UNIVERSITÄTS KLINIKUM FREIBURG

The complex veiled among the common Variables

CVID – Next generation

SLIPI Stromstad 2019

Klaus Warnatz

Centrum für Chronische Immundefizienz

http://www.worknetdupage.org/blog/wp-content/uploads/2016/09/featured-image-2-750x380.jpg

Disclosures

I have received honoraria as a speaker from Shire/Baxalta, Biotest, CSL Behring, LFB Octapharma, Abbott, Pfizer, Merck, Roche.

I have participated as a consultant on advisory boards of Baxalta, Biotest, CSL Behring, LFB.

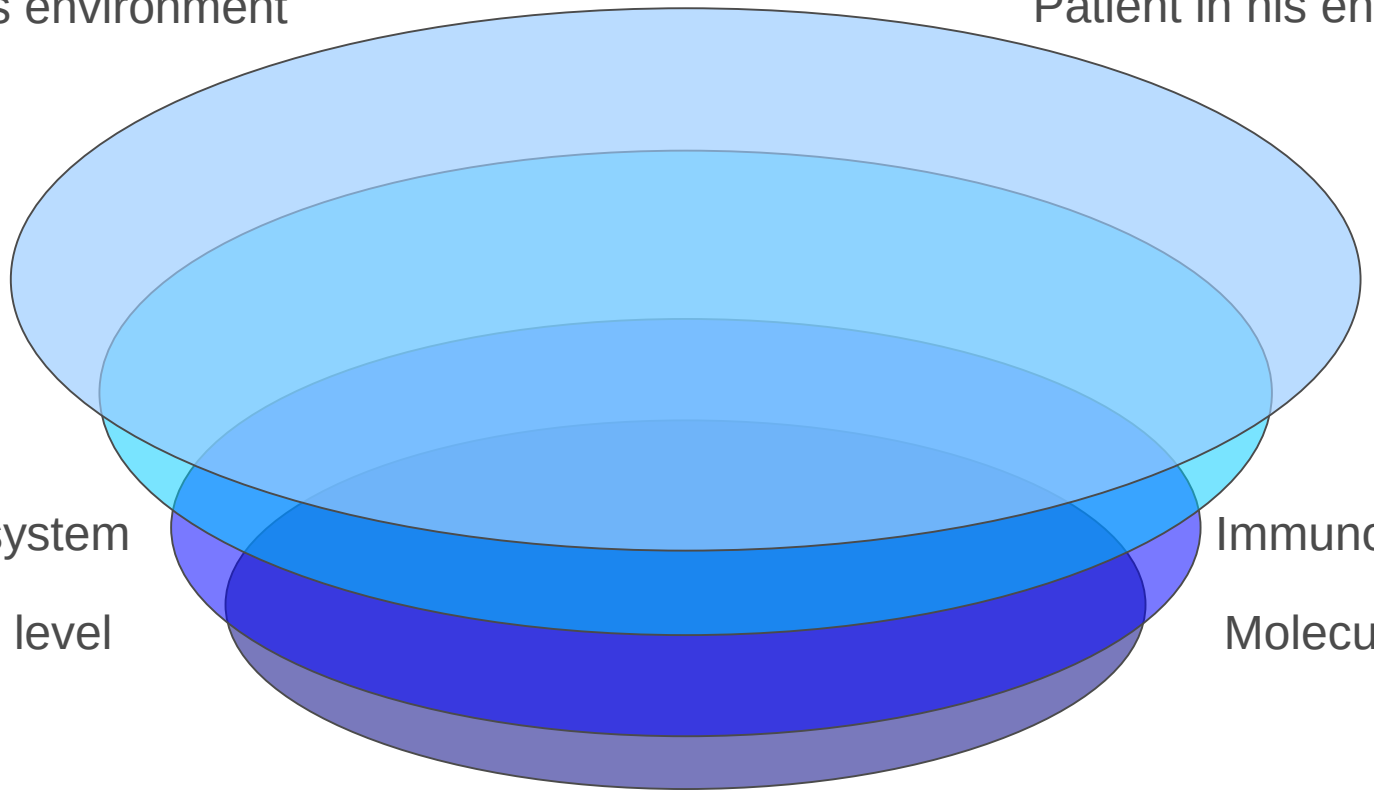
I have received scientific grants from Baxalta, Biotest, BMS, CSL Behring.

Complex systems - complex disorders

Some general introducing thoughts

Man in his environment

Patient in his environment



Man

Patient

Immune system

Immunodeficiency

Molecular level

Molecular defects

Example: Immunodeficiency

Case report

Male patient

History:

23y Recurrent sinusitis

Immunodeficiency (ID)?

Most likely not, but when should you think of ID?

Severity, Frequency,
    More than three antibiotic courses/year
Positive family history
Other clinical signs of ID

Case report

Male patient

History:

23y Recurrent sinusitis

24y Severe bout of Autoimmune hemolytic anemia

Diagnostics?

Immunoglobulins: IgG 4.1g/l (7-16), IgA < 0.07g/l, IgM 0.2g/l (0.4-2.3g/l)

Diagnosis: CVID

Correct?

Definition of Common variable Immunodeficiency

ESID Registry Criteria 2015

At least one of the following:

*increased susceptibility to bacterial infections

*autoimmune manifestation

*granulomatous disease

*unexplained polyclonal lymphoproliferation

*affected family members with antibody deficiency

Clinics

Ig serum

AND relevant reduction of IgG and IgA with or without IgM reduction (measured at 2 time points; <2SD below the reference values adjusted for age);

AND at least one of the following:

*poor antibody response to vaccination (and/or absent isohemagglutinins); i.e. lack of protective titers despite vaccination

Spec. AB/ B cell

Reduced switched memory B cells (<70% of age adjusted reference)

AND secondary hypogammaglobulinemia excluded (s. separate list)

AND diagnosis after the 4. year of life (symptoms can present earlier)

Age

AND no evidence of a severe T-cell defect

Exclusion

Case report

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Specific antibodies: Tet+Diphth – PnPS not tested
B cell phenotyping: B+smB-21low
No hint for secondary immunodeficiency

Diagnosis: CVID

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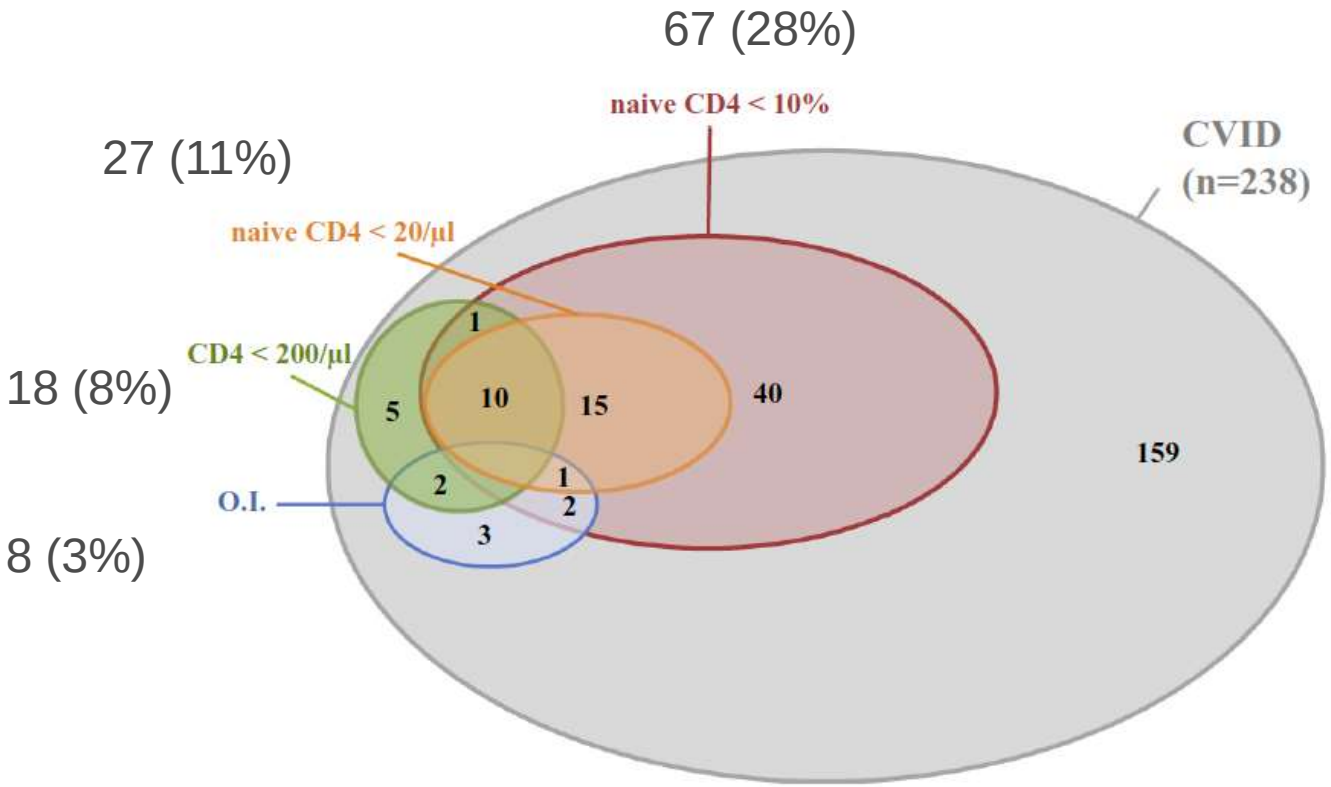
T cell Phenotyping: CD4: 290/µl, naive CD4 8%

Diagnosis: CVID?

LOCID

Definitions



Occurence of opportunistic infections (OI) was not reflected by the T cell status

DEFI 2009 (CD4<200/µl and or opportunistic infections in 24/10%)

DEFI 2015 (naive CD4< 20/µl and or opportunistic infections in 33/14%)

Freiburg 2019 (naive CD4 < 10% and or opportunistic infections in 74/31%)

T cell proliferation, TCR$\gamma\delta$ T cell expansion, oligoclonal CD4 T cells

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Von Spee-Mayer et al Clin Immunol 2019, Malphettes et al Clin Infect Dis 2009, Bertinchamp et al JACIP 2016

Laboratory Diagnostics 2019

Summary

Serum immunoglobulins

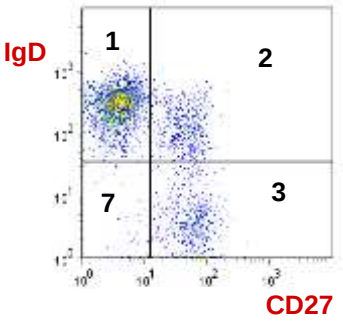
Specific serum immunoglobulins (Tet Tox, Diphth Tox, PnPS, others)

Differential blood count

Small lymphocyte panel (CD4, CD8, B and NK)

Extended B cell panel (CD27, CD21, CD38)

Extended T cell panel (CD4, CD8, CD45RA)



Functional assays

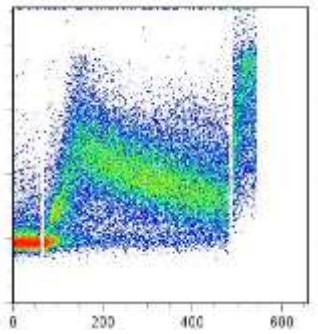
(T cell proliferation)

Immunoglobulin production *in vitro*

Class switch recombination

Signaling

T-B cell interaction *in vitro*



Genetics

Diagnostics: Three aspects in immunodeficiency

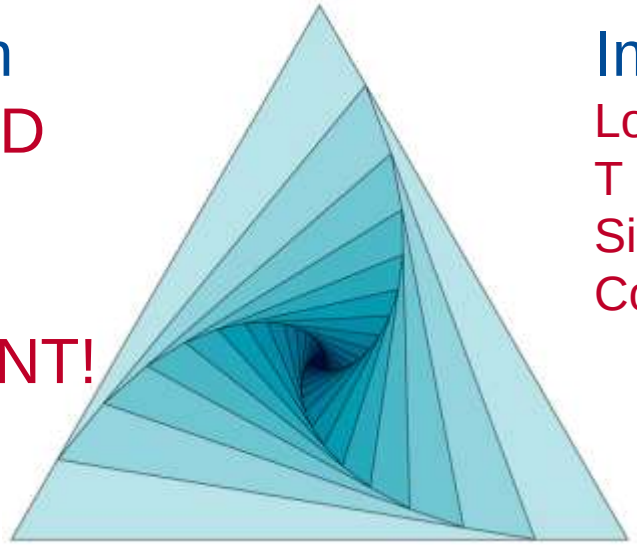
Evolving relevant aspects in CVID and CVID like disorders

Clinical presentation

Signs of combined ID

End organ disease

ALWAYS IMPORTANT!



Immune function

Local and systemic signatures

T cell Function

Signaling studies

Confirming new variants

Genetics

Next generation sequencing

Epigenetics

Microbiom

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Diagnosis: CVID

Genetics?

Extended diagnostics for humoral ID

Genetic diagnostics

Indication:

Requires special patient consent

Familial case

All complex forms of CVID (to be explained)

Method:

NGS Extended Panel or exome sequencing

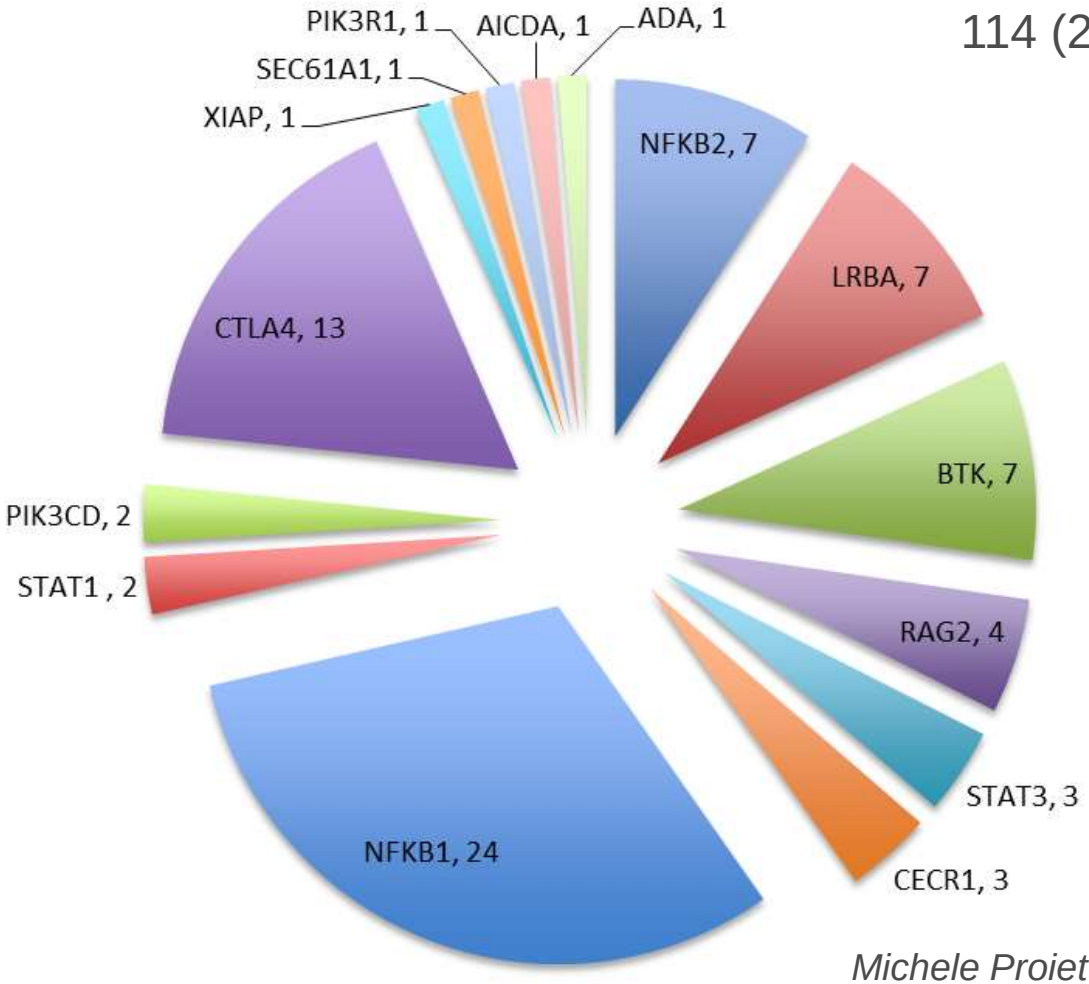
Challenge:

Variants of unknown significance (VUS)

Molecular screening of patients with antibody deficiency

Impact of Next Generation Sequencing (NGS)

N = 451 patients
114 (25%) with informative mutation



Michele Proietti, Jessica Rojas, Bodo Grimbacher
CCI Genetics Unit

Centrum für Chronische Immundefizienz

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Extended diagnostics for humoral ID

Assays to screen for monogenetic disorders with CVID-like presentation

APDS: pS6 in fresh blood samples

CTLA4: (Transendocytosis of CD80/CD86)

PKCδ: (Protein staining) to be determined

NFκB1: (Cloning: nuclear translocation, EMSA, reporter assay)

NFκB2: to be determined

STAT1 GOF: ex vivo and pSTAT1 after IFNg/IFNa stimulation

STAT3 GOF: pSTAT3 not reliable, very low IgE

IKAROS: (Cloning: Nuclear localization)

LRBA: Protein staining

ADA2: enzyme activity in dry plasma spots

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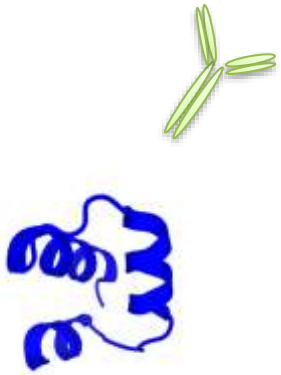
Genetics: no known mutation identified

Diagnosis: CVID

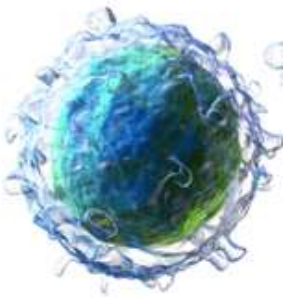
Diagnostics

The need to address all levels

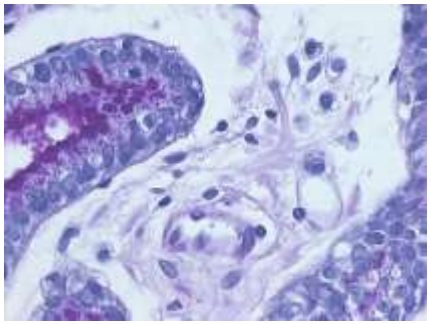
Molecule



Cell



Tissue



Person

Case report

Male CVID patient

History:

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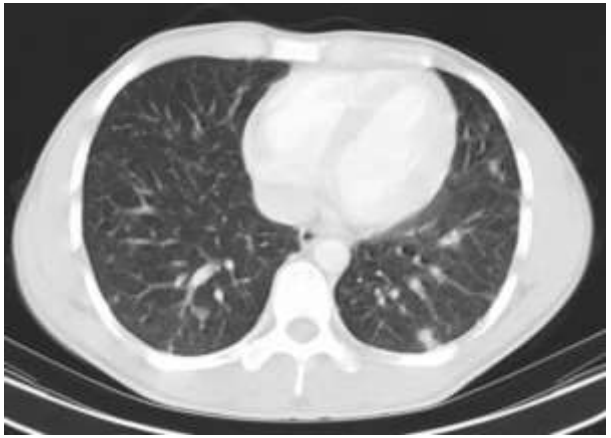
Additional diagnostics:

CLINICS?!

Diagnostics for secondary complications

Freiburg scheme



Lung

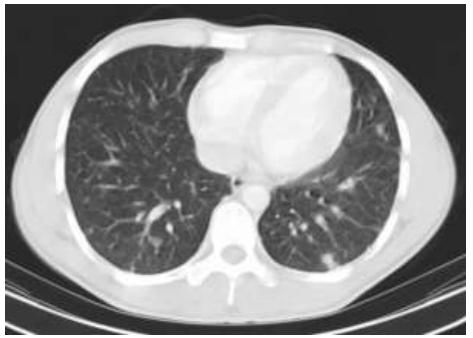
Initial CT scan, follow up 5-10y, if ILD: 2-3y
Lung function incl. CO diffusion
BAL (biopsy?)
Exercise testing

Diagnostics for secondary complications

Freiburg scheme

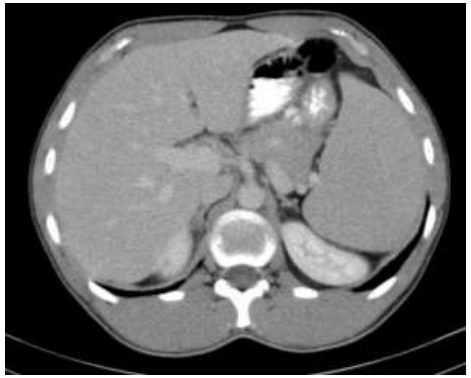
Lung

Initial CT scan, follow up 5-10y, if ILD: 2-3y
Lung function incl. CO diffusion
sIL2R, Neopterin
BAL (biopsy?)
Exercise testing



Lymphoproliferation

LDH, b2 MG, (clonality)
Annual abdominal ultra sound
CT scan (PET)



Case report

Male CVID patient

History:

23y Recurrent sinusitis

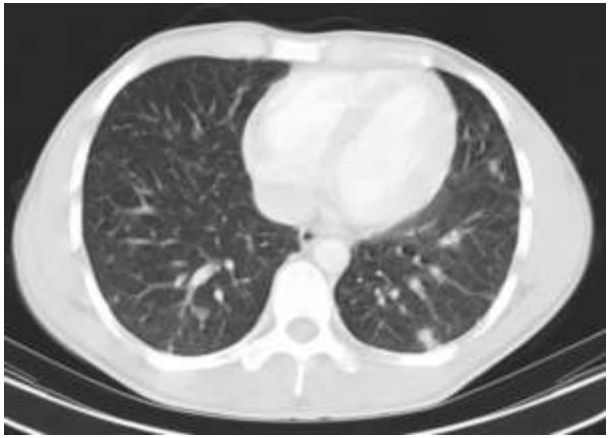
24y Severe bout of AIHA

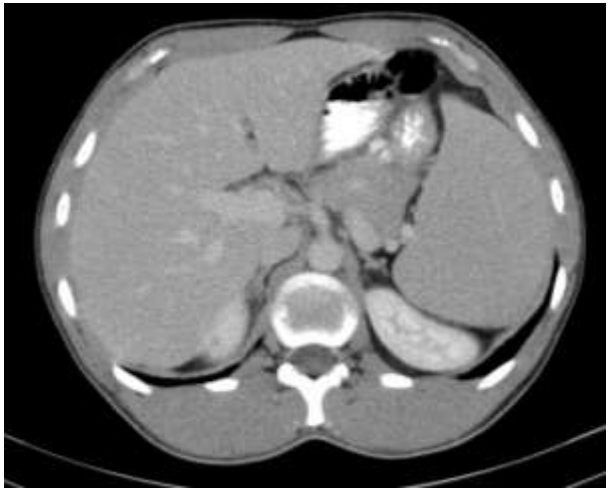
- Splenomegaly+ lymphadenopathy
- Granulomatous lymphocytic interst. lung disease

Extensive histology (Lung, LN, BM)

NO signs of lymphoma

sIL2R 2800U/ml





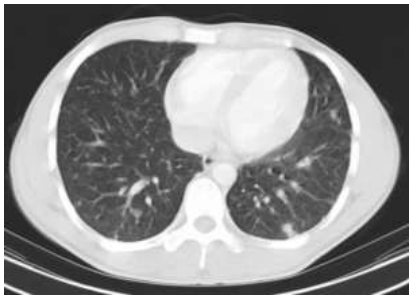
Other diagnostics?

Diagnostics for secondary complications

Freiburg scheme

Lung

Initial CT scan, follow up 5-10y, if ILD: 2-3y
Lung function incl. CO diffusion
sIL2R, Neopterin
BAL (biopsy?)
Exercise testing



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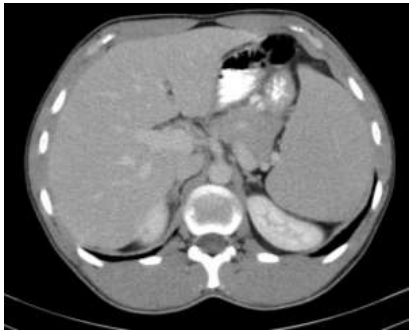
LDH, b2 MG, (clonality)
Annual abdominal ultra sound
CT scan (PET)



Gut

No complaints, no signs of malabsorption
-> no further diagnostics at this time

Liver

Ultrasound + duplex, biopsy?; if portal hypertension: gastroscopy (varicosis?)

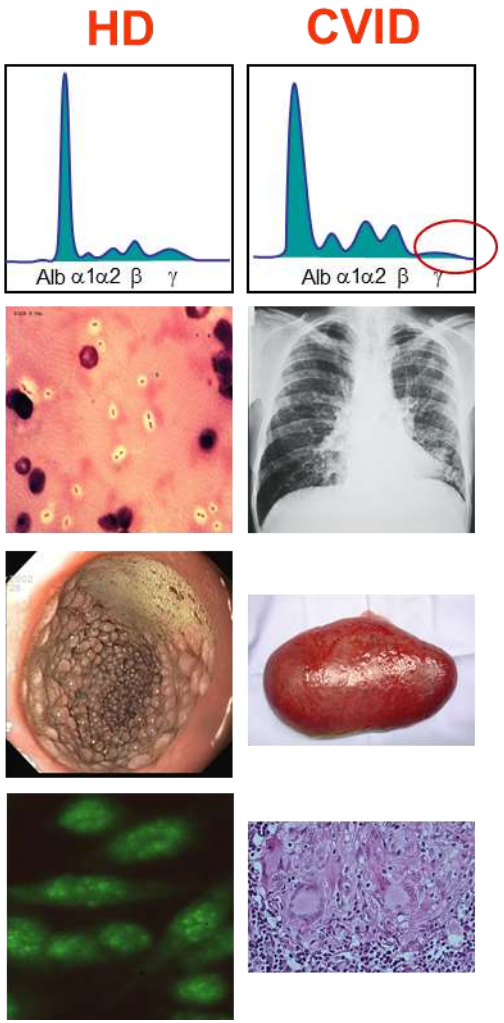
Common Variable Immunodeficiency (CVID)

Clinical presentation

Leading symptoms
Hypogammaglobulinemia
Recurrent bacterial RTIs

In addition

- Lymphoproliferation, Splenomegaly 35%
  - Lymphoma 4%
- Autoimmunity 29%
  - Autoimmune cytopenia 15%
- Granulomatous disease 10%
- Interstitial lung disease 20%
- Enteropathy 10%
- Hepatopathy 7%



Gathmann et al JACI 2016 and CCI Freiburg data

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Clinical heterogeneity of CVID

Towards a meaningful clinical classification

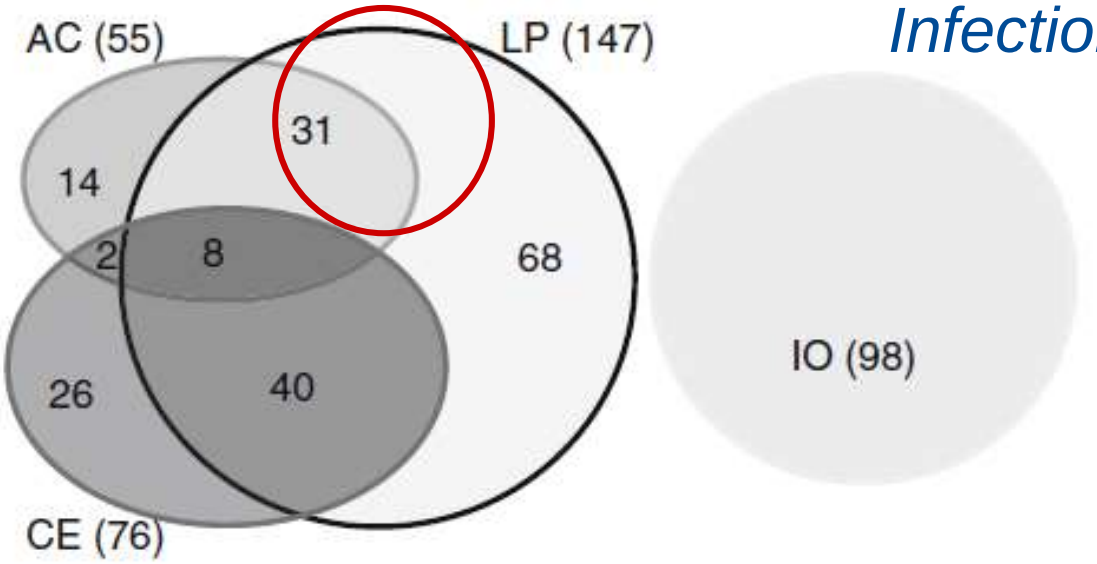
Complex form of CVID

DEFI Cohort (n=287)

interstitial lung disease

Autoimmune cytopenia

Lymphoproliferation



Infection only CVID

Chronic enteropathy

Bronchiectasis

Liver disease

Chronic sinusitis

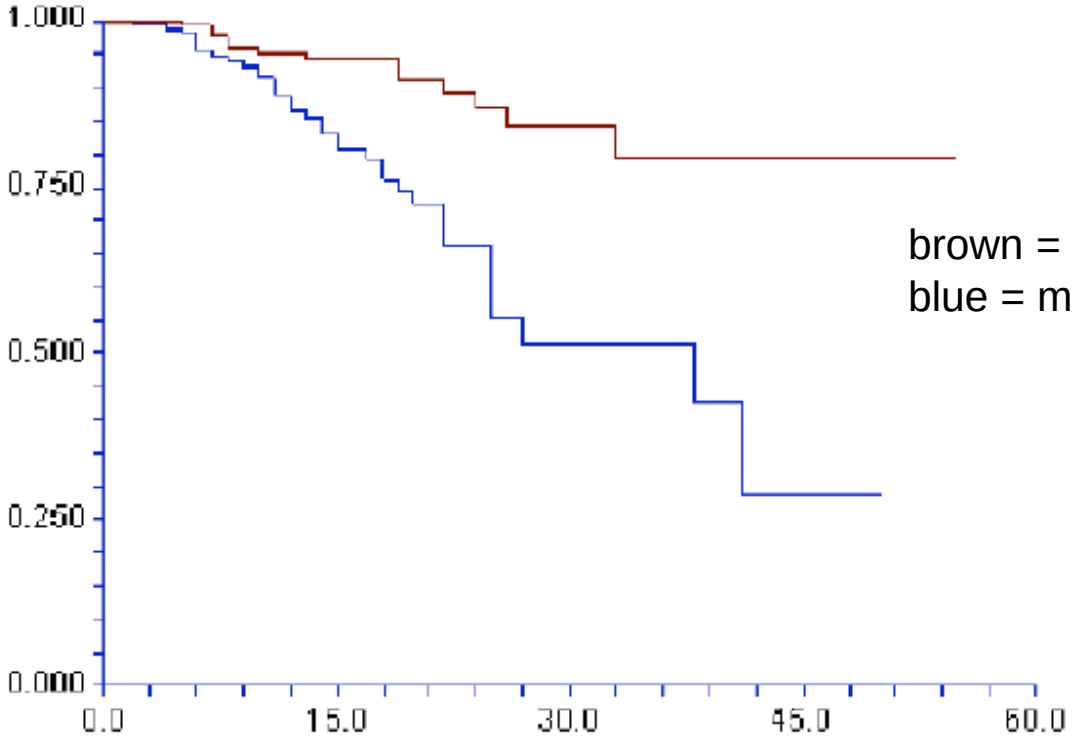
Granulomatous disease

Mouillot et al J Clin Immunol 2010, Chapel et al JACI 2012

Survival of CVID patients

Impact of secondary manifestations

Mortality/year since diagnosis of CVID depending on clinical phenotype



brown = no complication
blue = min. one complication

Already the manifestation of one complication is associated with a reduced medium survival of CVID patients.

H. Chapel et al Blood 2008 + JACI 2012, E Resnick et al Blood 2012

Case report

Male CVID patient

History:

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24y Severe bout of AIHA

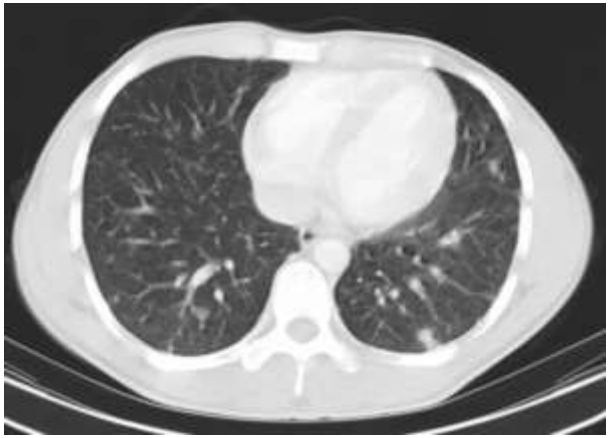
- Splenomegaly+ lymphadenopathy
- Granulomatous lymphocytic interst. lung disease

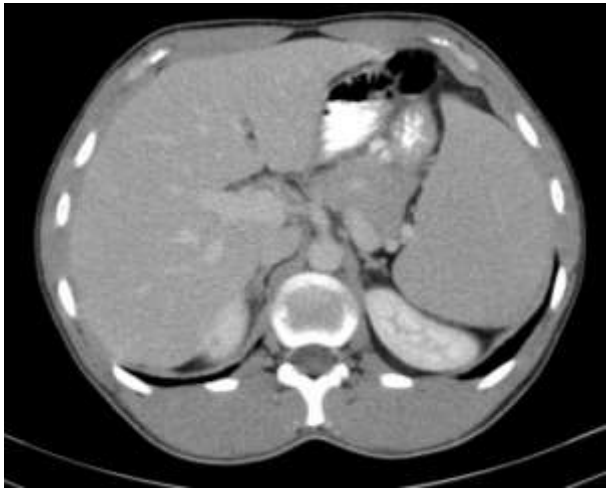
Extensive histology (Lung, LN, BM)

NO signs of lymphoma

sIL2R 2800U/ml

No overt gut or liver involvement

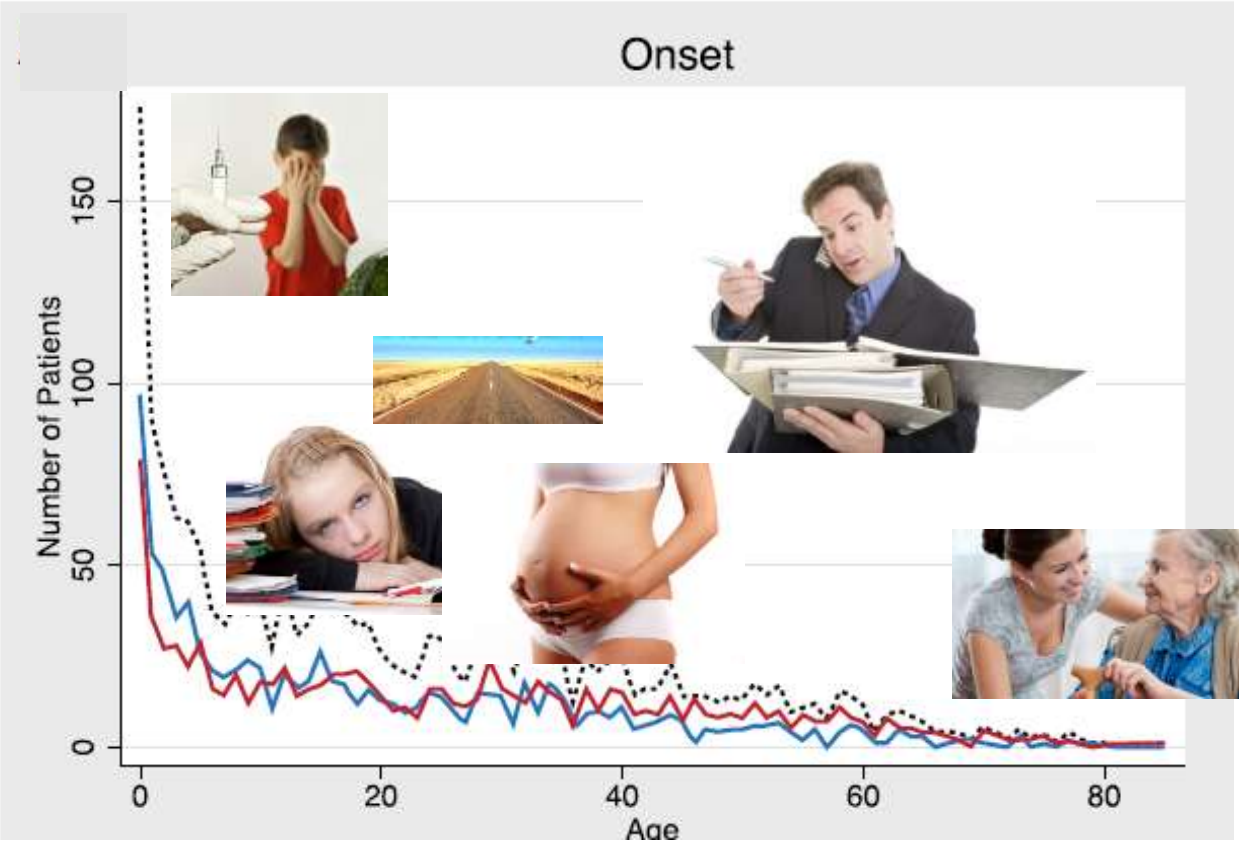




IgG replacement therapy and steroids for AIHA were started

Management

Targeted therapy: IgG replacement



Application methods

Iv Ig
scIg pump
scIg rapid push
facilitated scIg

Aim

Prevention of infections
Surrogate: IgG trough within the normal range

Lifelong therapy with different individual needs at different times.

Gathmann et al 2014

www.paradisi.de; www.mausebaeren.de; www.in-australien.com; krankheitenundsymptome.net; img.welt.de; www.pflege-in-hessen.de

Lymphoproliferation/lymphoma

About 25%/4% of patients

Diagnostics:

Clinical suspicion: B symptoms, persisting / growing LN

AI thrombocytopenia/splenomegaly

Imaging annual Ultrasound, CT/MRI depending on previous findings and suspicion

Laboratory: LDH, low CD4 counts, (clonal expansion), EBV?

Histology: Often difficult

First line:

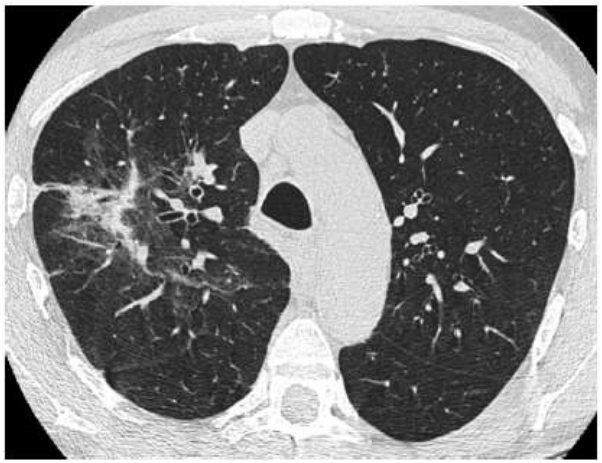
Standard chemotherapy

Recurrent disease or first remission:

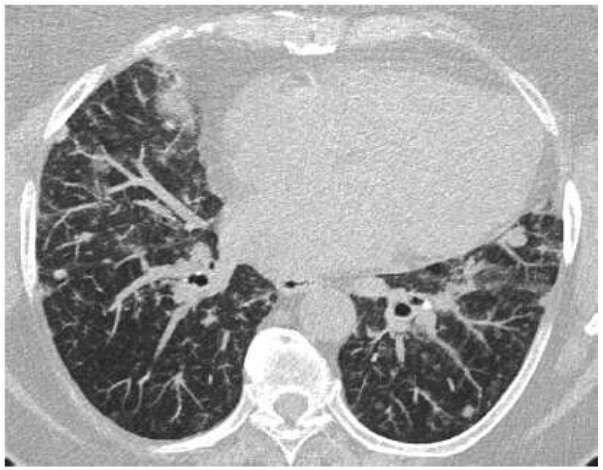
HSCT?

Lung disease: CT parameters

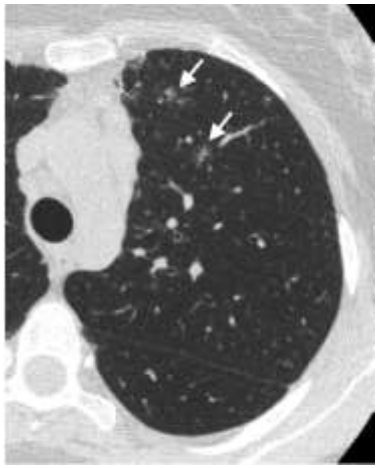
Literature



Organizing Pneumonia



GLILD



Follicular bronchiolitis

GLILD encompasses different granulomatous, lymphoid (i.e., lymphoid hyperplasia, follicular bronchiolitis, and LIP), and inflammatory lesions (i.e., OP).

In a few patients reticular pattern resembling NSIP.

Difficulties in comparative analysis of CT scans.

Cereser et al Clin Rad 2017

Lung disease: Management

Indication for treatment Consensus of British lung foundation/UKPID network

	Symptoms	Lung Function	Function (CT?) Trajectory	% agree Rx
✓	Symptomatic	Abnormal	Deteriorating	Consensus: 100%
✓	Asymptomatic	Abnormal	Deteriorating	Consensus: 100%
✓	Symptomatic	Normal	Deteriorating	Consensus: 81%
	other…			
	Symptomatic	Normal	Stable	no consensus
	Symptomatic	Abnormal	Stable	no consensus
	Asymptomatic	Normal	Deteriorating	no consensus
	Asymptomatic	Abnormal	Stable	no consensus
✗	Asymptomatic	Normal	Stable	Consensus: 6%

Hurst et al JACI P 2017

First line therapy

Consensus of British lung foundation/UKPID network

Special Article

British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders

John R. Hurst, PhD, FRCP[a], Nisha Verma, MRCP[b], David Lowe, MRCP[b], Helen E. Baxendale, MRCP, PhD[c], Stephen Jolles, FRCP, FRCPath, PhD[d], Peter Kelleher, PhD[e], Hilary J. Longhurst, FRCPath[f], Smita Y. Patel, PhD, FRCPath[g], Elisabetta A. Renzoni, PhD[h], Clare R. Sander, PhD, FRCP[i], Gerard R. Avery, FRCR[j], Judith L. Baber, FRCR[k], Matthew S. Buckland, PhD, FRCP[l], Siobhan Burns, FRCPath[m], William Egner, FRCP, FRCPath, PhD[n], Mark M. Gompels, MD[o], Pawela Gordins, FRCPath[p], Jamanda A. Haddock, FRCR[q], Simon P. Hart, PhD, FRCPE[r], Grant R. Hayman, FRCP, FRCPath[s], Richard Herriot, FRCPath[t], Rachel K. Hoyles, PhD, FRCP[u], Aamoud P. Huissoon, PhD, FRCP, FCRPath[v], Joseph Jacob, MD(Res)[w], Andrew G. Nicholson, FRCPath[x], Doris M. Rassl, FRCPath[y], Ravishenkar B. Sargur, FRCP, FRCPath[z], Sinisa Savic, PhD[aa], Suranjith L. Seneviratne, FRCP[ab], Michael Shaaff, MD[ac], Prashantha M. Vaitla, FRCPath[ad], Gareth I. Walters, MD[ae], Joanna L. Whitehouse, PhD, FRCP[af], Penny A. Wright, FRCPath[ag], and Alison M. Condliffe, PhD[ah] *London, Cambridge, Cardiff, Oxford, Hull, Sheffield, Bristol, Ipswich, Aberdeen, Birmingham, Leeds, and Nottingham, United Kingdom*

- 90% agreed that when treatment was required, first-line should be corticosteroids alone.
- Of these 21 respondents, all but 1 preferred oral prednisone (1 preferred intravenous methylprednisone).
- Of the 20 using oral prednisone, the minimum dose used was 10 to 20 mg/d, and the maximum 1 to 2 mg/kg/d.
- For a 70-kg subject, the median (IQR) dose was 40 (30-70) mg/d.
- For respondents using prednisone with a second agent, the 2 most commonly used second agents were azathioprine (6 respondents) and mycophenolate (4 respondents).

Hurst et al JACI P 2017

Second line therapy

Consensus of British lung foundation/UKPID network

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British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders

John R. Hurst, PhD, FRCP[1], Nisha Verma, MRCP[2], David Lowe, MRCP[3], Helen E. Baxendale, MRCP, PhD[4], Stephen Jolles, FRCP, FRCPath, PhD[5], Peter Kelleher, PhD[6], Hilary J. Longhurst, FRCPath[7], Smita Y. Patel, PhD, FRCPath[8], Elisabetta A. Renzoni, PhD[9], Clare R. Sander, PhD, FRCP[2], Gerard R. Avery, FRCR[2], Judith L. Babar, FRCR[10], Matthew S. Buckland, PhD, FRCP[11], Siobhan Burns, FRCPath[12], William Egner, FRCP, FRCPath, PhD[13], Mark M. Gompels, MD[14], Pavela Gordins, FRCPath[15], Jamanda A. Haddock, FRCR[16], Simon P. Hart, PhD, FRCPE[17], Grant R. Hayman, FRCP, FRCPath[18], Richard Herriot, FRCPath[19], Rachel K. Hoyles, PhD, FRCP[1], Asmoud P. Huissoon, PhD, FRCP, FCRPath[1], Joseph Jacob, MD(Res)[20], Andrew G. Nicholson, FRCPath[21], Doris M. Rassl, FRCPath[22], Ravishenker B. Sargur, FRCP, FRCPath[23], Sinisa Savic, PhD[24], Suranjith L. Seneviratne, FRCP[25], Michael Shovlin, MD[1], Preshantha M. Vaitla, FRCPath[26], Gareth I. Walters, MD[27], Joanna L. Whitehouse, PhD, FRCP[28], Penny A. Wright, FRCPath[29], and Alison M. Condliffe, PhD[30] *London, Cambridge, Cardiff, Oxford, Hull, Sheffield, Bristol, Epsom, Aberdeen, Birmingham, Leeds, and Nottingham, United Kingdom*

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TABLE IV. Consensus on second-line drug therapy in GLILD

Criteria	No. of respondents	% Agree	% Disagree	Mean ± SD score*
Which of the following drugs would you consider as second-line therapy in GLILD?				
Consensus				
Azathioprine	21	100	0	0.71 ± 0.25
Rituximab	21	90	5	0.67 ± 0.40
Mycophenolate	21	81	5	0.62 ± 0.44
No consensus				
Abatacept	18	33	28	0.03 ± 0.50
Anti-TNF agents	17	29	47	−0.12 ± 0.57
Ciclosporin	16	25	25	0.00 ± 0.48
Hydroxyxchloroquine	19	42	32	0.07 ± 0.56
Methotrexate	17	35	29	0.03 ± 0.51
Sirolimus	18	28	28	0.03 ± 0.53
Tacrolimus	18	22	33	−0.08 ± 0.43

*See text. Scale of −1 (strongly disagree) to +1 (strongly agree), with more extreme scores and smaller SD indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.

Hurst et al JACI P 2017

Case report

Male CVID patient

History:

23y Recurrent sinusitis

24y Severe bout of AIHA

Splenomegaly+ lymphadenopathy

Granulomatous lymphocytic interst. lung disease

Extensive histology (Lung, LN, BM)

NO signs of lymphoma

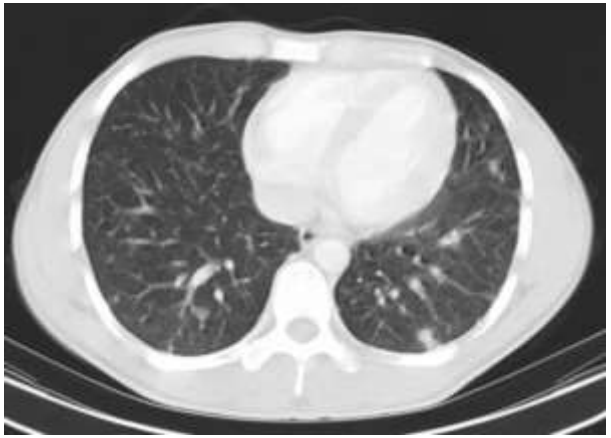
sIL2R 2800U/ml

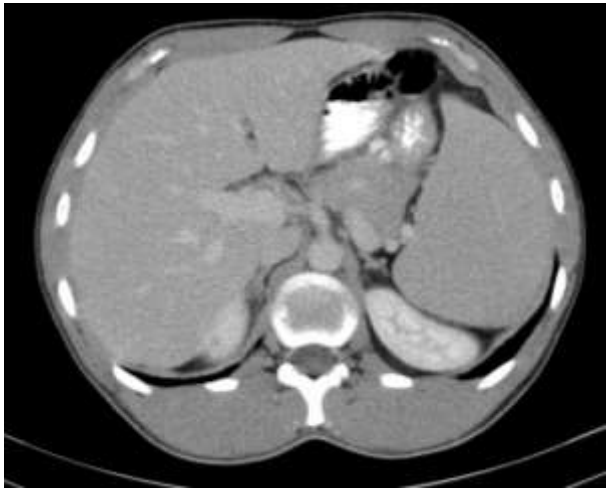
No overt gut or liver involvement

TREATMENT: IgGRT and steroids (cont‘ 5mg/d)

26y Severe bout of AIHA + AITP

Lung disease stable, splenomegaly





TREATMENT?

Autoimmune cytopenias

About 15% of patients

First line:

Steroids +/- High dose IgG

Recurrent disease:

Rituximab either 2x750mg/m^2 or 4x375mg/m^2

(Romiplostin maintenence for AITP)

Rescue therapy

Plasmapheresis (Daily exchange volume of 40ml/kg body weight (1 plasma volume). Replacement fluid was 100 % Fresh Frozen Plasma + 10g ivIG)

Alternatives:

Splenectomy if necessary for other reasons

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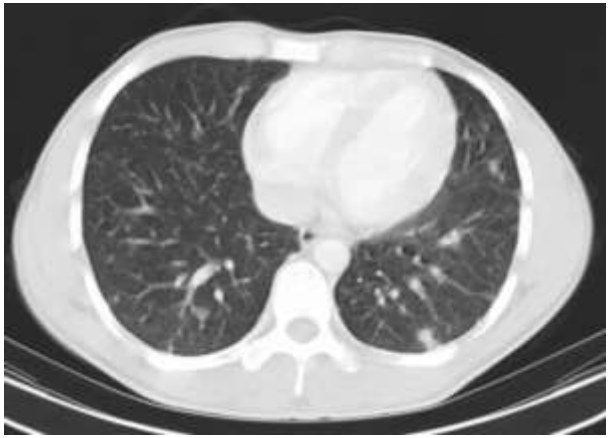
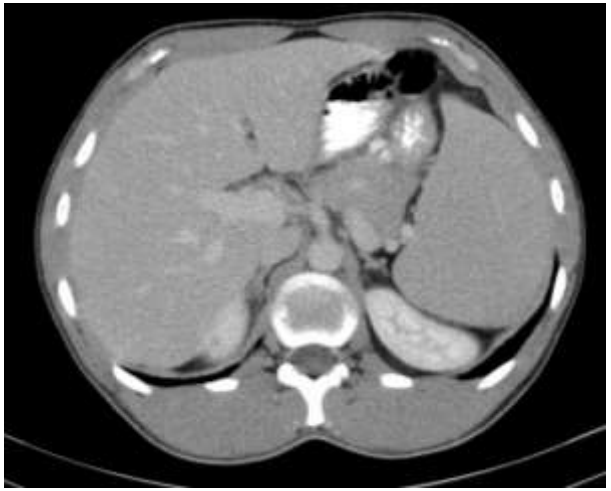
TREATMENT: RTX and steroids

28y diarrhoea





Diagnostics?

Enteropathies

About 15% of patients

Diagnostics:

Stool culture, incl. test for giardiasis and enteroviruses (esp Norovirus)

Gastroscopy and colonoscopy with multiple biopsies (even in absence of macroscopic alterations)

Lactose/Fructose intolerance, HLA DQ2/8

Ultrasound/MRI of the abdomen

Laboratory: signs of malabsorption, calprotectin and a1AT in stool

Currently no good laboratory parameters indicating the presence of activity of enteropathy

Enteropathies: Treatment of non-infectious forms

About 15% of patients

First line: a) Diet if indicated

b) Budesonide (different release forms, MMX)

c) Steroids (oral vs iv, dose 0.5(-1)mg/kgBW)

Recurrent disease:

d) Steroid sparing agent:

T cell targeted: Calcineurin inhib

mTOR inhib

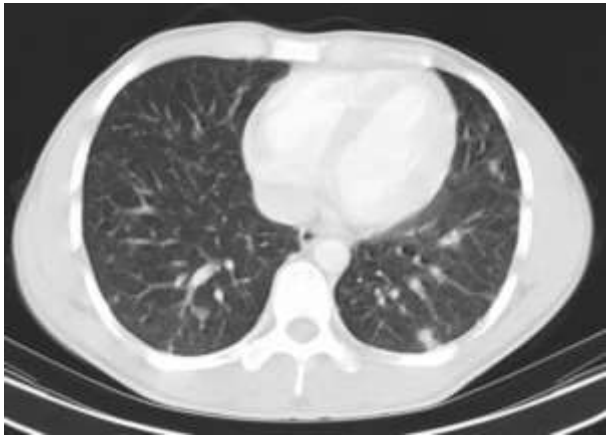
anti TNF: Infliximab, Adalimumab

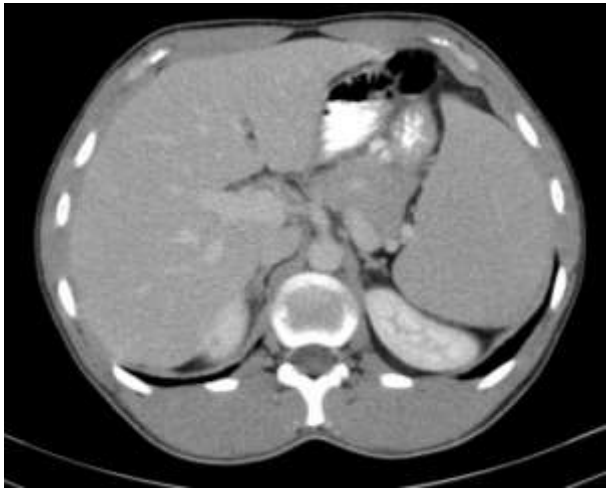
others: 5 ASA, Abatacept, AZA, ...

Vedolizumab

Case report

Male CVID patient





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Lung disease stable, splenomegaly

TREATMENT: RTX and steroids

28y non-infectious enteropathy on diet and budesonide and abatacept discussed

The Challenges of the next 10 years

A personal view

Awareness	Earlier diagnosis
Diagnostics	Better Diagnosis
Multiple layers:	Genetics, epigenetics, systemic and local Immunics, comorbidities, prognost. markers
Pathogenesis	Learning the broader context
Management	
Therapy	Personalized IgG substitution Infection control Immune reconstitution HSCT, gene therapy Treatment of comorbidities
Health care	Quality of life, Workability
Economics	

Puzzle pieces of immune dysregulation in CVID

Putting together a better picture

https://de.freeimages.com/premium/pile-of-unfinished-puzzle-pieces-in-detail-1789965

Puzzle pieces of immune dysregulation in CVID

Putting together a better picture

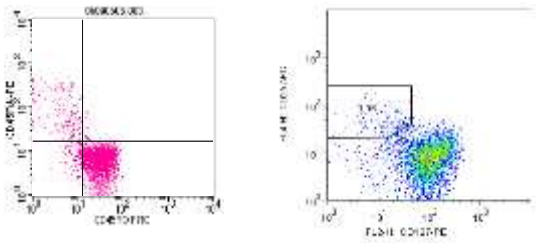
Genes and Environment

- PI3Kδ
- CTLA4
- LRBA
- NFkB1
- NFKB2
- STAT3 GOF
- STAT1 GOF
- PKCδ

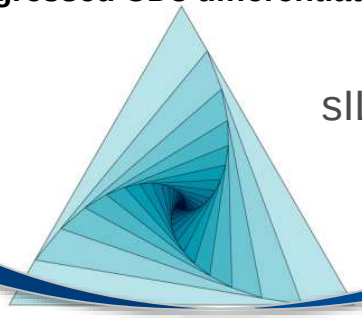
Microbiom

Immune Dysregulation

Low CD4 naive T cells **Low Treg cells**

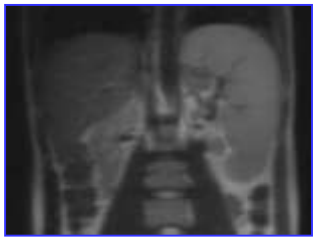


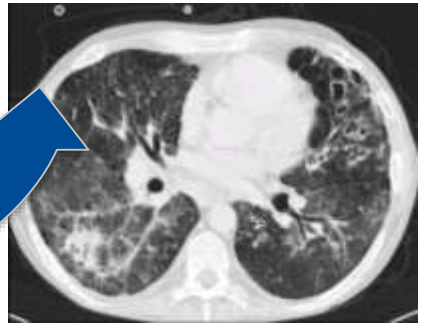
Progressed CD8 differentiation



sIL2R ↑

Clinic



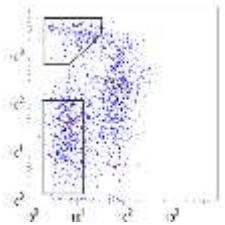


Viral infection?

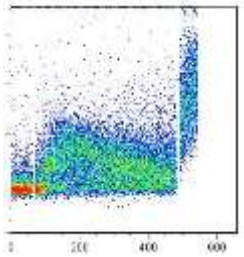
???

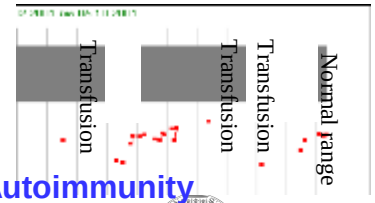
Not HHV8 in Europe

High CD21^{low} B cells



BCR signaling





Autoimmunity

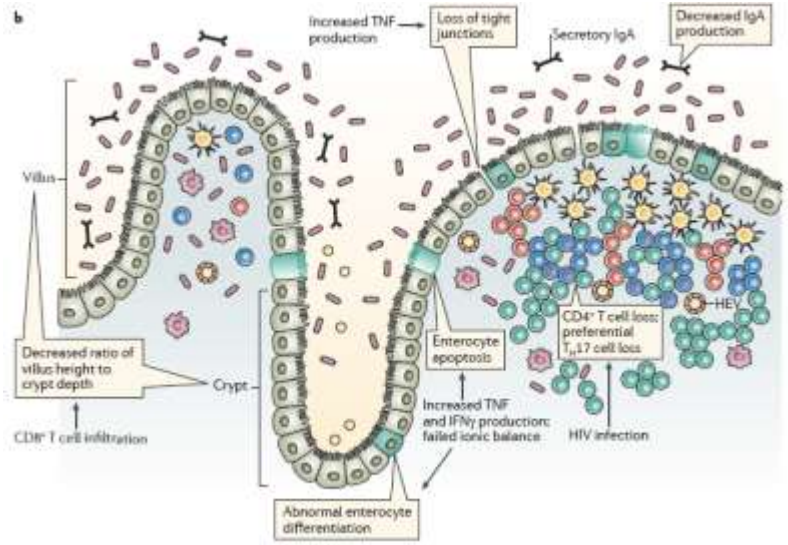
Centrum für Chronische Immundefizienz

UNIVERSITÄTS KLINIKUM FREIBURG

CVID associated secondary complications

Concepts of pathophysiology of local immune dysregulation

Enteropathy



??

Lung disease

T and B cells, cytokines (Baff, IP10, others...), ??

Liver disease

???

Adapted from: Sandler et al Nature reviews Microbiology 2012; 10:655-66

Diagnostics 2025

Prospects

Serum immunoglobulins

- **Specific serum immunoglobulins (Defined panel of ±6 antigens)**

Differential blood count

- **One extended flowcytometric/CyTOF? Panel incl. Indicator populations**

Genetics

- **Exome (Genome?)**
- **Bi-/multigenetic background**

Immune signatures

- **Epigenetics**
- **RNA expression profile, multiplex PCR/nanostring or similar**
- **Possibly (serum) „proteomics“ esp. drugable molecules/pathways**

Functional assays

- **in vitro platforms for evaluation of gene variant**

Case report

Male CVID patient

Young man running his own business, loves sports and traveling

Genetic screening: no known PID

- What do I have?
- Will my children inherit it?

Infection control sufficient under IgG RT

- but still three URTI/year

Loves traveling to remote places

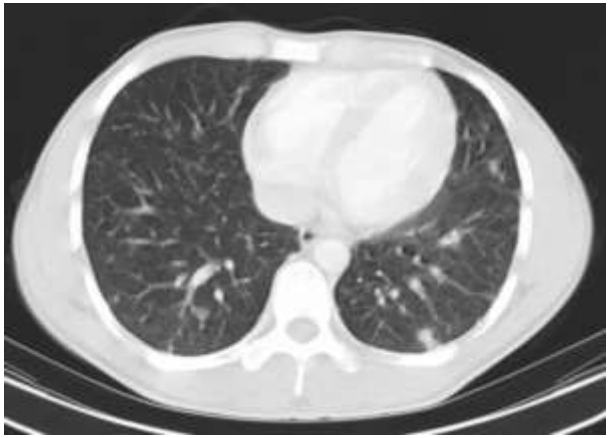
- what to do with IgG RT

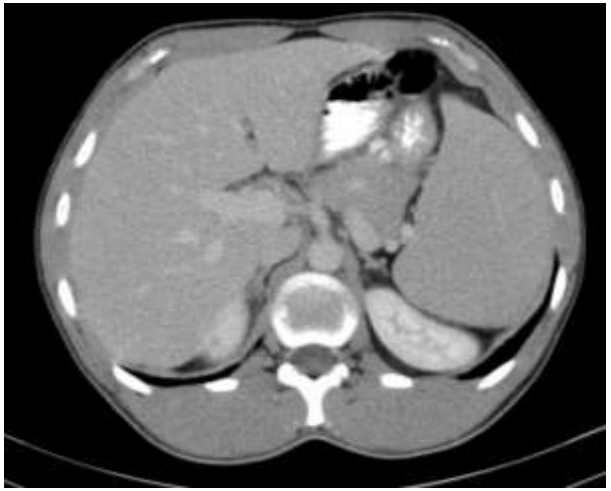
No more bouts of AITP

- But still the fear that they may return

Lung disease, gut disease

- Do I need stem cell transplantation?





Management of comorbidities

Targeting therapies

Evolving pathogenic concepts allow employing new targeted therapies:

mTOR inhibition

PI3K inhibition

(for PI3Kδ GOF)

CTLA4-Ig

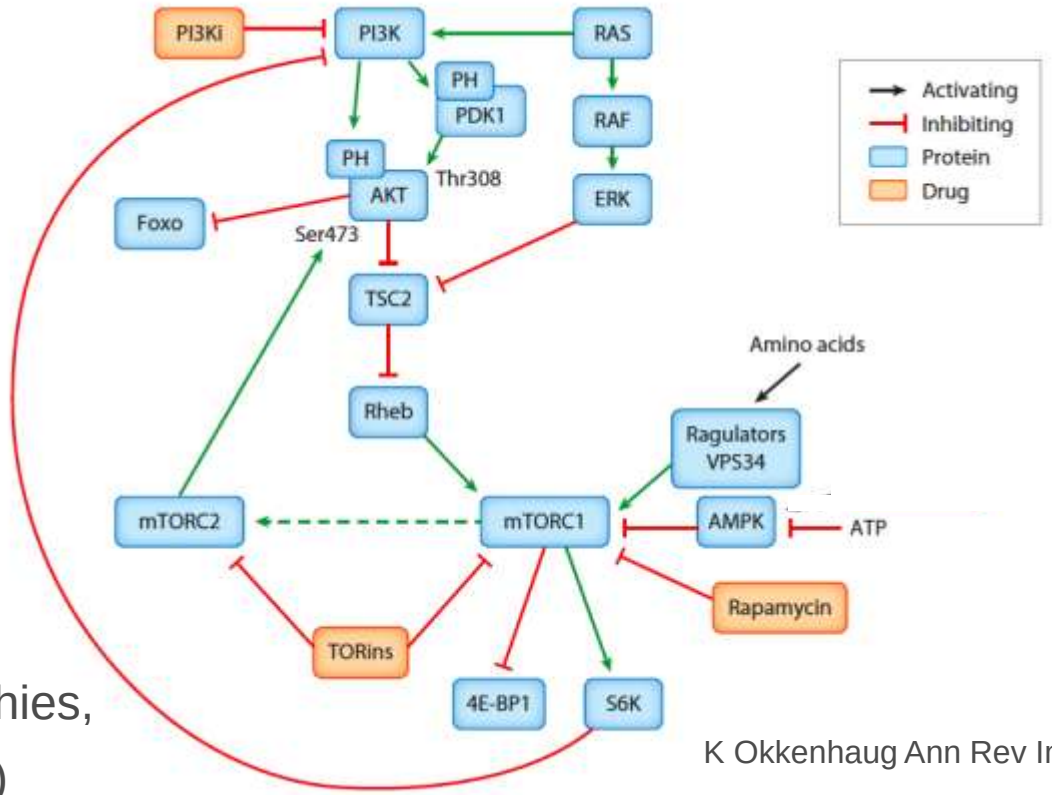
(CTLA4 /LRBA)

RTX

(PKCδ, CTLA4?)

JAK inhibition (?)

(for Stat-GOF, IFNopathies, and TH1 driven CVID?)



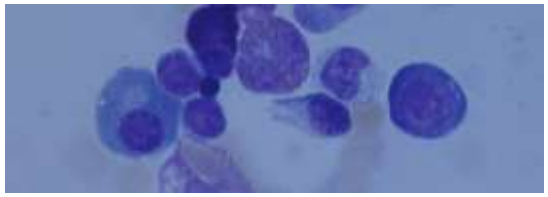
K Okkenhaug Ann Rev Immunol 2013

Management

Resetting the immune system

Transplantation

Currently only limited experience



StemPAD

C.Wehr, K.Warnatz, M.Rizzi JACI 2015

Retrospective study of 25 CVID patients from 16 centers worldwide

receiving HSCT between 1993 and 2012, 50% died, good disease control in survivors,

Only 50% of surviving patients are off IgG-RT

⇒ Prospective survey

Gene therapy

Potential option in CVID like disorders, most of them probably requiring gene repair rather than replacement.

The Future

A personal wish list

Better Awareness programs

Diagnostics will cover clinical, immunological, histological, genetic and epigenetic aspects of the disease and will be analyzed with the help of algorithms developed by systems biology.

Insights into pathogenesis will allow for personalized medicine.

Management will seek to address individual needs of IgG-RT, improved infection control and seek immune reconstitution.

Treatment of comorbidities will be well integrated into the treatment plan, rather by immune repair than suppressive strategies.

Patients with need for HSCT/gene therapy will be identified early and included in clinical trials to improve outcome.

Addressing all layers: Perceived health matters!

Thank you for your attention

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