

Immunologie „meets“ Hämatologie



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AWMF-Register Nr.	112-001	Klasse:	S2k
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Leitlinie

„Diagnostik auf Vorliegen eines primären Immundefekts“

- Abklärung von Infektionsanfälligkeit, Immundysregulation und weiteren Symptomen von primären Immundefekten –**

Immundefekte sind nicht nur Infekthäufung

ELVIS (pathologische Infektanfälligkeit)

- E** – Erreger
- L** – Lokalisation
- V** – Verlauf
- I** – Intensität
- S** – Summe



<https://www.horror-shop.com/p/elvis-presley-kostuem.html>

Immundefekte sind nicht nur Infekthäufung

ELVIS (pathologische Infektanfälligkeit)



<https://www.horror-shop.com/p/elvis-presley-kostuem.html>

- E** – Erreger
- L** – Lokalisation
- V** – Verlauf
- I** – Intensität
- S** – Summe

GARFIELD (Störung der Immunregulation)

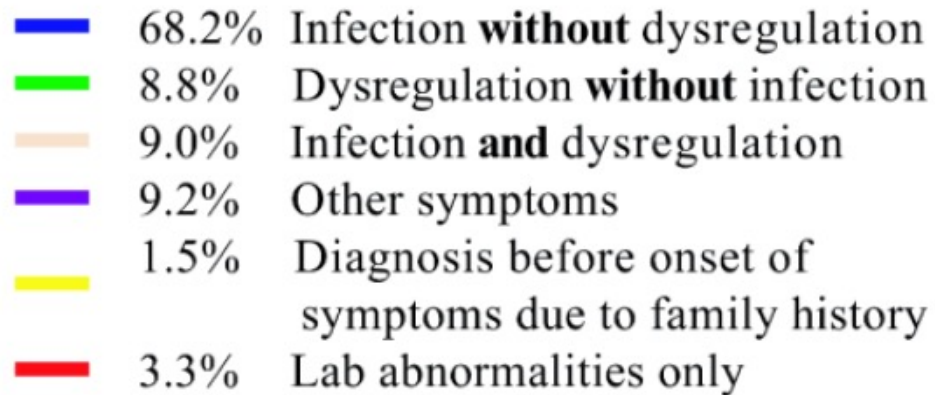


<https://tmnt.fandom.com/de/wiki/Garfield>

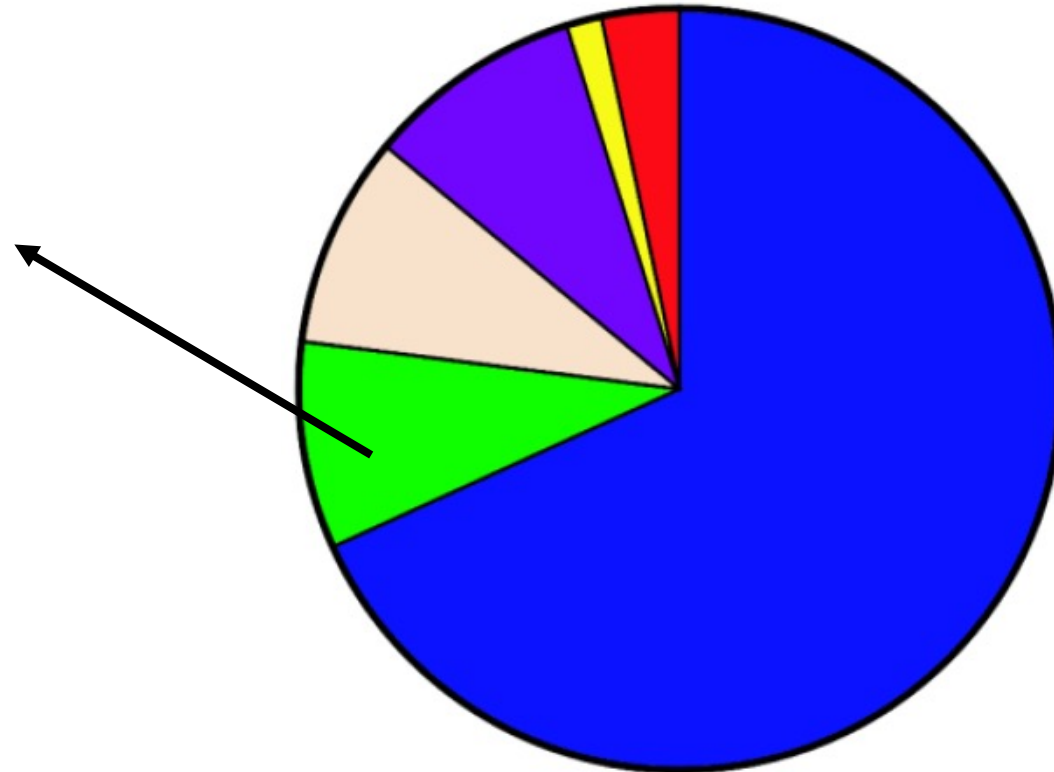
- G** – Granulome
- A** – Autoimmunität
- RFI** – Rezidivierendes Fieber
- E** – Ekzematöse Hauterkrankungen
- L** – Lymphoproliferation
- D** – Darmentzündung

Immundefektpatient:innen in der Hämatologie

Presenting symptoms

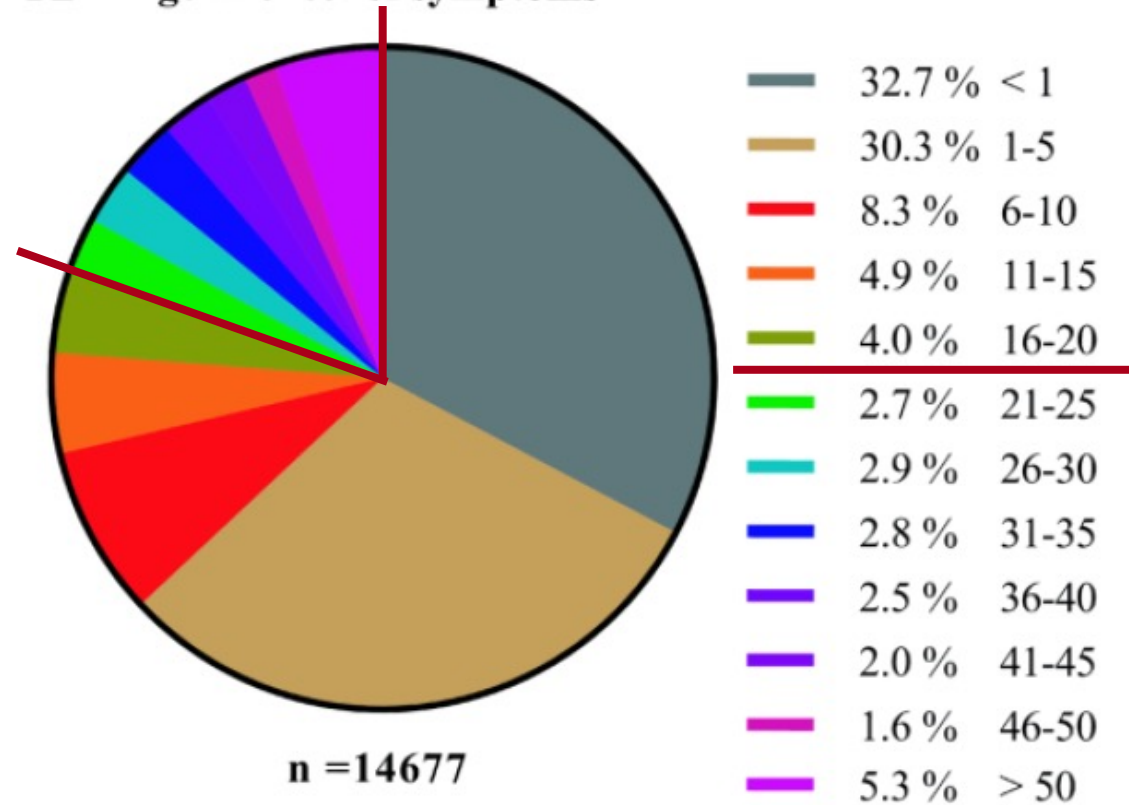


Total = 16574



Immundefekte bei Kindern und Erwachsenen

A Age at onset of symptoms



Warnsymptome für Hämatonkolog:innen

Familienanamnese	Eigenanamnese	Klinik
IEI in Familie	Gedeihstörung	Mikrozephalie
rez. Fehlgeburten	unerklärte Diarrhoe	Entwicklungsverzögerung
unerklärter Säuglingstod	rez. sinopulmonale Infektionen	Ataxie
Konsanguinität	schwere Infektionen	Teleangiektasien
	rez. Abszesse	Faziale Dismorphien
	pers. Pilzinfektionen	Bronchiektasen

Auszug aus: Van der Werff ten Bosch et al. *Ped Hem Oncol* 2016

...gemeinsame Patient:innen Hämatologie/Immunologie?

Zytopenien

- ITP
- AIHA
- Evans Syndrom
- Auto-/Alloimmunneutropenie
- Zyklische Neutropenie
- Schwere kongenitale Neutropenie (SCN)

Lymphoproliferation

- Lymphadenopathie
- Hepatomegalie
- Splenomegalie

Maligne hämatologische Erkrankungen

- Akute Lymphome
- Akute Leukämien

...gemeinsame Patient:innen Hämatologie/Immunologie?

Knochenmarksversagen

Hämatologische „Inflammation“

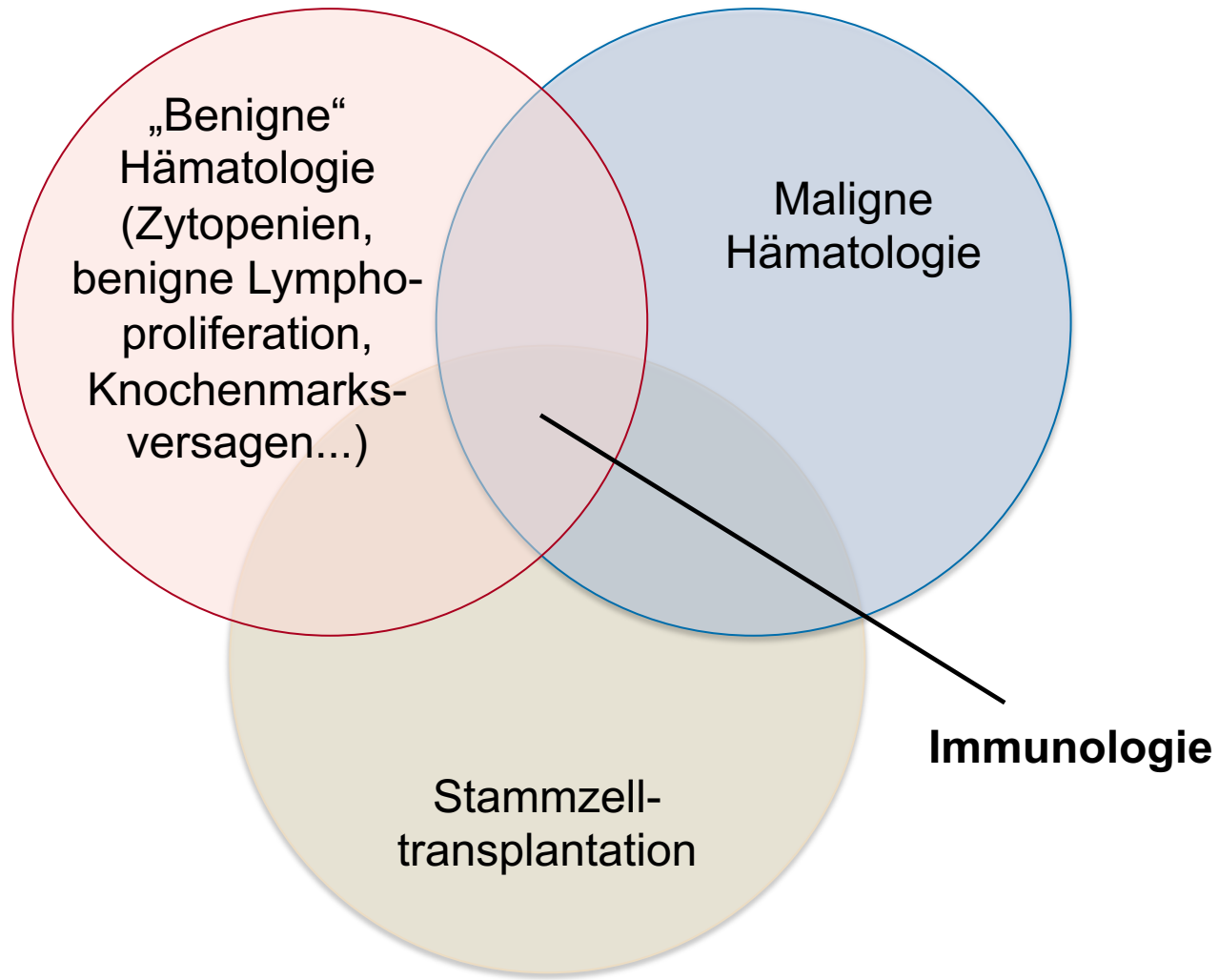
Sekundäre Immundefekte

- MDS
- Fanconi

- primäre HLH
- sekundäre HLH

- Bei Immunsuppression
 - Nach CTx
- Nach B-Zell-Depletion
- Nach CAR-Therapien

Immundefektpatient:innen in der Hämatologie

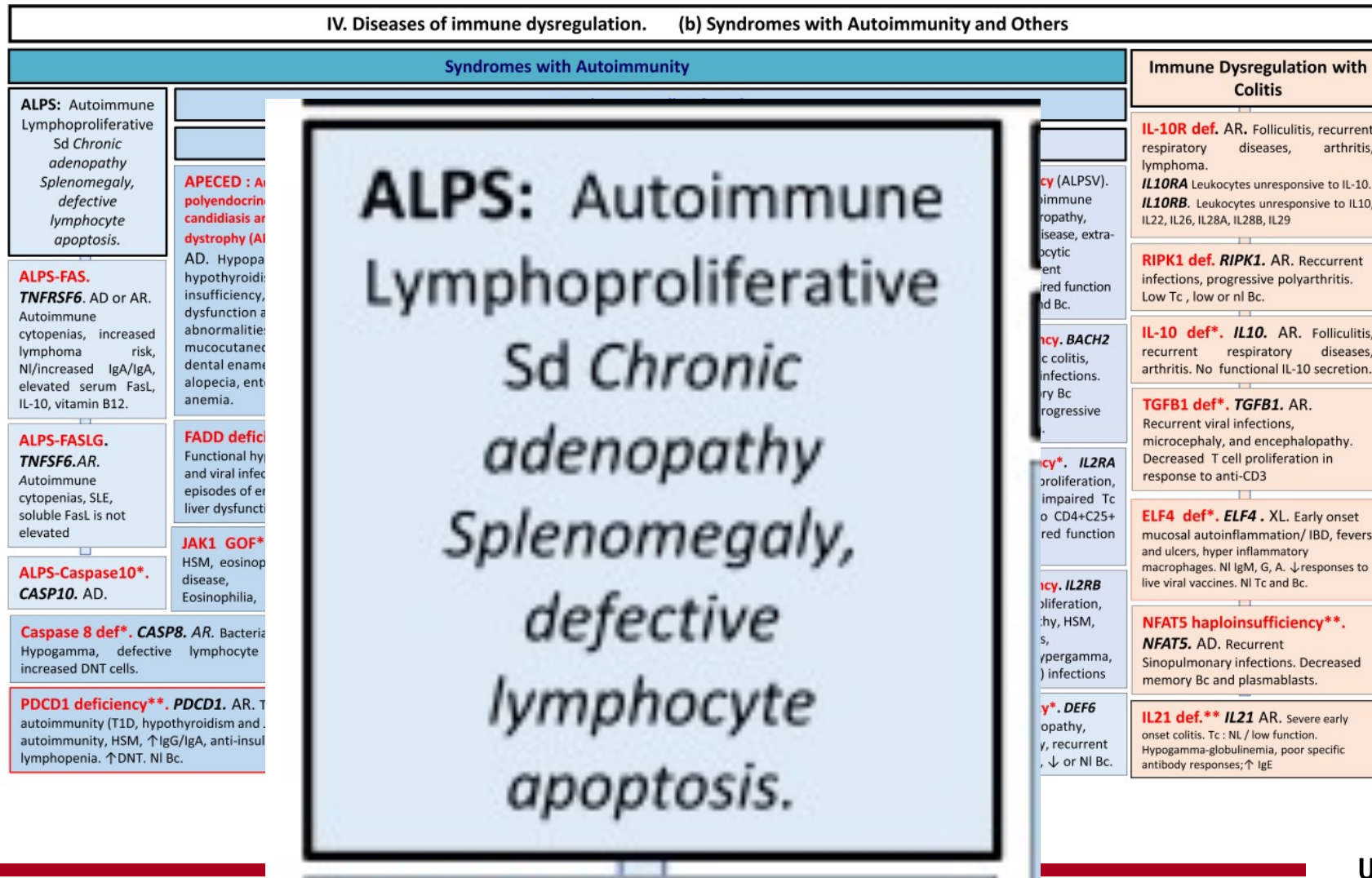


Beispielkrankungen - IUIS Klassifikation

V. Congenital defects of phagocyte number, function, or both. (a) Neutropenia (without anti-PMN)		
Syndrome associated	No syndrome associated	
<p>Shwachman-Diamond Syndrome. <i>DNAJC21</i> AR. <i>EFL1*</i> AR. Pancytopenia, exocrine pancreatic insufficiency. <i>SBDS</i> AR. +chondrodysplasia SRP54 deficiency*. <i>SRP54</i> AD. Neutropenia and exocrine pancreatic insufficiency .</p>	<p>G6PC3 deficiency (SCN4). <i>G6PC3</i> AR. Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O₂⁻ production.</p>	<p>Elastase deficiency. (SCN1). <i>ELANE</i> AD. Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).</p>
<p>Glycogen storage disease type 1b. <i>G6PT1</i> AR.</p>	<p>Cohen syndrome. <i>COH1</i> AR. Dysmorphism, mental retardation, obesity, deafness.</p>	<p>HAX1 deficiency (Kostmann Disease) (SCN3). <i>HAX1</i></p>
<p>3-I</p>	<p>Elastase deficiency. (SCN1). <i>ELANE</i> AD. Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).</p>	
<p>CL</p>		
<p>ab</p>		
<p>ata</p>		
<p>Cl</p>		
<p>ne</p>		
<p>C1</p>		
<p>de</p>		
<p>JAGN1 deficiency. <i>JAGN1</i> AR. Osteopenia. Myeloid maturation arrest.</p>	<p>autoinflammatory disease. ↑ proinflammatory serum cytokines.</p>	<p>CXCR2 deficiency*. <i>CXCR2</i> AR LOF. Profound neutropenia, myelokathexis, recurrent gingivitis, oral ulcers. Hypergammaglobulinemia (↑IgG, IgA, IgM). NI CD4+ Tc, variable CD8+ Tc, NI NKc. NI Bc.</p>
<p>WDR1 deficiency. <i>WDR1</i> AR. Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.</p>	<p>HYOU1 deficiency**. <i>HYOU1</i> AR. Hypoglycemia, inflammatory complications.</p>	<p>GFI 1 deficiency (SCN2)**. <i>GFI1</i> AD. B/T lymphopenia</p>
<p>SMARCD2 deficiency. <i>SMARCD2</i> AR. Developmental aberrations, bones defect, myelodysplasia</p>	<p>P14/LAMTOR2 deficiency**. <i>LAMTOR2</i> AR. Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.</p>	



Beispielkrankungen - IUIS Klassifikation



Beispielkrankungen - IUIS Klassifikation

IV. Diseases of immune dysregulation. (a) Hemophagocytic Lymphohistiocytosis and EBV susceptibility	
Familial Hemophagocytic Lymphohistiocytosis (FHL)	Diseases associated with EBV susceptibility
<p>FHL Type 1 Hypopig Partial albinism ↓ NK and cytotoxicity</p> <p>GrisCELLI Syndrome AR. Fever, HS</p> <p>Chediak-Higashi Syndrome AR. Recurrent fever, HS tendency, neurological Giant lysosomes neutropenia, Increased activity</p> <p>Hermansky-Rudolph Syndrome 2. AP3B1 AR infections, pulmonary, increased bleeding neutropenia.</p> <p>Hermansky-Rudolph Syndrome, type 10 AP3D1 AR. Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay.</p>	<p>BLTDP (CARMI2) deficiency BLTDP AR. Recurrent bacterial, fungal and</p> <p>EBV associated HLH</p> <p>XLP1 XLP1 XL, Clinical and immunologic features triggered by EBV infection: lymphoproliferation, Aplastic anemia, Lymphoma. Hypogammaglobulinemia, absent iNKT cells. Impaired NK cell and CTL cytotoxic activity. ↓ memory Bc.</p> <p>XLP2 XLP2 XL. Splenomegaly, lymphoproliferation, Colitis, IBD, Hepatitis. Hypogammaglobulinemia, absent iNKT cells. Increased T cells susceptibility to apoptosis to CD95 and enhanced FasL-induced cell death (ICD). Normal or reduced memory Bc.</p> <p>CD27 deficiency CD27 AR (TNFRSF7). Features triggered by EBV infection, aplastic anemia, ↓ iNKTc, B-lymphoma. ↓ Ig</p>
<p>Perforin deficiency (FHL2). PRF1 AR.</p> <p>UNC13D / Munc13-4 deficiency (FHL3). UNC13D AR.</p> <p>Syntaxin 11 deficiency (FHL4). STX11 AR.</p> <p>STXBP2 / Munc18-2 deficiency (FHL5). STXBP2 AR or AD. Enteropathy</p>	<p>TET2 deficiency**. TET2 AR LOF. ALPS-like (↑ sCD25, sFasL, IL10), recurrent viral infections, lymphadenopathy, HSM, autoimmunity, B-cell lymphoma, failure to thrive, developmental delay, EBV viremia, DNA hypermethylation, defective FAS-mediated apoptosis. Variable (hyper-/ hypogamma). ↑ DNT. ↓ Memory Bc.</p>
<p>lymphoproliferative disease. ↑ activated Tc. Failure to kill autologous EBV transformed Bc. NI NK cell function.</p> <p>RHOG deficiency**. RHOG AR. ↓ hemoglobin, hypertriglyceridemia, ↑ ferritin NI T cells, mild ↓ Bc; ↑ IgM, IgG</p>	<p>chronic active EBV infection. ↓ IgA and IgG, poor response to antigens, ↓ Tc proliferation</p>

Beispielkrankungen - IUIS Klassifikation

IX. Bone marrow failure			
<p>Fanconi anemia CNS, skeletal, skin, cardiac, GI, urogenital anomalies.</p> <p>Increased chromosomal breakage, pancytopenia.</p>	<p>Dyskeratosis congenita (DKC) Myelodysplasia, s</p> <p>Exclude oth Fanconi a Blackfan-D</p>	<p>Fanconi anemia Type A-W:</p> <p>-AR</p> <p>FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3,</p> <p>-XL</p> <p>FANCB</p>	<p>Others</p> <p>MIRAGE sd. SAMD9 AD GOF. I UGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen</p> <p>Ataxia pancytopenia sd. SAMD9L AD GOF. Cytopenia, predisposition to MDS with chromosome 7 aberrations and progressive cerebellar dysfunction</p> <p>COATS plus Sd: Intrauterine growth retardation, premature aging, <i>Intracranial calcification, abnormal telomeres, IUGR, gastrointestinal hemorrhage due to vascular ectasia, hypocellular bone marrow. pancytopenia</i> STN1 AR. premature aging, CTC1 AR. sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia,</p> <p>Osteopetrosis. TNFRSF11A, PLEKHM1 AR. TCIRG1, AR. + hypocalcemia CLCN7, OSTM1, AR. + hypocalcemia, neurologic features SNX10, AR. + visual impairment TNFSF11, AR. + severe growth retardation</p> <p>MECOM def. MECOM AD LOF. Thrombocytopenia/pancytopenia, clinodactyly, cardiac and renal malformations, Bc deficiency, radioulnar synostosis and presenile hearing loss.</p>
<p>Fanconi anemia Type A-W:</p> <p>-AR</p> <p>FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3,</p> <p>-XL</p> <p>FANCB</p>	<p>Dyskeratosis congenita</p> <p>IUGR, microcephaly, p hepatic fibrosis, nail dy scalp hair and eyelashe pigmentation; palmar premalignant oral leuk pancytopenia; +/- recu</p> <p>DKC1: XL, Bc and Tc: P decrease.</p> <p>NOLA2 (NHP2), NOLA: Decreased. RTEL1 : AD TERC, TINF2, ACD : AD TPP1: AD/AR, Tc: varia SNM1/APOLLO, WRAF variable.</p> <p><i>Hoyeraal-Hreidarsson</i>. Severe phenotype with delay and cerebellar h</p> <p>AR, RTEL1, PARN, ACD</p>	<p>Fanconi anemia Type A-W:</p> <p>-AR</p> <p>FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3,</p> <p>-XL</p> <p>FANCB</p>	<p>Others</p> <p>MIRAGE sd. SAMD9 AD GOF. I UGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen</p> <p>Ataxia pancytopenia sd. SAMD9L AD GOF. Cytopenia, predisposition to MDS with chromosome 7 aberrations and progressive cerebellar dysfunction</p> <p>COATS plus Sd: Intrauterine growth retardation, premature aging, <i>Intracranial calcification, abnormal telomeres, IUGR, gastrointestinal hemorrhage due to vascular ectasia, hypocellular bone marrow. pancytopenia</i> STN1 AR. premature aging, CTC1 AR. sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia,</p> <p>Osteopetrosis. TNFRSF11A, PLEKHM1 AR. TCIRG1, AR. + hypocalcemia CLCN7, OSTM1, AR. + hypocalcemia, neurologic features SNX10, AR. + visual impairment TNFSF11, AR. + severe growth retardation</p> <p>MECOM def. MECOM AD LOF. Thrombocytopenia/pancytopenia, clinodactyly, cardiac and renal malformations, Bc deficiency, radioulnar synostosis and presenile hearing loss.</p>



Fallbeispiele

Immunologie meets Hämatologie



Patientin 1: Charlotte *2007

Patientin 1: Anamnese

Dezember 2023

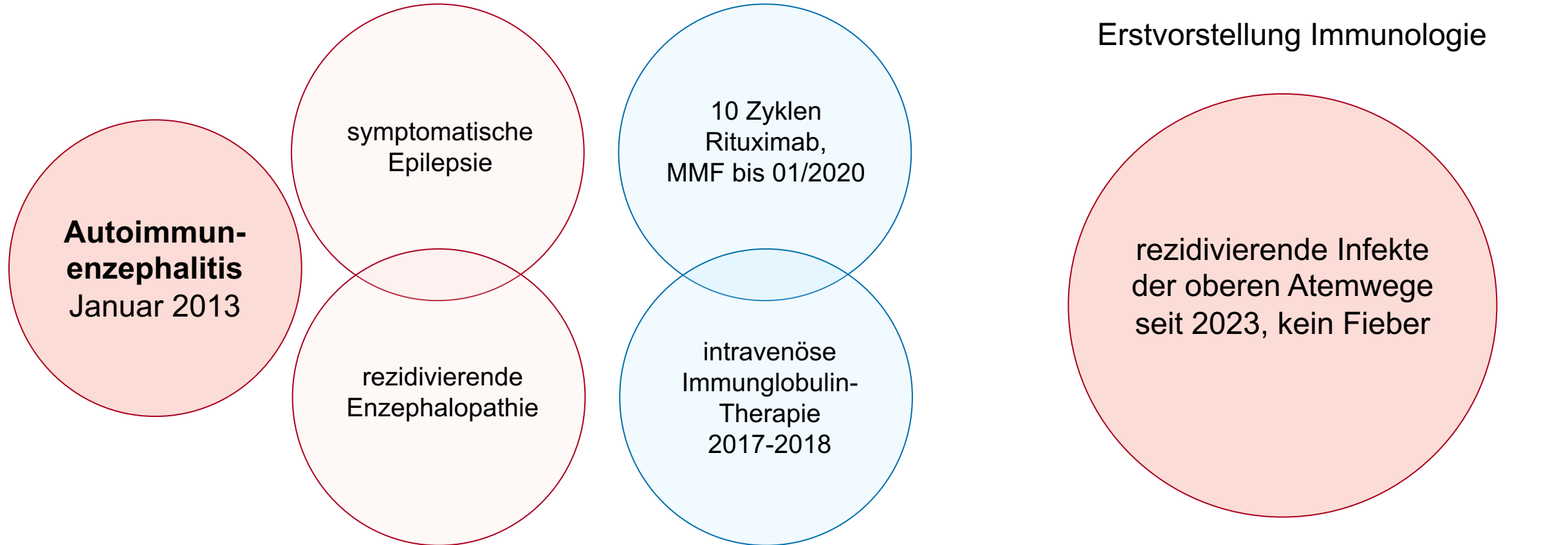
Erstvorstellung Immunologie

rezidivierende Infekte
der oberen Atemwege
seit 2023, kein Fieber

Patientin 1: Anamnese

Januar 2013

Dezember 2023



Patientin 1: Diagnostik

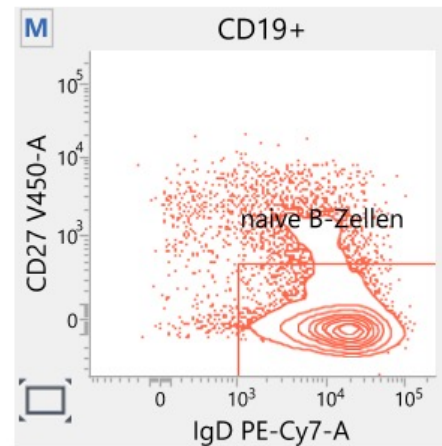
Immunologische Diagnostik

Hypogammaglobulinämie
(IgG 1,92 g/l)

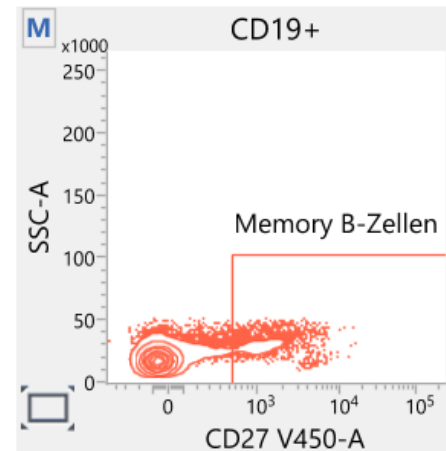
Masern-IgG negativ,
weitere Impfantikörper positiv

Immunphänotypisierung:
↑ B-Lymphozyten
↑ naive B-Zellen
↓ Memory-B-Zellen
↓ IgG-Memory B-Zellen

B-Zellen:



Naive: 90.7 %
(Norm: 66-88%)

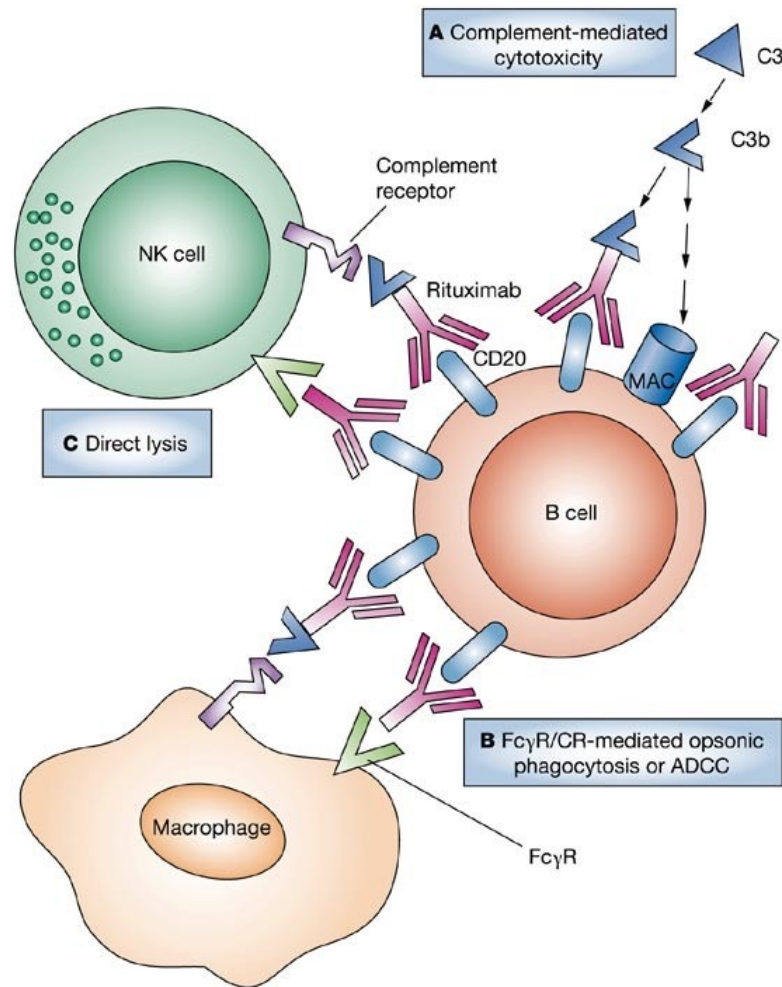


Memory: 7.5 %
(Norm: 11-21%)

Patientin 1: Therapie



Anhaltende Hypogammaglobulinämie nach Rituximab



- Schwere Hypogammaglobulinämie (<3g/l) nach Rituximab in 25% der Patient:innen mit Autoimmunerkrankungen
- Lymphom-Patient:innen höheres Risiko für Hypogammaglobulinämie (bis zu 50% bei NHL)
- bei 65% Atemwegsinfektionen
- Risikofaktoren: weibliches Geschlecht, Begleittherapie mit Steroiden, Cyclophosphamid, MMF
- **22% benötigen Immunglobulinsubstitution bis zu 60 Monate nach Rituximab-Therapie**



Patient 2: Daniel *2004

Patient 2: Anamnese

Seit 2013

Januar 2019

Januar + Februar 2021

April 2023

Januar 2024

- rez. Fieberschübe alle 3 Wochen
- Hepatosplenomegalie
- enorale Aphten
- Lymphadenitis mesenterialis

Erstvorstellung
Immunologie UKD

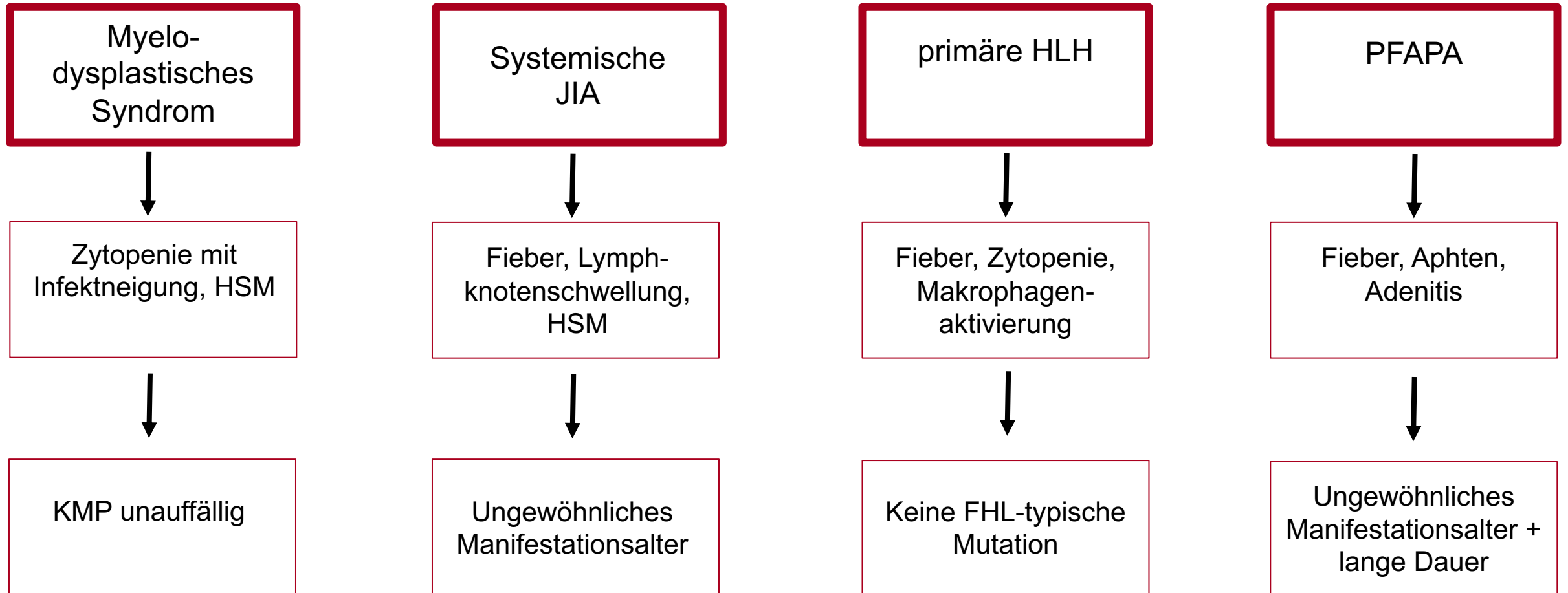
erneuter
Krankheitsschub

erneuter
Krankheitsschub

Labor im Fieberschub: Panzytopenie, Ferritinämie, erhöhtes CrP sowie SAA

Eigenanamnese: Z.n. Tonsillektomie bei gehäuft bakteriellen Tonsillitiden

Patient 2: Differentialdiagnosen



Hämophagozytische Lymphohistiozytose

- Primäre HLH (FHL): vorrangig autosomal-rezessive Genmutationen führen zu Funktionsstörung zytotoxischer T- und NK-Zellen sowie einer gestörten Immunregulation
- Sekundäre (erworbene) HLH: durch Infektionen, Autoinflammation, Malignome, Immunsuppressiva, Stoffwechselerkrankungen ausgelöst

Diagnosekriterien HLH (5/8 Kriterien notwendig)
Fieber
Splenomegalie
Zytopenie ≥ 2 Zellreihen
Hypertriglyceridämie und / oder Hypofibrinogenämie
Ferritinämie
Löslicher IL2-Rezeptor erhöht
NK Zellaktivität erniedrigt oder nicht nachweisbar
Hämophagozytose in Knochenmark, Liquor oder Lymphknoten

Mögliche Therapien

Prednisolon

Tocilizumab
i.v./s.c.

Colchizin

Canakinumab

Methyl-
prednisolon

MTX

Anakinra

Patient 2: Verlauf

2024

Erneuter Schub mit

- Fieber
- Bilytopenie
- Hepatosplenomegalie
- Feinfleckigem Exanthem

Anakinra
i.v.



Ruxolitinib

Autoinflammation

- Autoinflammationssyndrome z.T. schwer zu diagnostizieren
- vielfältige klinische und laborchemische Präsentationen
- Genetische Diagnostik kann Hilfestellung bieten
- Therapie muss patient:innenindividuell ausgewählt werden
- Interdisziplinäre Zusammenarbeit zwischen Immunologie, Rheumatologie, Hämatonkologie, Infektiologie u.a.
- Patient:innenorganisation wie **dsai** wichtig für Betroffene





Patient 3: Felix *2011

Patient 3: Anamnese und Klinik

4 Jahre

6 Jahre

Erstvorstellung Kinderklinik

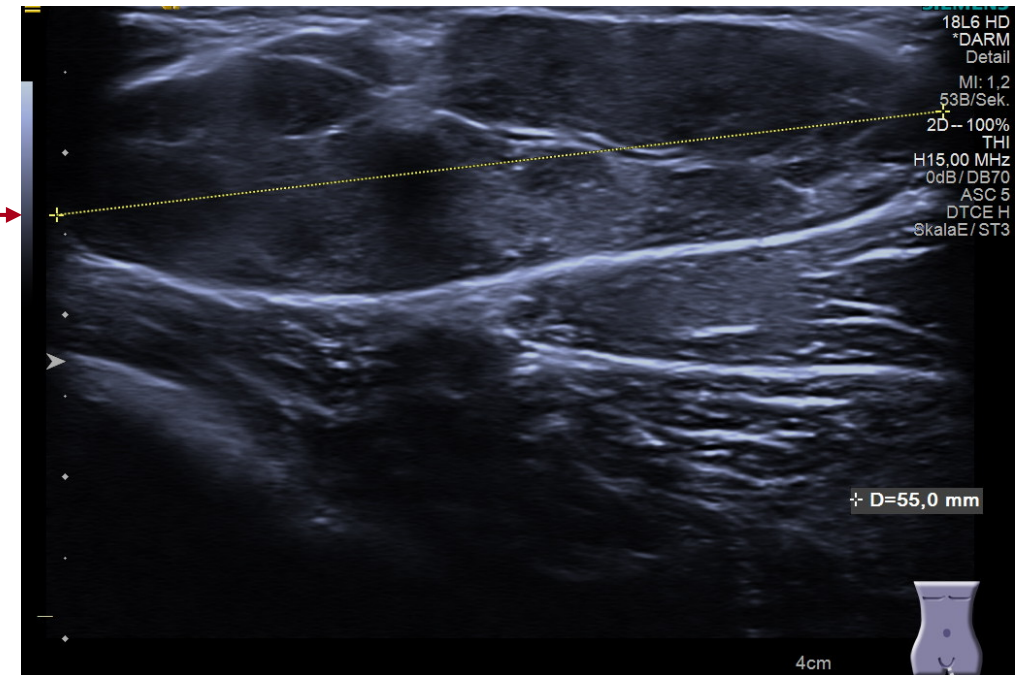
Splenomegalie

Inguinale LK-Schwellung (Paket)

Infektiologische Abklärung
(CMV, EBV, MAC, Toxoplasmose)
opB.

Infektiologische Abklärung
(CMV, EBV, MAC, Toxoplasmose)
opB.

KMP + LK-Biopsie:
Ausschluss Lymphom/
Leukämie



Patient 3: Anamnese und Klinik

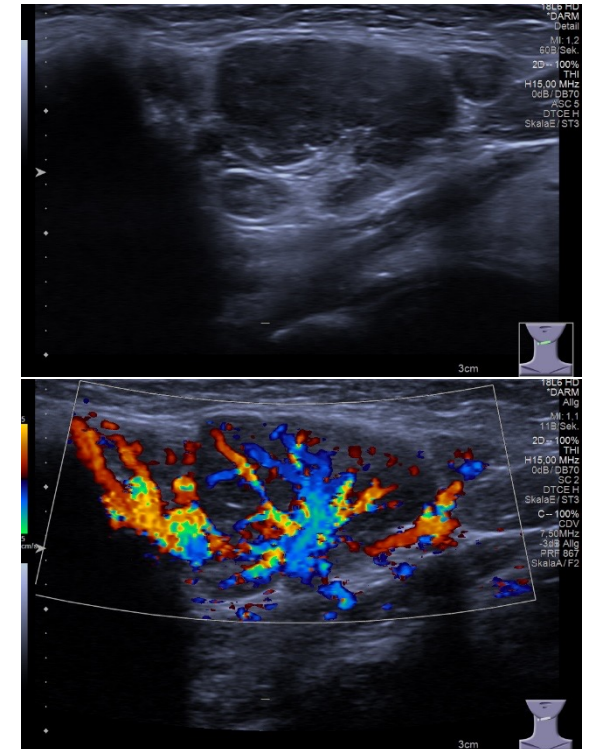
6-7 Jahre

Genetische Diagnostik: **ALPS FasR** variante heterozygot (maternal)

Rez. Thrombozytopenien < 30.000 GPt/L, rez. Petechien und Hämatomneigung

Massive zervicale Lymphadenopathie

Beginn Sirolimus-therapie



Patient 3: Diagnostik

Immunologische Diagnostik

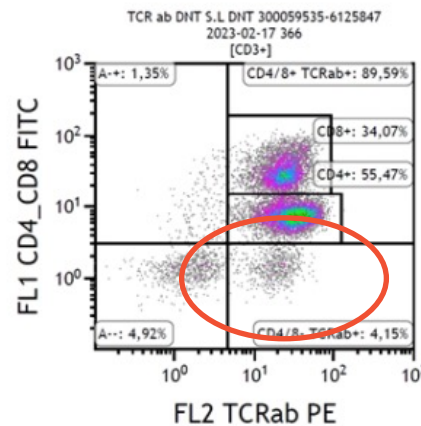
Vit. B12

Vit. B12 = **1844** pg/mL

(Normbereich: 245-1175 pg/mL)

doppelt negative T-Zellen

Gate: CD3+



CD4-CD8-TCRab+ von CD3+

Patient:

4,15 %

Norm:

kleiner 2,50%

sFAS-L

sFasL = **1952** pg/mL

(Normbereich: <250 pg/mL, hohe Wahrscheinlichkeit einer Fas-Variante wenn sFasL > 800 pg/mL)

Patient 3: Verlauf

7 Jahre

12 Jahre

Nach Beginn Sirolimus:
Regredienz der LK-Schwellung, normalisierte Thrombozytenwerte

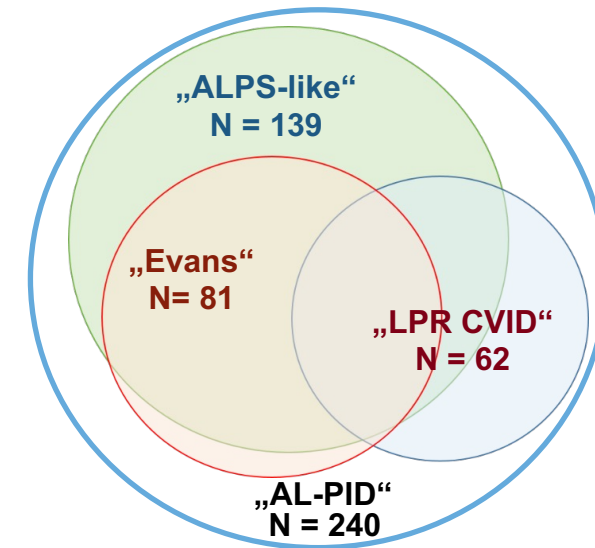
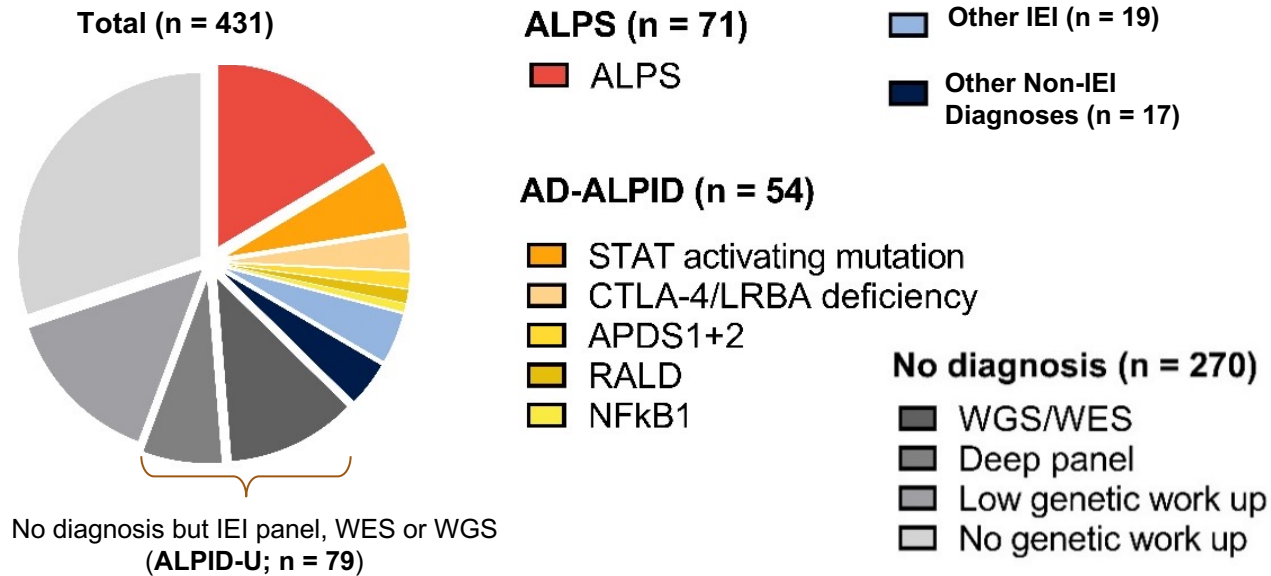
Wundheilungsstörungen

Art. Hypertonie

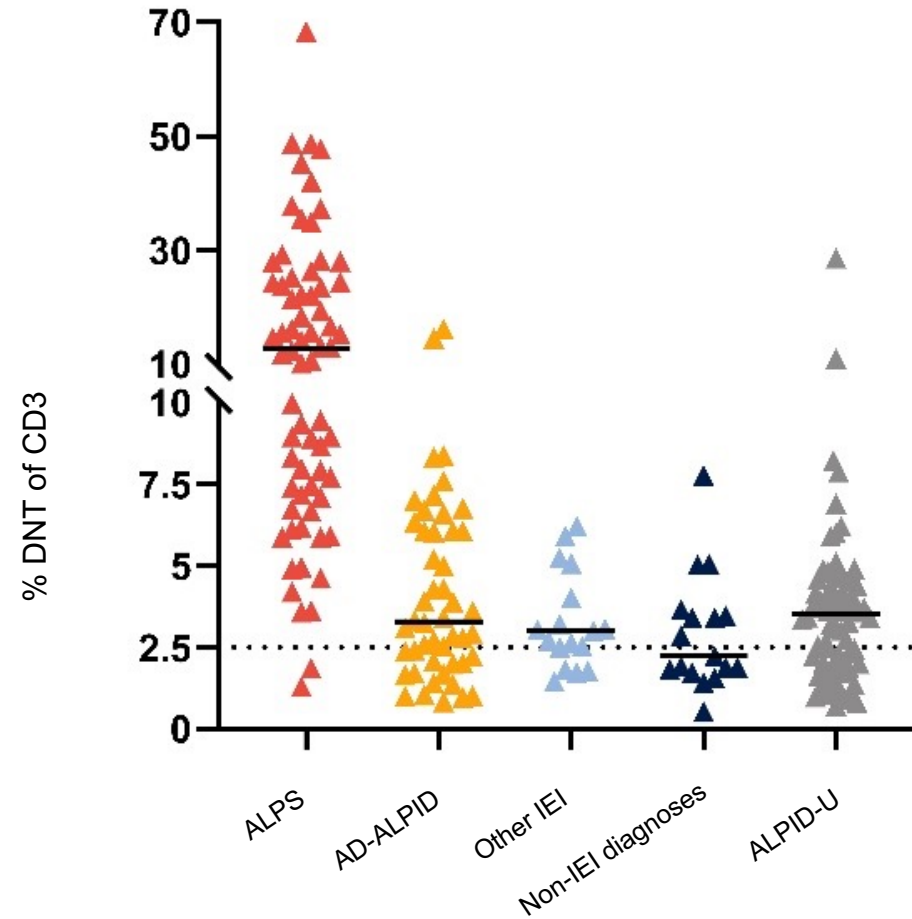
rezidivierende Angioödeme

Absetzen Sirolimus
→ Bislang beschwerdefrei

Exkurs ALPS und AL-PID Erkrankungen



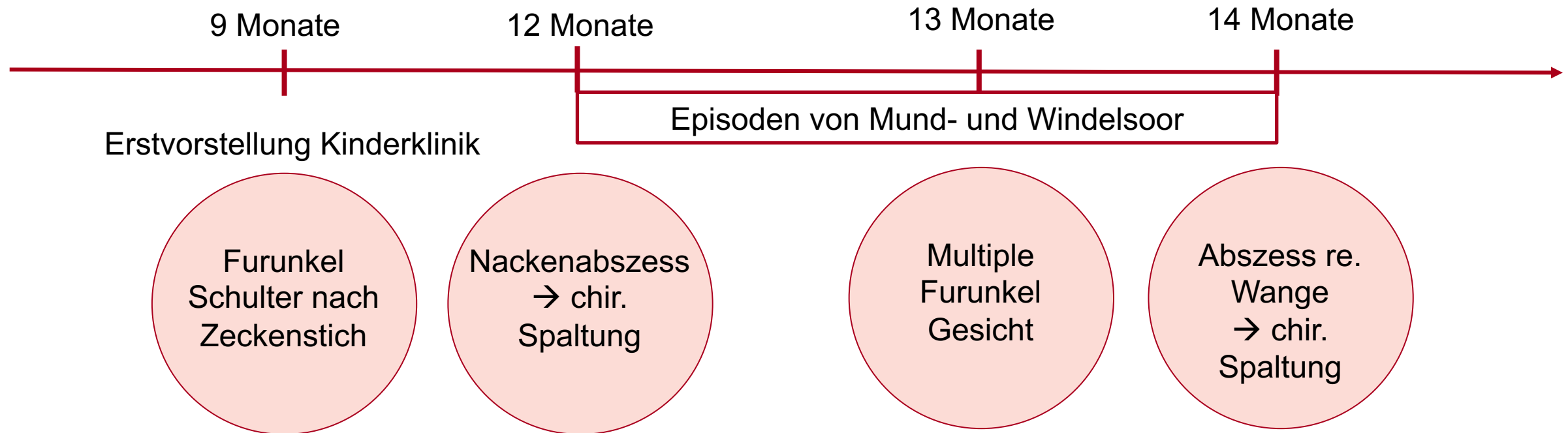
Exkurs ALPS und AL-PID Erkrankungen





Patientin 4: Elisa *2018

Patientin 4: Anamnese



Patientin 4: Befunde

14 Monate

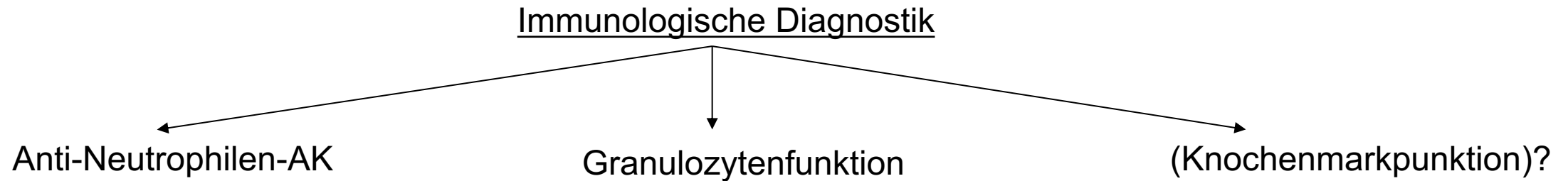
Erstvorstellung Immunologie

Mit 1 Jahr:
Tagesmutter

Mibi (Abszess):
S.aureus (R:
Penicillin);
MRSA-Screening
negativ

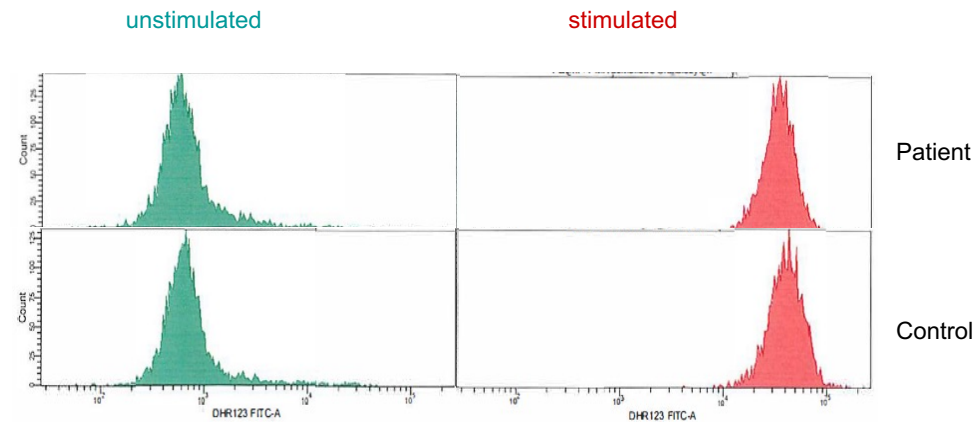
Normale
Lymphozyten,
Neutrohile < 0.5
GPT/L

Patientin 4: Elara *2018



Granulozytenimmunfluoreszenztest (GIFT) mit 4/4 Testzellen stark positiv

Freie AK im Serum nachweisbar.



Exkurs Autoimmunneutropenie

TABLE I. Clinical Characteristics of the Patients

	Autoimmune neutropenia of infancy (157)
Male	64.3%
Median age at onset (years)	0.70
Median age at diagnosis (years)	1.06
Median age at resolution	2.14
Median duration (years)	1.30
Recovery	89.1%
Median WBC at onset ($\times 10^9/L$)	6.1
Median ANC at onset ($\times 10^9/L$)	0.45
Leucopenia at onset	41.7%
Monocytosis at onset	19.3%
Increased IgG at onset ^a	6.0%
Selected IgA deficiency ^a	3%
Severe infections	9.6%

^a Data available on 133/157 patients.

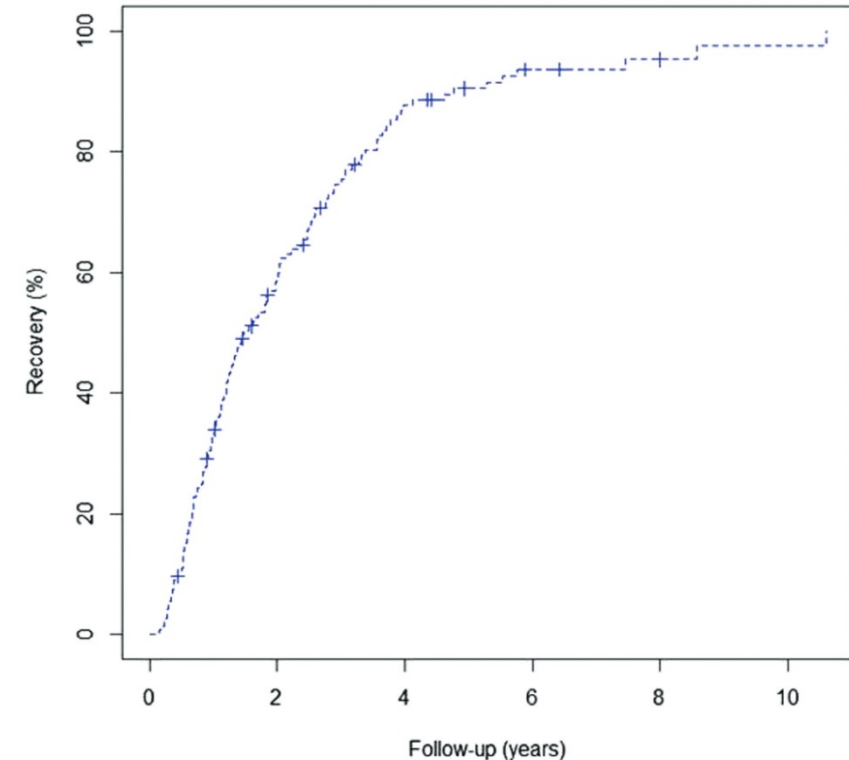
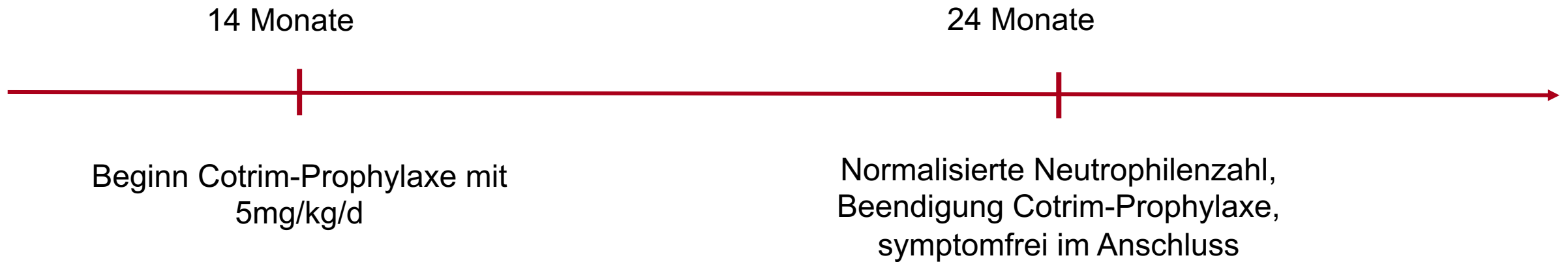


Figure 1. Kaplan Meier recovery curve.

Patientin 4: Elara *2018



Vielen Dank für Ihre Aufmerksamkeit.

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