



## The complex veiled among the common Variables

#### CVID – Next generation

SLIPI Stromstad 2019

Klaus Warnatz



für Bildung

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



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





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?





#### www.ESID.org

#### 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

**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)

**AND** no evidence of a severe T-cell defect





Age

lg serum

Clinics

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Diagnosis: CVID?







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

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

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## 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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#### 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

VIVERSITATS

## 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)

PKC $\delta$ : (Protein staining) to be determined

NFkB1: (Cloning: nuclear translocation, EMSA, reporter assay)

NF $\kappa$ B2: 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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## Diagnosis: CVID





#### Diagnostics The need to address all levels

Molecule



Tissue

Person









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Additional diagnostics:







# Diagnostics for secondary complications

#### 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:

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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

#### Lymphoproliferation

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

4%

10%

20%

10%

7%

#### Leading symptoms

Hypogammaglobulinemia **Recurrent bacterial RTIs** 

#### In addition

- Lymphoproliferation, Splenomegaly 35%
  - Lymphoma
- Autoimmunity 29% ۲ 15%
  - Autoimmune cytopenia
- Granulomatous disease
- Interstitial lung disease
- Enteropathy
- Hepatopathy ۲

Gathmann et al JACI 2016 and CCI Freiburg data







#### Clinical heterogeneity of CVID Towards a meaningful clinical classification

#### Complex form of CVID



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



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



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#### IgG replacement therapy and steroids for AIHA were started





#### Management Targeted therapy: IgG replacement



Application methods lv lg sclg pump sclg rapid push facilitated sclg

#### Aim

Prevention of infections Surrogate: IgG trough within the normal range

Female Male

Gathmann et al 2014

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

Lifelong therapy with different individual needs at different times.





#### 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



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.





## 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 Symptomatic Asymptomatic Asymptomatic	Normal Abnormal Normal Abnormal	Stable Stable Deteriorating Stable	no consensus no consensus no consensus no consensus
×	Asymptomatic	Normal	Stable	Consensus: 6%





Hurst et al JACI P 2017

## First line therapy

#### Consensus of British lung foundation/UKPID network

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#### 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

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- 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).





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## Second line therapy

#### Consensus of British lung foundation/UKPID network

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Criteria	No. of respondents	% Agree	% Disagree	Mean ± SD score*	
Which of the following in GLILD?	drugs would you	consid	ler as seco	nd-line therapy	
Consensus					
Azathioprine	21	100	0	$0.71\pm0.25$	
Rituximab	21	90	5	$0.67 \pm 0.40$	
Mycophenolate	21	81	5	$0.62\pm0.44$	
No consensus					
Abatacept	18	33	28	$0.03 \pm 0.50$	
Anti-TNF agents	17	29	47	$-0.12\pm0.57$	
Ciclosporin	16	25	25	$0.00\pm0.48$	
Hydroxyxchloroqui	ne 19	42	32	$0.07\pm0.56$	
Methotrexate	17	35	29	$0.03 \pm 0.51$	
Sirolimus	18	28	28	$0.03 \pm 0.53$	
Tacrolimus	18	22	33	$-0.08\pm0.43$	

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

\*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.





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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

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<sup>2</sup> or 4x375mg/m<sup>2</sup>

(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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26y Severe bout of AIHA + AITP

Lung disease stable, splenomegaly 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





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26y Severe bout of AIHA + AITP

Lung disease stable, splenomegaly

TREATMENT: RTX and steroids

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





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# The Challenges of the next 10 years A personal view

Awareness

Diagnostics Multiple layers:

Pathogenesis

Management Therapy

Health care Economics Earlier diagnosis

Better Diagnosis Genetics, epigenetics, systemic and local Immunics, comorbidities, prognost. markers Learning the broader context

Personalized IgG substitution Infection control Immune reconstitution HSCT, gene therapy Treatment of comorbidities Quality of life, Workability





#### 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

Centrum für Chronische 🗰 Berteren Immundefizienz

#### Puzzle pieces of immune dysregulation in CVID Putting together a better picture

**Genes and Environment** 

in Europe

Immune Dysregulation

**ΡΙ3Κ**δ Low CD4 naive T cells Low Treg cells CTLA4 LRBA NFkB1 1111111 NFKB2 DAIL ON DOT **STAT3 GOF Progressed CD8 differentiation** STAT1 GOF S timber **ΡΚC**δ sIL2R **↑ Microbiom BCR** signaling High CD21<sup>low</sup> B cells Viral infection? Transfusion Normal range ??? ransfusion usion Not HHV8

400

100



Clinic

#### 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  $\pm 6$  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

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?)







#### 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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