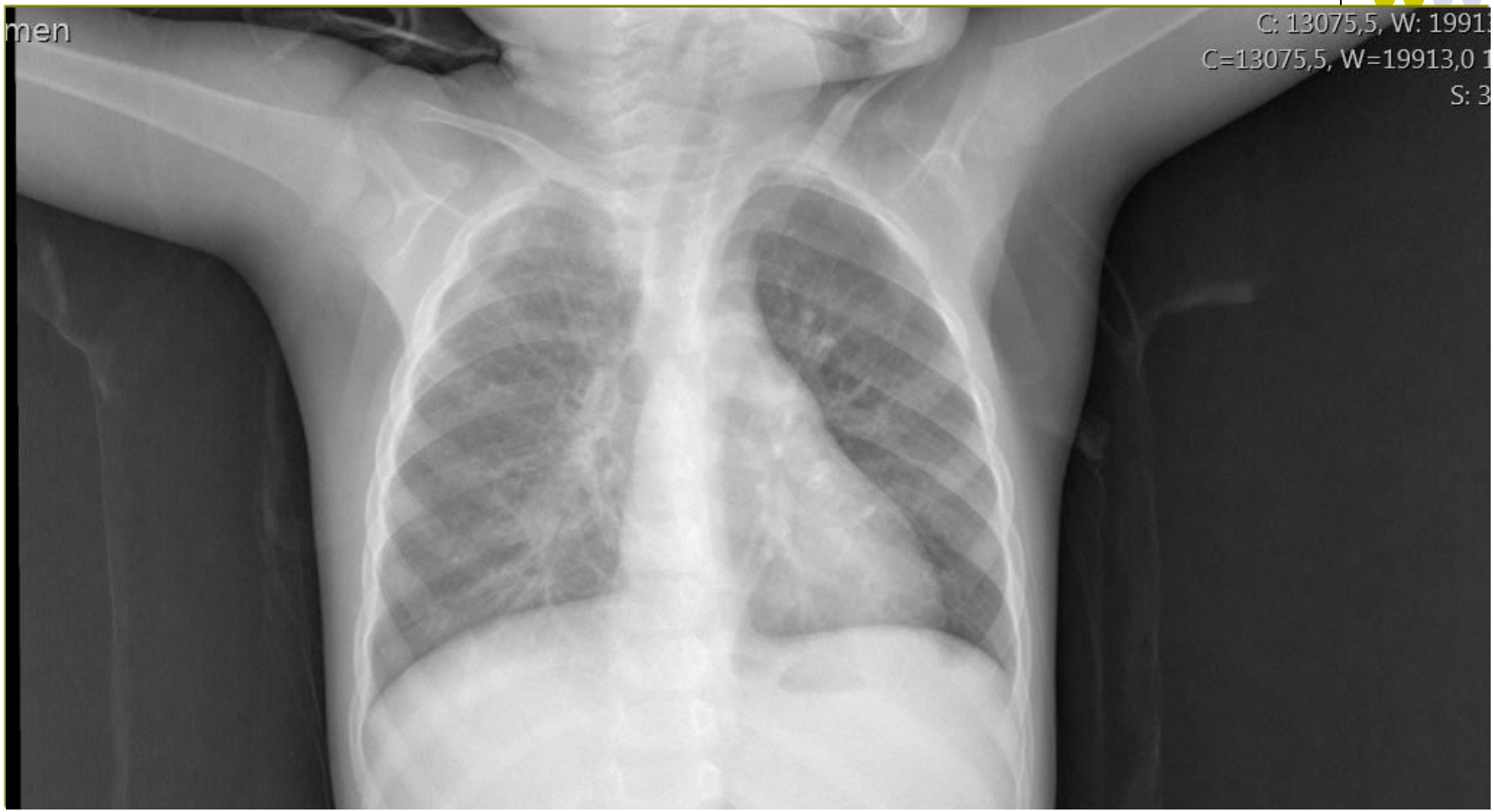
- 2,5 yaş, erkek hasta
- Son 1 aydır geçmeyen öksürük ve hırıltı
- 1 yaşına kadar atopik dermatit dışında yakınma yok, 1 yaşında bir kez ve son 6 ay içinde 2 kez pnömoni tanısı ile yatış olmuş. 3 kez de ayaktan bronşit tanısı ile antibiyoterapi almış.
- Haftada 2-3 kez cıvık ve mukuslu dışkılama oluyormuş, 2-3 ayda bir AGE nedeni ile hastane başvurusu var.

OLGU 1

- Anne-baba 3. derece akraba, ailenin tek çocuğu
- Annenin 3 kuzeni 1 yaş altında ishal nedeniyle ölmüş.

- Lenf bezi palpe edilemedi. Tonsiller bilateral görülemedi, sağ hemitoraksta belirgin olmak üzere krepitan ral+

- Hemogram, akut faz reaktanları, biyokimyasal parametreler normal
- (Beyaz küre: 9700/mm3 (lenf: 4800/mm3))


men
C: 13075,5, W: 1991
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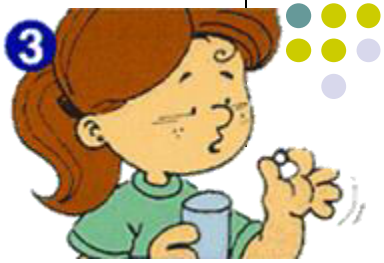
Ön tanı?

Tetkik ?

İmmün Yetmezlik Düşündüren 10 Klinik Bulgu

Yılda sekizden fazla ÜSYE

Yılda ≥ 2 sinüs infeksiyonu



≥ 2 ay antibiyotik kullanımı

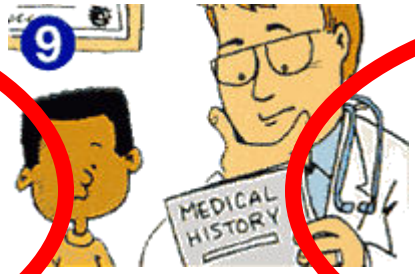
Yılda ≥ 2 pnömoni

Gelişme geriliği

Tekrarlayan cilt veya organ abseleri

Persistan oral moniliazis

IV tedavi gereksinimi



≥2 derin doku infeksiyonu, Fırsatçı m.o enf

Aile öyküsü

Jeffrey Modell Foundation

Birinci basamak testler

- Tam kan sayımı, periferik yayma
- Kantitatif immunglobulin(IgG,IgM,IgA,IgE)
- Doğal antikor titreleri(izohemaglutininler, anti-A,B)
- Spesifik antikor titreleri (protein,polisakkarid)
- Nitroblue tetrazolium (NBT) ve dihidrorhodamin (DHR) testleri
- Kompleman sistemi taraması
- Geç tip aşırı duyarlılık testleri(PPD,candidin)
- Radyolojik değerlendirme

Laboratuvar İncelemeler

Genel İncelemeler; Tam kan sayımı, tam idrar tetkiki,

Mikrobiyolojik ; Kültür

Humoral immün yetersizliklerde;

Serum IgG, IgM. IgA düzeyi

Isohemaggülitinin titreleri

Spesifik antikor yanıtı (AntiHbs,tetanoz,difteri,Hib gibi)

Hücresel immün yetersizliklerde

Lökosit ve lenfosit sayımı

Total B, T lenfosit ve Th, Ts oranları

Geç aşırı deri duyarlık testleri.

In vitro T hücre stimulasyonumitojenler (PHA,ConA) antijen (kandida,tetanoz)

Akciğer grafisi: Timus görüntülemesi

Fagosit fonksiyonları

Total Nötrofil sayımı,NBT

NK hücre sayımı

Kompleman Sistemi; CH 50 , kompleman düzeyi

Laboratuvar

IgA: 1 mg/dl (14-123)

IgM: 10 mg/dl (48-168)

IgG: <75 mg/dl (424-1051)

izohemaglutinin: yeterli antikor oluşturamadığı için bakılamadı.

AntiHbs :negatif

III. Predominantly Antibody deficiencies. a: Hypogammaglobulinemia

IgG, IgA and/or IgM ↓↓

Exclude second causes: drugs [Hx], myeloma [bone marrow], lymphoma. Ig loss (not hypo-IgM) in urine, gastro-intestinal or skin.

→ B Lymphocyte (CD19+) chamberation (CMF)

Bc absent

Severe bacterial infection. All Ig isotypes decreased.

X-Linked Agammaglobulinemia. *BTK.* Some patients have detectable Ig. ProBc: Nl

AR :

μ heavy chain Def. *IGHM*
Igα def*. *CD79A*, Igβ def*. *CD79B*
BLNK def*. *BLNK*, λ5 def. *IGLL1*,** ProBc: Nl

E47 transcription factor def*. *TCF3* Severe, failure to thrive.
p85 def. *PIK3R1*.** Cytopenia. ProBc:↓
p110δ def. *PIK3CD*.** Autoimmune complications.
ZIP7 def*. *SLC39A7*. Early onset infections, blistering dermatosis, thrombocytopenia

AD

E47 transcription factor def*. *TCF3*.
Hoffman syndrome*. *TOP2B*. Facial dysmorphism, limb anomalies

Bc >1 %

Commun Variable Immunodeficiency Phenotype

CVID with no gene defect specified. Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease

Activated p110δ syndrome (APDS) AD. Severe bacterial infections. Lymphadenopathy, lymphoproliferation, lymphoma. Reduced memory Bc and increased transitional Bc. ***PIK3CD GOF***. EBV± CMV viremia, autoimmunity. ***PIK3R1***. Developmental delay.

PTEN Deficiency (LOF)*. *PTEN*. *AD*. Lymphoproliferation, Autoimmunity. Developmental delay.

ARHGEF1 deficiency. *ARHGEF***. Recurrent infections, bronchiectasis.

SH3KBP1 deficiency *SH3KBP1*** *(CIN85). XL*. Severe bacterial infections.

SEC61A1 deficiency.* *SEC61A1*. *AD,* Severe recurrent respiratory tract infections

RAC2 deficiency. *RAC2***. *AR,* Recurrent sinopulmonary infections, poststreptococcal glomerulonephritis; urticaria. Some have selective IgA def.

CD19 deficiency*. *CD19*. Recurrent infections, may have glomerulonephritis.

CD81 deficiency*. *CD81*. Recurrent infections, may have glomerulonephritis. Phenocopy of CD19 deficiency.

CD21 deficiency*. Recurrent infections. Low IgG, impaired anti-pneumococcal response.

TRNT1 deficiency. *TRNT1*. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and hypogammagl.

NFKB1 deficiency. *NFKB1*. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia and autoimmune thyroiditis. Ig Nl or ↓, Bc ↓ or Nl, ↓ memory Bc.

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BAFF receptor deficiency*. *TNFRSF13C* *(BAFF-R)*. Variable clinical expression. Low IgG and IgM.

TWEAK deficiency. *TWEAK*** *(TNFSF12). AD*. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody.

IRF2BP2 deficiency. *IRF2BP2***. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulenia, absent IgA.

Sekonder İY

- İlaçlar

-steroid

-kemoterapi

- Lenfosit-antikor kaybı

-nefrotik sendrom

-protein kaybettiren enteropati

-yanık

- Dalağın alınması

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CD45-SS grafiğindeki hücre bölge dağılımı şu şekildedir:

-Myeloid	: %37,64	Monosit	:%10,66
-Lenfosit	: %47,50	R1	: %1,14
-CD45 negatif	: %1,41		

CD45- SS grafiğinde **LENFOSİT** %47,50 oranında yer almaktadır. Okumalar, **LENFOSİT** bölgesinin FS-SS grafiğine aktarılması ile elde edilen ve söz konusu hücre populasyonunun %46,92 kadar temsil edildiği *gate* 'lerde yapılmıştır.

	%46,92	NORMAL DEĞER
CD3+	: %88,90	(51-79)
CD3+16-56-	: %83,90	(51-79)
CD3-16+56+	: %8,13	(5-23)
CD3+4+	: %44,18	(31-54)
CD3+8+	: %36,09	(10-31)
CD45RA+	: %74,06	(72-93)
CD45RO+	: %31,98	(9-31)
CD4+CD45RA+	: %29,95	(25-45)
CD4+CD45RO+	: %11,56	(6-21)
CD19+	: %0,27	(17-41)
CD20+	: %0,18	(13-40)
HLA-DR (Lenfosit)	: %10,77	(13-48)
TCR γ/δ (GAMA/DELTA)	: %15,79	
HLA-CLASS I (ABC)	: %98,94	

YORUM

Tip ve alt tip ayrımının klinik bulgular, morfolojik ve diğer yöntemlerle yapılması/ desteklenmesi uygundur.

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- TANI

X-LİNKED AGAMMAGLOBULİNEMİ
(BRUTON AGAMMAGLOBULİNEMİSİ)

OLGU 2

- 14 yaş, erkek hasta
- 4 yaşından sonra yılda yaklaşık 6 kez hastane başvurusu gerektirecek kadar yoğun öksürükleri ve hırıltıları nedeniyle astım tanısı konmuş.
- Son 2-3 yıldır anti-astmatik ilaçlardan yarar görmüyormuş, persistan produktif öksürük şikayeti gelişmiş.
- Son 1 yılda pnömoni nedeniyle yatışı olmuş ve 3 kez sinüzit tanısı ile ayaktan antibiyoterapi almış

OLGU 2

- Anne-baba akraba değil.
- Babada astım tanısı var, 9 yaş erkek kardeş sağlıklı.
- Boy ve kilo 10 p, 3-4 cm boyutunda dalak büyüklüğü mevcut.
- BK: 6230 /mm3 (lenf: 2400/mm3), Hb:14.4 gr/dl Sedimentasyon:11 mm/saat
- PA akc : normal
- İnhaler alerjen prik test:negatif,SFT normal

Laboratuvar İncelemeler

Genel İncelemeler; Tam kan sayımı, tam idrar tetkiki,

Mikrobiyolojik ; Kültür

Humoral immün yetersizliklerde;

Serum IgG, IgM. IgA düzeyi

Isohemaggülitinin titreleri

Spesifik antikor yanıtı (AntiHbs,tetanoz,difteri,Hib gibi)

Hücresel immün yetersizliklerde

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Akciğer grafisi: Timus görüntülemesi

Fagosit fonksiyonları

Total Nötrofil sayımı,NBT

NK hücre sayımı

Kompleman Sistemi; CH 50 , kompleman düzeyi

Laboratuvar

IgA: 58 mg/dl (65)
IgM: 69 mg/dl (56)
IgG: 555 mg/dl (748)
izohemaglutinin: 1/32
Anti-hbs: 6.3 U

- Pnömokok antikorları: Aşı öncesi:0.12 mcg/dl
  4 hafta sonra:0.15 mcg/dl

Ön tanı?

Tetkik ?

- Flowsitometrisinde

CD 3: %69

CD4 : %14

CD 8 : %52

CD 16+56+: %15

CD 19 : %12.2

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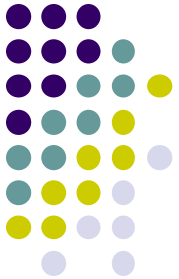
TANI

Yaygın değişken immün yetmezlik (CVID)

OLGU 3:



- 10 aylık kız hasta
- 5. aydan sonra başlayan, ayda bir kez olan ve acil başvurusu gerektiren hırıltı, öksürük
- Anne-baba akrabalık yok.
- 7 yaşında erkek kardeşi astım tanılı
- Ailede bilinen immün yetmezlik tanısı yok
- Gelişimi normal
- Fizik muayene normal
- BK:9300/mm3(lenfosit:3920/mm3)

Laboratuvar

(dış merkezde bakılan)
IgA: 35 mg/dl (12-99)
IgM: 45 mg/dl (34-215)
IgG: 300 mg/dl (381-1221)
Anti-hbs: 150 U
İzohemaglutinin:1/8

Laboratuvar

- FLOW SİTOMETRİ:
  - CD 3 %65
  - CD 4 %40
  - CD 8 %25
  - CD 16+56+%5
  - CD 19 %12
  - CD 20 %10
  - HLA DR %64

Ön tanı?

Tetkik ?

III. Predominantly Antibody deficiencies.

b: Other Antibody deficiencies

Severe Reduction in Serum IgG and IgA with Normal or elevated IgM and Normal Numbers of Bc : Hyper IgM Syndromes

AID deficiency.
AICDA. AR or AD.
Bacterial infections, enlarged lymph nodes and germinal centers. Nl memory Bc, but lacking somatic hypermutation in AR form.

UNG deficiency. ***UNG.***
Enlarged lymph nodes and germinal centers.

INO80 def*. ***INO80 .***
Severe bacterial infections.

MSH6*. ***MSH6 .***
Family or personal history of cancer. Variable IgG, defects, increased IgM in some, Nl Bc, low switched memory Bc.

Isotype, Light Chain, or Functional Deficiencies with Generally Nl Numbers of Bc

Selective IgA deficiency. ***Unknown.***
May be asymptomatic. Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies.

Transient hypogammaglobuliemia of infancy. Unknown.
Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased.

IgG subclass deficiency with IgA deficiency. ***Unknown.***
Recurrent bacterial infections. May be asymptomatic. Reduced IgA with decrease in one or more IgG subclass.

Isolated IgG subclass deficiency. ***Unknown.***
Usually asymptomatic, a minority may have poor antibody response t specific antigens and recurrent viral/bacterial infections. Reduction in one or more IgG subclass.

Specific antibody deficiency with normal Ig levels and normal B cells ***Unknown.***
Reduced ability to produce antibodies to specific antigens. Ig: Nl.

Ig heavy chain mutations and deletions.
Mutation or chromosomal deletion at 14q32.
May be asymptomatic. One or more IgG and/or IgA subclasses as wel as IgE may be absent.

Kappa chain deficiency*. ***IGKC.***
Asymptomatic. All immunoglobulins have lambda light chain.

Selective IgM deficiency. ***Unknown.*** Pneumococcal / bacterial infect ns. Absent serum IgM.

High Bc numbers due to constitutive NF-κB activation

ARD11 GOF .

ARD11. AD. BENTA syndrome

plenomegaly,

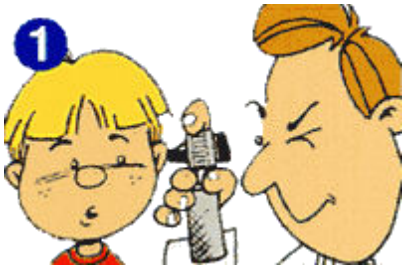
mphadenopathy,

oor vaccine responses.

TANI

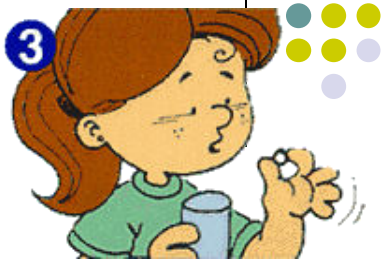
- SÜT ÇOCUĞUNUN GEÇİCİ HİPOGAMMAGLOBULİNEMİSİ(SGHG)

İmmün Yetmezlik Düşündüren 10 Klinik Bulgu



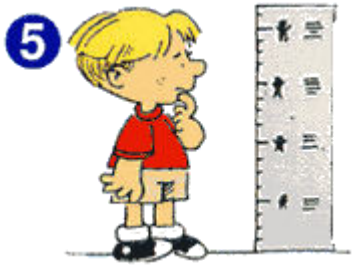
Yılda sekizden fazla AOM

Yılda ≥ 2 sinüs infeksiyonu



≥ 2 ay antibiyotik kullanımı

Yılda ≥ 2 pnömoni



Gelişme geriliği

Tekrarlayan cilt veya organ abseleri

Persistan oral moniliazis

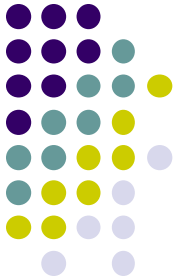
IV tedavi gereksinimi

2 derin doku infeksiyonu, Fırsatçı m.o enf

Aile öyküsü

Jeffrey Modell Foundation

Labaratuvar değerlendirmede 1. basamak testler



Tam kan sayımı ve periferik yayma

Kantitatif Ig seviyeleri: Ig A,M,G,E

İzohemaglutiniler

Gecikmiş tipte hipersensitivite testleri

Akciğer grafisi: Timusun görüntülenmesi için

CH50

NBT

İmmun yetersizlik düşündüren özellikler-Laboratuvar

- Kronik lenfopeni

-1 yaş altı 3000/mm3

-1 yaş üstü 1500/mm3

- Nötropeni
- Kronik lökositoz
- Eozinofili(%<4)
- Trombositopeni, anemi
- Agammaglobülinemi,hipogammaglobülinemi
- PY: nötrofil granül yokluğu,mikrotrombosit,dev granül

Primer İmmün Yetersizlikler

I-Antikor Eksiklikleri

II- Kombine İmmün Yetersizlikler

III-Diğer iyi tanımlanmış immün yetersizlikler

IV-Immün sistemin regülasyon bozukluğuna bağlı hastalıklar

V- Fagositin sayısal, işlev bozukluğu

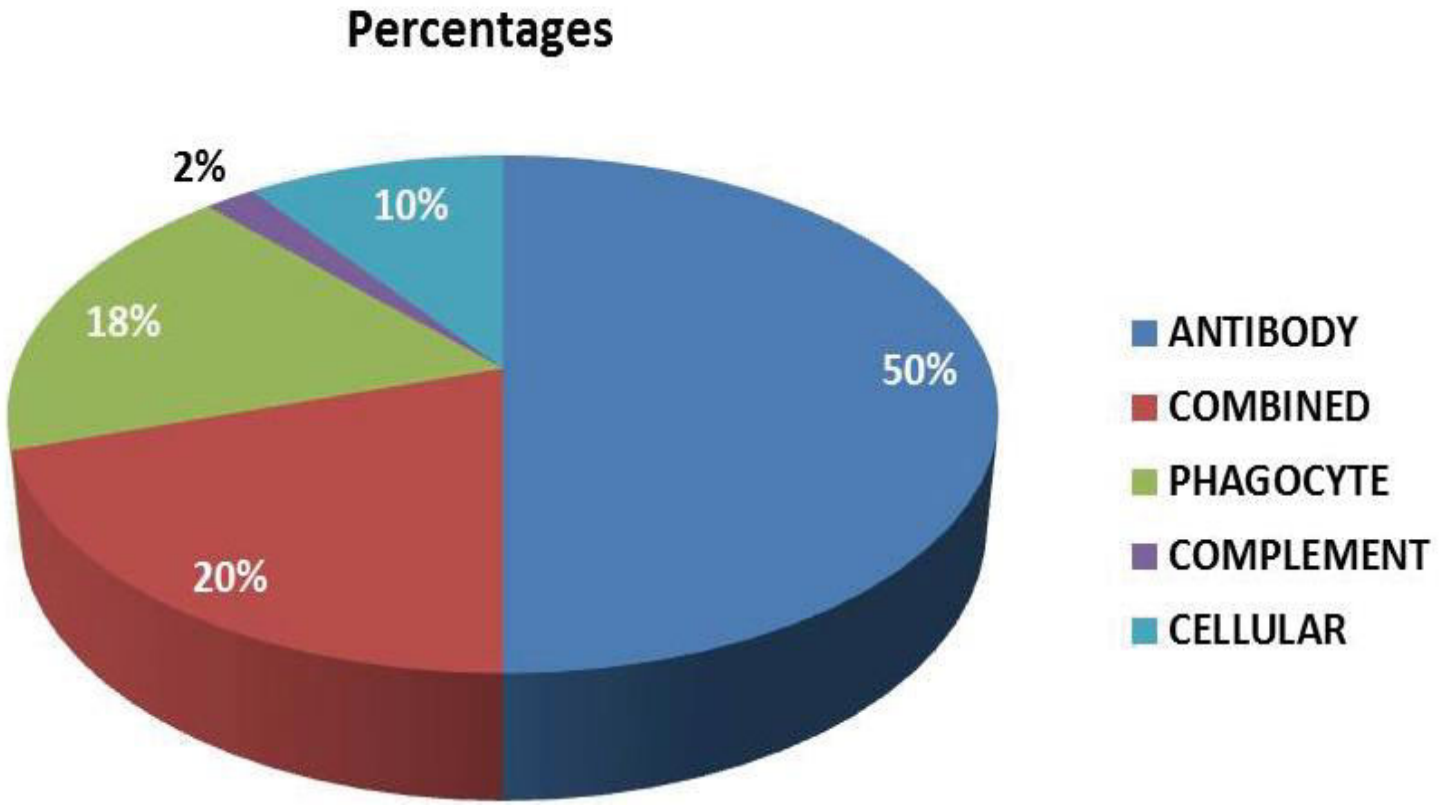
VI- Doğal immün Sistemde eksiklik ile seyreden

VII- Otoinflamatuvar hastalıklar

VIII- Kompleman eksikliği

Notarangelo L, Casanova JL ve ark .
J Allergy Clin Immunol 2006;117;4;883-896

The Primary Immune Deficiencies



Humoral İmmün Yetmezlik Hastalıklar:

- Süt çocuğunun geçici hipogammaglobulinemisi
- Konjenital X'e bağlı agammaglobülinemi (Bruton) hastalığı
- Yaygın değişken immün yetmezlik (CVID)
- Selektif IgA eksikliği
- Selektif IgM eksikliği
- IgG subgrup eksikliği

Süt çocuğunun geçici hipogammaglobulinemisi:

- 6 aydan büyük çocuklarda altta yatan başka bir neden olmaksızın IgG' nin düşük olması
- Süt çocukluğu döneminde immünoglobulin sentezinde gecikme
- Sık enfeksiyon geçirebilir ya da asemptomatik olup tarama sırasında tesadüfen tanı alabilirler.
- Hastaların muayenesi normaldir (tonsil dokusu var) ve akciğer filminde timus dokusu görülür.
- SGH tanısı hastanın klinik ve laboratuar bulgularının takibi ve bu bulguların düzeldiğinin görülmesi ile konulur.

X-bağımlı agamaglobulinemi (Bruton hastalığı)

- X' e bağlı resesif, Bruton tirozin geninde mutasyon
- Pre-B→B diferansiasyon bozukluğu
- İmmünglobülin (Ig) oluşmaz
- Erkeklerde görülür, erken yaşta belirir
- Otoimmün hastalıklar artmıştır
- İnfeksiyonlar,bakteri,enterovirüs ,Giardia lambdia inf. artmıştır

Common variable" Yaygın değişken immün yetmezlik

- Bruton hastalığına benzer, ancak her iki cinste de görülür
- B hücrelerinin → plazma hücrelerine dönüşümünde sorun vardır
- Hipogamaglobulinemi (özellikle IgG' de)
- Çoğu zaman ileri yaşlarda belirir
- Otoimmün hastalık ve lenfoid tümörlere eğilim vardır

İzole IgA yetmezliği

- Primer immün yetmezlikler içinde en sık olandır
- Nüks sinopulmoner infeksiyonlar ve diare görülür
- %40 ında IgA' ya karşı antikorlar vardır
- IgA içeren kan ürünlerinin transfüzyonu anafilaksiyi tetikleyebilir
- %20 sinde IgG2 eksikliği vardır
- Otoimmün hastalıklar artmıştır

Özellikler	Süt çocuğunun Geçici Hipogammaglobulinemisi	Selektif IGA Eksikliği	Bruton Hastalığı	CVID
Başlangıç	1-2 yaş	Her hangi bir yaş	Kongenital (>6 ay)	Herhangi bir yaş (>2 yaş)
Görülen Enfeksiyonlar	Beklenmez	Belirgin enfeksiyon yok yada tekrarlayan otit, sinüzit,	Tekrarlayan pnömoni, sinüzit ve otit	Tekrarlayan pnömoni, sinopulmoner enfeksiyonlar,
IgG	Düşük	Normal	Düşük/yok	Düşük
IgA	Normal	<7mg/dl	Düşük/yok	Düşük/yok
IgM	Normal	Normal	Düşük/yok	Normal/Düşük
CD19 B lenfosit yüzdesi	Normal	Normal	%0	Normal veya %2-10
Moleküler defekt	Bilinmiyor	Bilinmiyor	B-hücre tirozin kinaz	Bilinmiyor

Özellikler	Süt çocuğunun Geçici Hipogammaglobulinemisi	Selektif IGA Eksikliği	Bruton Hastalığı	CVID
Tonsil dokusu	var	var	yok	var
Hepatosplenomegali	yok	nadir	yok	sık
Büyüme gelişme geriliği	yok	nadir	Nadir	sık
Bronşiektazi	Yok	Nadir	Bezen	Sık
Sık görülen MO	Hayır	Hayır	Evet	Evet
Eşlik eden hastalıklar	Süt çocuğunun Geçici Hipogammaglobulinemisi	Alerji (astım) ve otoimmün hastalıklar (JRA, otoimmün troidit)	CVID kadar sık değil ancak malignite ve otoimmün hastalıklar eşlik edebilir	Malignite (özellikle lenfoma), IBD, romatizmal hastalıklar (özellikle JRA) ve diğer otoimmün
IgG replasmanı	Hayır	Hayır	Evet	Evet

- TEŞEKKÜRLER…