Immunodeficiency

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Immunodeficiency

- Very large subject
- Primary and Secondary Immunodeficiency

Primary Immunodeficiency (PID) or Inborn errors of immunity (IEI)

Primary Immunodeficency

- Many illnesses that are mainly the domain of pediatrics
- More and more of responsible genes are being described (almost 500)
- Most frequents PID present in adults (IgA deficiency, Common variable immunodeficiency)
- Delayed diagnosis is common

Primary Immunodeficency

increased susceptibility to :

- Infections
- autoimmunity
- auto-infammatory diseases
- allergy
- bone marrow failure
- malignancy

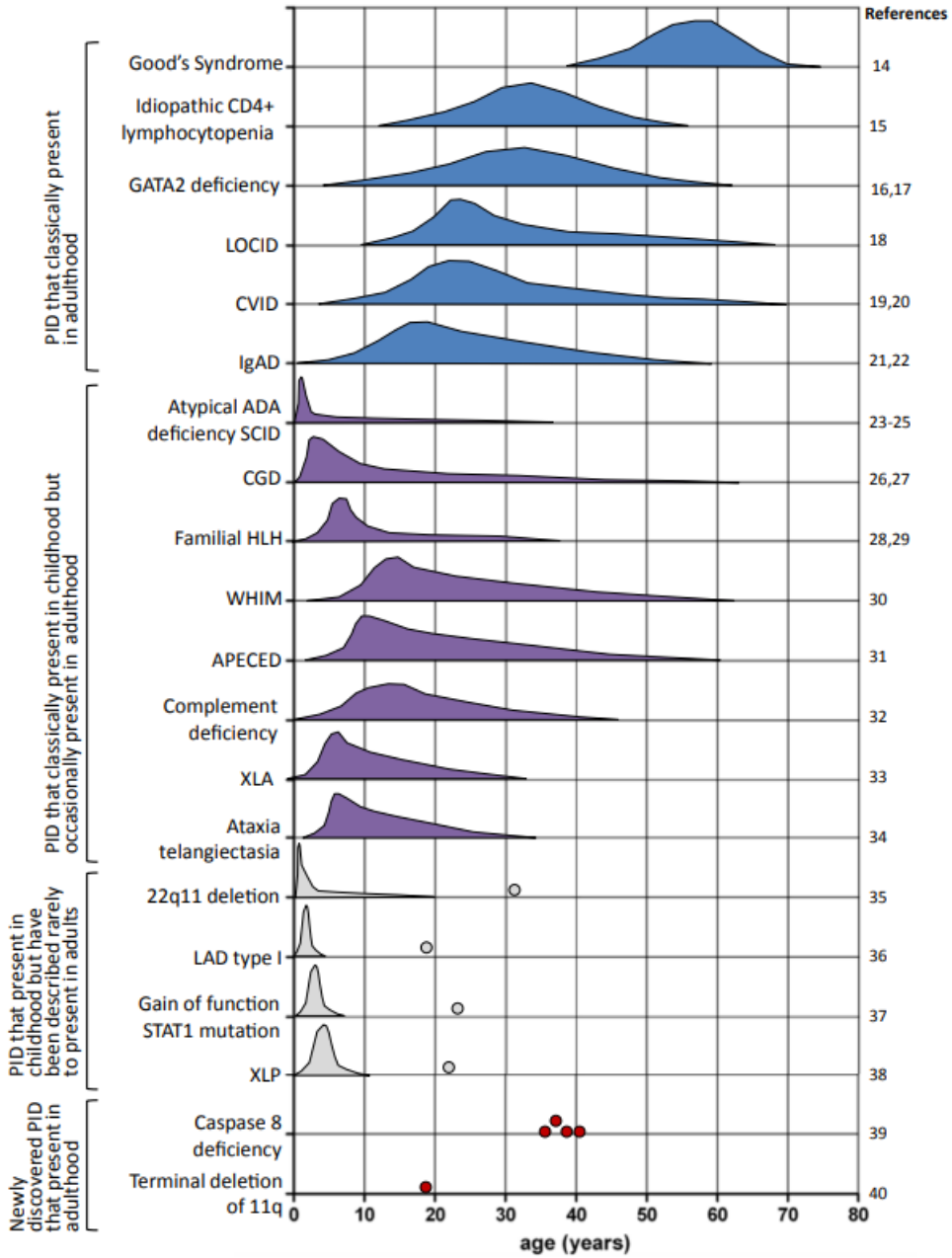


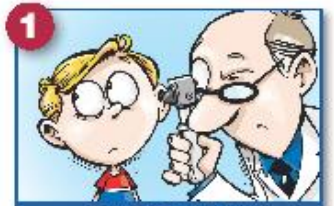
FIGURE 1. Examples of various PID diseases and their age of onset. Each schema approximates the relative incidence per age. Several

Warning signs of possible PID

- Recurrent **sinus** infection
- Recurrent **otitis** media
- Recurrent **pneumonia**
- Severe infections requiring **intravenous antibiotics**
- Failure to thrive or growth retardation (child)
- Recurrent **skin** or **organ abcesses**
- Persistant oral ok skin **candidiasis**
- **Severe infections** leading to septicemia
- **Unusual infections**
- Family history of PID

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. 
Four or more new ear infections within one year.

2. 

Two or more serious sinus infections within one year.

3. 
Two or more months on antibiotics with little effect.

4. 
Two or more pneumonias within one year.

5. 

Failure of an infant to gain weight or grow normally.

6. 
Recurrent, deep skin or organ abscesses.

7. 
Persistent thrush in mouth or fungal infection on skin.

8. 
Need for intravenous antibiotics to clear infections.

9. 

Two or more deep-seated infections including septicemia.

10. 
A family history of PI.

Presented as a public service by:

Jeffrey Modell Foundation | Curing PI Worldwide

Funding was made possible in part by a grant from the U.S. Centers for Disease Control and Prevention (CDC).

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board.
Consultation with Primary Immunodeficiency experts is strongly suggested.

For information or referrals, contact the Jeffrey Modell Foundation: **info4pi.org**

10 Warning Signs of Primary Immunodeficiency

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1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

10 FOR ADULTS Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
9. Infection with normally harmless tuberculosis-like bacteria.
10. A family history of PI.

PID

- B –lymphocytes immunodeficiency (CVID…)
- T-Cell immunodeficiency (SCID, CID…)
- Immune dysregulation Syndromes (ALPS, Autoinflammatory syndromes…)
- Innate immune defects (Congenital neutropenia, Chronic Granulomatous Disease, Primary immunodeficiency of complement, NK cells defects, mucocutaneous Candidiasis)

Primary humoral immunodeficiency or B lymphocyte Immunodeficiency

- **CVID (Common variable immunodeficiency)**
- Agammaglobulinemia (XL or AR, early-onset infections, profound hypogammaglobulinemia, less than 2% CD19+ B cell in peripheral circulation)
- Class switch defects (Hyper IgM syndrom)
- Transient Immunodeficiency of infancy
- **Selective isotype immunodeficiency** (IgG subclass deficiency, IgA deficiency, Specific antibody deficiency (poor reponse to polysaccharide antigens))

CVID

- Difficult to know the exact prevalence : at least 1/30.000 persons worldwide
- Infectious and non-infectious presentation

CVID : Diagnostic criteria (International Consensus Document ICON)

- Low Ig G (compared to age-speficic norms)
- With either low IgA or IgM (low IgA preferred)
- Impaired vaccine response (not necessary if IgG very low <1g/l to 3 g/l) -> more risk of infection)
- Other causes of hypogammaglobulinemia being exclued

- Clinical manifestations such as infections or autoimmunity NOT required for the diagnosis, but most patients will have clinical manifestations at the time of diagnosis (and present in ESID criteria)
- vaccine response evaluation not necessary if IgG very low <1g/l to 3 g/l -> start immunoglobulin replacement therapy without waiting immune response assessment

Table 3 | Revised ESID (2014) diagnostic criteria for CVID.

At least one of the following:

- Increased susceptibility to infection
- Autoimmune manifestations
- Granulomatous disease
- Unexplained polyclonal lymphoproliferation
- Affected family member with antibody deficiency

AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2 SD of the normal levels for their age);

AND at least one of the following:

- Poor antibody response to vaccines (and/or absent isohemagglutinins); i.e., absence of protective levels despite vaccination where defined
- Low switched memory B cells (<70% of age-related normal value)

AND secondary causes of hypogammaglobulinemia have been excluded (see separate list)

AND diagnosis is established after the fourth year of life (but symptoms may be present before)

AND no evidence of profound T-cell deficiency, defined as two out of the following (y = year of life):

- CD4 numbers/microliter: 2–6 y < 300, 6–12 y < 250, >12 y < 200
- % Naive CD4: 2–6 y < 25%, 6–16 y < 20%, >16 y < 10%
- T-cell proliferation absent

http://esid.org/Working-Parties/Registry/Diagnosis-criteria.

CVID : Diagnostic

- CVID: decreased switched memory B cells (on specific flow cytometry)
- Majority of patients with CVID have NO history of affected family members. However 10-20% of patients have one or more family members with either CVID or a more subtle antibody deficiency such as IgA deficiency

- Low total immunoglobulins but intact functional response to vaccine -> NOT indicative of PID -> control immunoglobulins dosages

Clinical Case 1

- 62 years old woman
- Adressed by pneumologist for hypogammaglobulinemia founded during hospitalisation for « pneumonia », bilateral pulmonary condensations on CT scan, fibroscopy with lavage finaly showing presence of Mycobacterium Xenopi.

Clinical Case 1 : question

- What do you want to know/do ?
  - Ig G, A, M dosages
  - Subclass Immunoglobulins dosages
  - Electrophoresis on blood and urine (with proteinuria test)
  - Past Ig G, A, M dosages
  - Medical History
  - Immunophenotyping
  - Vaccination

Clinical Case 1 : question

- What do you want to know/do ?
  - Ig G, A, M dosages -> IgG : 3,53g/l, IgM lowered 0,2g/l (NV: 0,56-1,59), IgA : 0,91 g/l (normal)
  - Subclass Immunoglobulins dosages -> normal, except slightly lowered IgG3 (0,19g/l NV 0,2-1,1)
  - Electrophoresis on blood and urine (with proteinuria test) -> No monoclonal peak, no proteinuria
  - Past Ig G, A, M dosages -> not available
  - Medical History
  - Immunophenotyping -> no clonality
  - Vaccination

Clinical Case 1 : question

- Medical History :
  - At the age of 5 years, the patient spent 1 year at sea, possibly for asthma...
  - No notion of frequent infections during childhood.
  - Pneumonia in 2015, treated at home (no x-ray performed)
  - Pneumonia in 2017, treated at home (no x-ray performed)

- Février 2021 : Hospitalised for pneumonia
  - Pneumonologists concluded in bronchiectasis infection by Mycobacterium Xenopi
  - Biology showed signs of undernourishment and folate and vitamin D deficiency.
- Before pneumonia the patient reported sweating but did not take her temperature. She had lost her appetite and lost weight.
- At the time of hospitalization, she weighed 41kg

Clinical case 1

- Evolution
  - She was treated by Clarithromycine, Myambutol, Pyridoxine and Rifadine during 9 months
  - Two month after the begining of treatment, she weighed 49kg (+8kg)
  - IgG: 7.32 g/L , IgA still normal : 0.96 g/L , IgM levels remain low: < 0,25g/l

  - Hypogammaglobulinemia was probably secondary to undernourishment, but was the undernourishment due to the atypical mycobacteria infection?

CVID : infectious complications

- Sinusitis
- Bronchitis
- Otitis media
- pneumonia
- And also higher risk of invasive infections (meningitis and sepsis)
- Gastrointestinal infections : sometimes lead to chronic diarrhea and malabsorption (Giardia, Campylobacter jejuni, salmonella, Helicobacter pylori, Shigella, Norovirus…)

- Upper and lower respiratory infections :
  - Encapsulated bacteria (haemophylus influenza, streptococcus pneumonia)
  - Atypical bacteria (Mycoplasms)
  - Reccurent viral infecctions with common pathogens, such as rhinovirus

- Infectious complications drastically decreased after immunoglobulin replacement

CVID : non infectious complications

- Pulmonary :
  - Lymphocytic interstitial pneumonitis
  - Nodular lymphoïd hyperplasia
  - GLILD (granulomatous lymphocytic interstitial lung disease)
- Dermatologic
  - Psoriasis
  - Vitiligo
  - Lichen planus
  - Alopecia
- Gastrointestinal
  - Atrophic gastritis
  - Gastric carcinoma
  - Pernicious anemia
  - Autoimmune enteropathy
  - Small bowel villous flattening
  - Primary biliary cirrhosis
  - Primary scleroting cholangitis
- Rheumatologic
  - Lupus
  - Rheumatoïd arthritis
  - Vasculitis
- Hematologic
  - ITP
  - Hemolytic anemia
  - Autoimmune neutropenia
  - Evan’s syndrome
- Lymphoïd
  - Lymphoïd hyperplasia
  - Splenomegaly
  - Non-Hodgkin’s lymphoma
- Cancer:
  - Gastric cancer
  - Thyroïd cancer
  - Skin cancers
  - Lymphoma

CVID : Management

- Immunoglobulin replacement -> for all CVID? for those who get infected ?
- Automatically if:
  - profound hypogammaglobulinemia (IgG less than 1 (or 3) g/l)
  - Bronchectasis
- Immunoglobulin substitution:
  - 0,4-0,5gr/kg/month IV
  - 0,4-0,6 gr/kg/month Subcutaneous
  - Adapt to minimize significant breakthrough infections (IgG 7-10g/l)
- Unfortunately replacement immunoglobulin don’t prevent or treat non infectious inflammatory complications of CVID

	POINT VALUE	0	1	2	3	4	5
Laboratory	IgG (mg/dl)	600+	350-599		150-349		0-149
	IgA (mg/dl)	normal			reduced		≤10
	IgM (mg/dl)	normal			reduced		≤15
	diphtheria or tetanus	protective					nonprotective
	% of protective pneumococcal serotypes	≥50%			20-49%		0-19%
Clinical History	Pneumonia/lifetime	none	1	2	3	4	five or more
	Upper Respiratory Infections/year	none	1	2	3		>3
	Antibiotic Courses/year	none	1	2	3	4	five or more or prophylactic
	Autoimmune Disease-ITP, AIHA, or other	none			present		
	Sepsis / Meningitis/ Osteomyelitis/ Empyema/ Septic Arthritis	none					present
	Splenomegaly or Splenectomy	none			present		
	Lymphadenopathy	none			present		
	Infectious Diarrhea (excluding *Clostridium difficile)*	none			present		
	Malabsorption, Chronic Gastroenteritis, Inflammatory Bowel-like Disease	none			present		
	Weight Loss/ Failure to Thrive	none			present		
	Hospitalizations/5 years	none	1	2	3	4	five or more
Other	Pulmonary Function Tests	normal	FEV1/FVC or TLC < 80% predicted		FEV1/FVC or TLC <70% predicted		FEV1/FVC or TLC < 60% predicted
	Bronchietasis	none					present

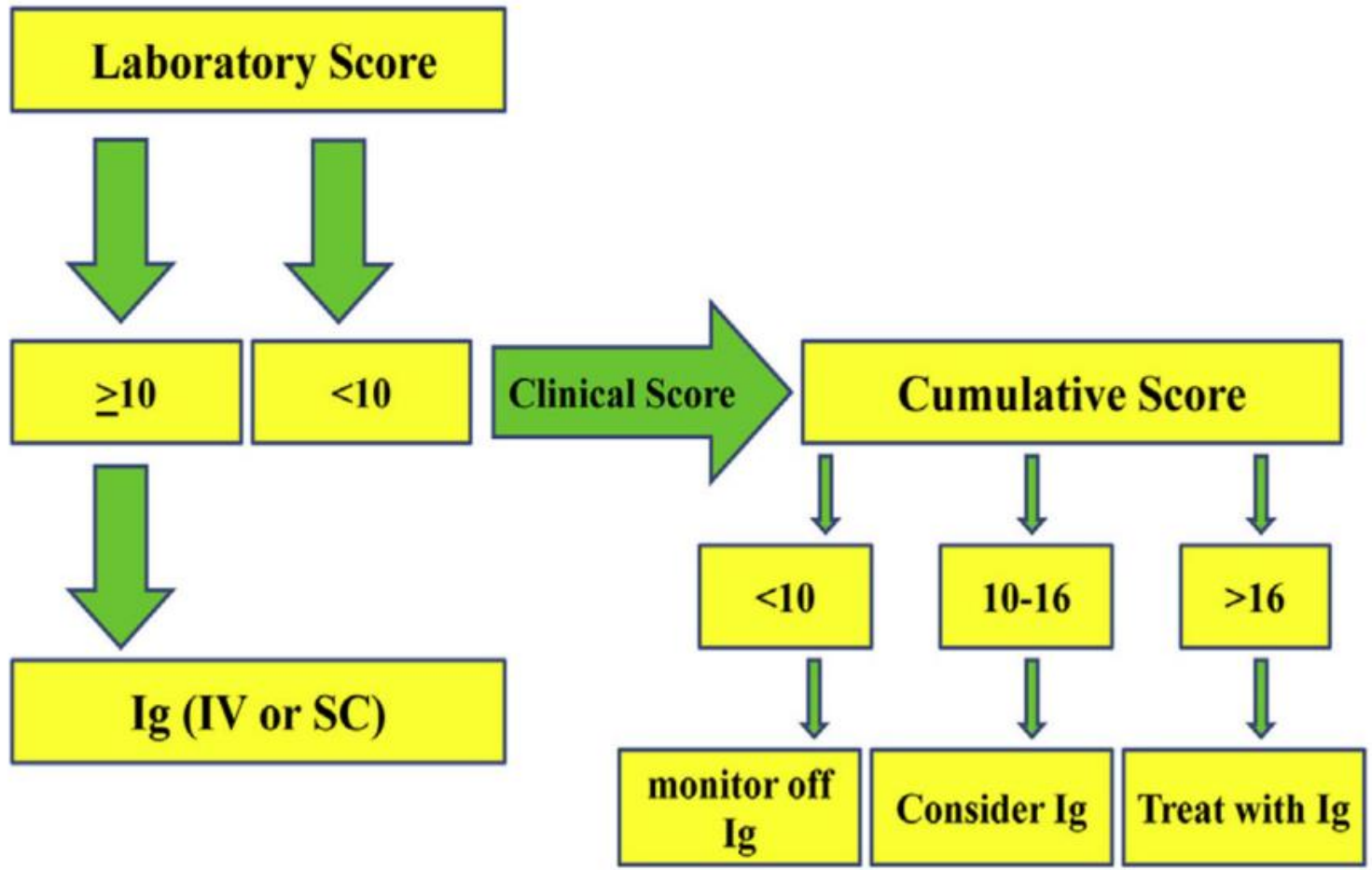

FIG 2.
Scoring decision tree. *Ig*, Immunoglobulin; *IV*, intravenous; *SC*, subcutaneous.

Clinical case 2

- 39 years old man
- Referred by rheumatologist who discovered hypogammaglobulinemia during workup for back pain
- Clinical History:
  - Does not recall frequent childhood infections but :
    - Meningococcal meningitis around 5 years of age
    - Trans-tympanic drains in childhood
    - Tympanic perforation in childhood
    - mumps in childhood
  - Pneumonia in 2022 confirmed by X-ray, treated at home

Clinical case 2

- And now:
  - Infections 2 or 3 times a year, such as otitis or sinusitis, but does not need antibiotics each time.
  - More frequent infections since the covid vaccination
  - He has had covid 3 times in the past year, with fever, bronchitis...
  - If you insist he reports coughing with sputum every morning and during episodes of otitis or sinusitis.
  - No recurrent diarrhea

Clinical case 2

- Family history:
  - 3 healthy children
  - Father : hypercholesterolemia, Mother: hypertension
  - 2 healthy brother
  - 2 twin sisters : one have hepatitis around age 20 and the other sister one sister has Crohn's disease
  - a paternal cousin has Crohn's disease

Clinical case 2

- Biology
  - IgA : 0.08 g/L (NV: 1,04-3,31)
  - IgG : 1.22 g/L (NV: 6,45-11,98)
  - IgM : 0.33 g/L (NV: 0,52-1,47)

Clinical case 2

- What will you do?
  - I start immunoglobulin replacement therapy now
  - Serology against tetanus, other serology…?
  - Pneumococcal vaccination and antipneumoccocal serotype evaluation
  - Specific flow cytometry
  - Thorax CT scan
  - Abdomen ultrasound
  - Urine analysis

Clinical case 2

- What will you do?
  - I start immunoglobulin replacement therapy now -> why not, but why?
  - Serology against tetanus, other serology…? -> tetanus antibodies: not protective despite recent vaccination (less than 2 years)
  - Pneumococcal vaccination and antipneumoccocal serotype evaluation -> It take some time
  - Specific flow cytometry -> Decrease in age-switched memory B lymphocytes
  - Thorax CT scan -> Bronchiectasis and bronchiolitis in the left lower lobe
  - Abdomen ultrasound -> Splenomegaly measuring 18 cm. Dilated portal vein with discrete venous shunts in the hepatic hilum, probable signs of portal hypertension.
  - Urine analysis -> no proteinuria

Clinical case 2

- Start immunoglobulin replacement therapy and prophylaxis with azithromycin (bronchectasis with probable surinfections episodes) -> cough and sputum decrease rapidly
- Hepatic evaluation:
  - normal hepatic laboratory test
  - No hepatic fibrosis on fibroscan
  - suspicion of focal nodular hyperplasia
  - Gastroscopy planned but not yet performed

T-cell immunodeficiency

- Severe Combined Immunodeficiency (SCID)
- Late onset combined immunodeficiency (LOCID)
- Idiopathic CD4 lymphopenia

Others

- Autoimmune lymphoproliferative syndrome (ALPS) -> children with lymphadenopathy, splenomegaly and autoimmune cytopenias
- Chronic Granulomatous disease -> Look for in patients with severe or recurrent cutaneous abcesses, lymphadenitis, and/or pneumonia, deep tissue abcess…

Work up in cases of suspected immunodeficiency

- Complete blood counts :
  - Neutrophils
  - Monocyts
  - Absolute lymphocyte count
- Immunophenotyping : CD4/CD8/NK/CD19
- Immunoglobulins : IgG, IgA, IgM and subclass (IgG2 IgG3 IgG4)
- CH50/AP50 (complement deficiencies: invasive meningococcal or pneumococcal infections)

Work up in cases of suspected immunodeficiency

- Vaccinal responses :
  - Tetanos
  - Pneumococcus (response to polysaccharid antigens after pneumovax 23)
- Lymphocyte proliferations assays (CID)
- Specific flow cytometry:
  - Double negative T cells (ALPS)
  - Naive T cells (CID)
  - Memory/Switched memory B cells (CVID)
- Whole exome sequencing

Secondary Immunodeficency

Secondary Immunodeficency

- Secondary immunodeficiencies are much more frequent than primary immunodeficiencies (about 30 times more frequent)

Secondary immunodeficiencies

- Diabetes mellitus
- Human immunodeficiency virus (HIV) infection
- Cirrhosis
- Nephrotic syndrome
- Other protein-losing states, such as enteropathies, severe exudative skin disease including burn injury, and peritoneal dialysis
- Malnutrition
- Hemoglobinopathy
- Inflammatory bowel disease or rheumatoid arthritis receiving immunosuppressive therapies (particularly tumor necrosis factor [TNF] inhibitors)
- Neurologic disease
- Autoimmune disease
- Splenectomy
- Malignancy
- Radiation therapy
- Immunosuppressive agents, such as glucocorticoids and others
- Immunomodulatory agents

Secondary causes for hypogammaglobulinemia

- Corticoides
- Nephrotic syndrom
- Digestive loss
- MGUS
- Hematological malignancy, multiple myeloma, Chronic lymphocytic leukemia
- Malnutrition
- Rituximab, CAR-T-cell, Bispecific antibody, and other…
- Drugs (anti-epileptic ! immunosuppressive drugs)
- Good syndrome (adult-onset hypogammaglobulinemia or aggamaglobulinemia associated with thymoma)

Hypogammaglobulinemia work-up

- Anamnesis and clinical examination (diarrhea, infections and frequency, auto-immune disease… lymphadenopathies, splenomegaly, …)
- Urine analysis with electrophoresis
- Blood immunophenotyping
- Medications (corticoïds, immunosuppressants drugs, anti-epileptic drugs…)
- Thoraco-abdominal CT scan? Thymoma, lymphoma, other cancer…

Hypogammaglobulinemia work-up

- Blood immunophenotyping:
  - In search of a circulating clone
  - But also measurement of B lymphocyte subpopulations: decrease in switched B lymphocytes in CVID

- In the absence of monoclonal gammopathy, and especially if hypogammaglobulinemia is moderate

-> check at a distance (e.g. 12 weeks) to rule out transient hypogammaglobulinemia (especially if discovered during a period of active infection).

Drug-induced hypogammaglobulinemia

- Corticoïds
- AntiCD20 (rituximab)
- AntiCD38 (daratumumab)
- CD19 CAR-T Cell, Bispecific antibody
- BTK inhinitors (ibrutinib)
- Bortezomib
- Methotrexate
- Mycophenolate
- Cyclophosphamide
- Purin analogs (azathioprine, cladribine, fludarabine)
- Clozapine (antipsychotic)
- Antiepileptic drugs (phenytoin, carbamazepine, valproate)
- Antimalarial agents
- Captopril
- Penicillamine
- Sulfasalazine

Clinical case 3

- 62 years old man
- Referred by his general practitioner for lymphopenia : 1100/microL
- Anamnesis
  - He complains of severe shortness of breath on exertion since several months and he could no longer work in his garden or walk more than five minutes
  - He see cardiologist, pneumologist and ear-nose-throat specialist and the work up showed no explanation for dyspnea
  - No nocturnal sweating. No fever
  - He complained about indurated belly
- Clinical history :
  - Prostate cancer treated by prostatectomy in 2021
  - Paroxysmal atrial fibrillation.
  - Hypertension

Clinical case 3

- Laboratory tests:
  - No anemia
  - Platelets : 137.000/MicroL
  - Normal leukocyte count except for lymphopenia
  - Creatinine : 2mg/dl
  - Slight elevation of yGT
  - Electrophoresis: Significant hypogammaglobulinemia, immunofixation in progress
  - Ig G <3g/l, Ig A < 0,5g/l, IgM < 0,25g/l
  - total urinary proteins 0,16g/l (NV <0,15)

Clinical case 3

- What diagnosis are you thinking of?
  - Late onset CVID with pneumological complication
  - Disseminated lupus erythematosus
  - Nephrotic syndrome
  - Lymphoma
  - Multiple myeloma
  - Other?

Clinical case 3

- Which test do you request?
  - Blood immunophenotyping
  - Urine analysis
  - Lights chains dosage
  - Cardiac ultrasound
  - Chest CT scan
  - Renal ultrasound
  - NtproBNP and troponin
  - Cardiac MRI

Clinical case 3

- Which test do you request?
  - Blood immunophenotyping -> no clonality on immunophenotyping
  - Urine immunofixation -> Non-selective tubular glomerular proteinuria, associated with kappa light chain
  - Lights chains dosage -> Kappa chain : 8090 mg/l , lambda: 3,9mg/l
  - Cardiac ultrasound -> consistent with cardiac amyloidosis
  - Chest CT scan -> Performed 3 months previously: no pulmonary embolism or other abnormality
  - Renal ulstrasound -> No urinary tract obstruction
  - total body bone scanner -> Numerous lacunar lesions, mainly in the spine
  - NtproBNP -> 13300pg/ml (<300) and troponin -> 93pg/ml (<14)
  - Cardiac MRI -> Hypertrophic heart disease with signs of cardiac amyloidosis

Clinical case 3

- Multiple myeloma with AL amyloidosis with cardiac involvement
- No significant infection before diagnosis
- At the time of the check-up, the patient had a mildly symptomatic Sars-cov 2 infection, but despite treatment with paxlovid, covid-positive smears persisted for more than 6 weeks.

Secondary immunodeficiency: treatment

- Removal of iatrogenic causes
- OR treatment of the underlying condition (eg, management of nephrotic syndrome)

- And if it’s not possible
  - Monitoring for clinical infections
  - Antimicrobials
  - And in some case Immunoglobulin replacement therapy

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