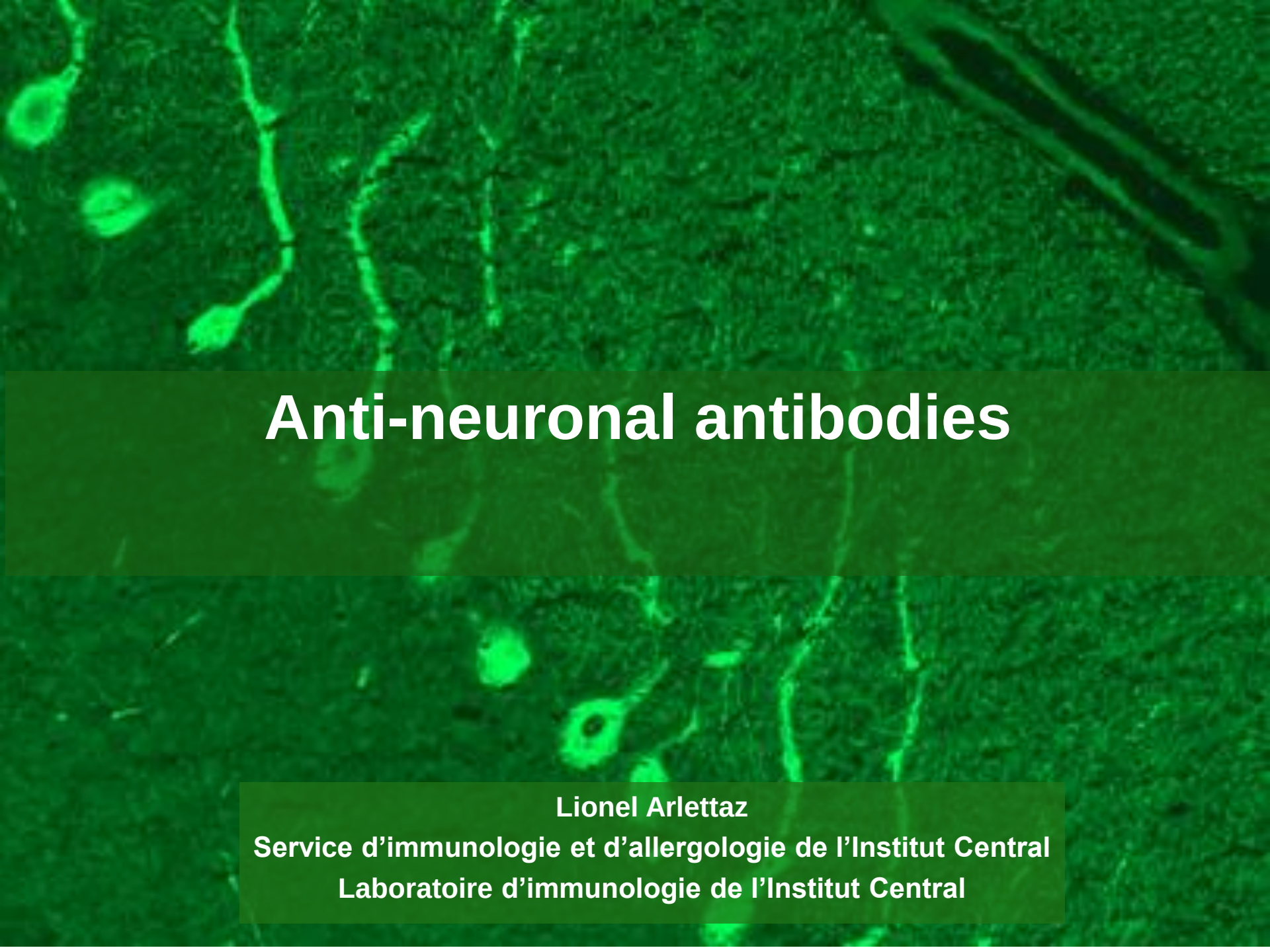

Anti-neuronal antibodies

Lionel Arlettaz
Service d'immunologie et d'allergologie de l'Institut Central
Laboratoire d'immunologie de l'Institut Central

Plan

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Zentralinstitut der Spitäler

Clinical cases

- **One patients with anti-GlyR antibody**
  - **brief description of the associated illness**
- **One patient with anti-NMDA R antibody**
  - **brief description of the associated illness**

Anti-neuronal antibodies

- **challenges for the laboratory diagnosis**

M. C. 1950

CASE 1

PERM

Progressive Encephalomyelitis with Rigidity and Myoclony

One patients with anti-GlyR antibody

M. C. 1950

History
- arterial hypertension
- active smoking
- pulmonary emphysema
- cachexia

MC : 1st ENT consultation for jaw pain, March 2019

→ Dislocation of the right temporomandibular joint

One patients with anti-GlyR antibody

M. C. 1950

5 days later

2nd consultation, emergency room

- anxiety
- urinary disorder
- balance disorders
- marked worsening of diplopia

Brain MRI:
- -vascular leukoencephalopathy
- -minimal ischemia (?)

The patient returned home with Aspirin treatment

Ambulatory investigations are scheduled

One patients with anti-GlyR antibody

M. C. 1950

One week later

3rd consult, emergency room

the patient cannot eat anymore, agitation ++

Hospitalization in maxillofacial surgery

for open reduction of Temporo-Mandibular Joint dislocation

Bad evolution with development of "weird" symptoms...

"spasms," "intermittent tremors," confusional state...

Evaluated by psycho-geriatrists: 3mg Haldol

Neurological assessment is scheduled

One patients with anti-GlyR antibody

M. C. 1950

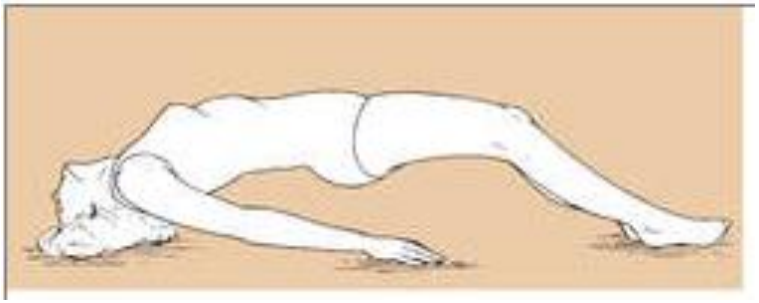
Development of an hyperactive confused state, with hallucinations,

Abnormal movements

Hyperthermia 38.7°C

Then opisthotonos and rigidity of the 4 limbs

Eyes deflection to the right



The free disctionnary

Transfer to the intensive care unit

Hypothesis: neuroleptic malignant syndrome

film

One patients with anti-GlyR antibody

M. C. 1950

After two days

Lack of improvement under high dose of benzodiazepines

Worsening of opisthotonos at the slightest stimulus

Orotracheal intubation due to respiratory failure
(neuromuscular impairment)...

Deep sedation and curarization to "calm down" the patient.

Performing a lumbar puncture and biological examinations

One patients with anti-GlyR antibody

CK increase from 1000 to 2000U/L in 9h

Differential diagnosis

1. Neuroleptic Malignant Syndrome
2. Tetanus
3. Meningo(-encephalitis)
4. Status epilepticus
5. Other

film

One patients with anti-GlyR antibody

M. C. 1950

Search for causes of meningoencephalitis -> all negative

Tumor screening -> no evidence of tumor

Brain MRI :	no stroke, no abnormalities that could explain the clinical picture
Lumbar puncture :	WBC 80/ul (85% lymphocytes) mild proteinorachy
Thoraco-abdominal CT :	no abnormalities
Whole body PET-CT :	no (hypermetabolic) lesions

One patients with anti-GlyR antibody

M. C. 1950

Anti-NMDA IgG	<10 1/DIL	<10
Anti-AMPA IgG	<10 1/DIL	<10
Anti-DPPX, IgG	<10 1/DIL	<10
Anti-GABAB IgG	<10 1/DIL	<10
Anti-LGI1, IgG	<10 1/DIL	<10
Anti-CASPR2, IgG	<10 1/DIL	<10
Anti-IgLON5 IgG	<10 1/DIL	<10 (§)
Anti-mGluR5	<10 1/DIL	<10 (§)
Anti-GlyR	<10 1/DIL	320 * (§)

One patients with anti-GlyR antibody

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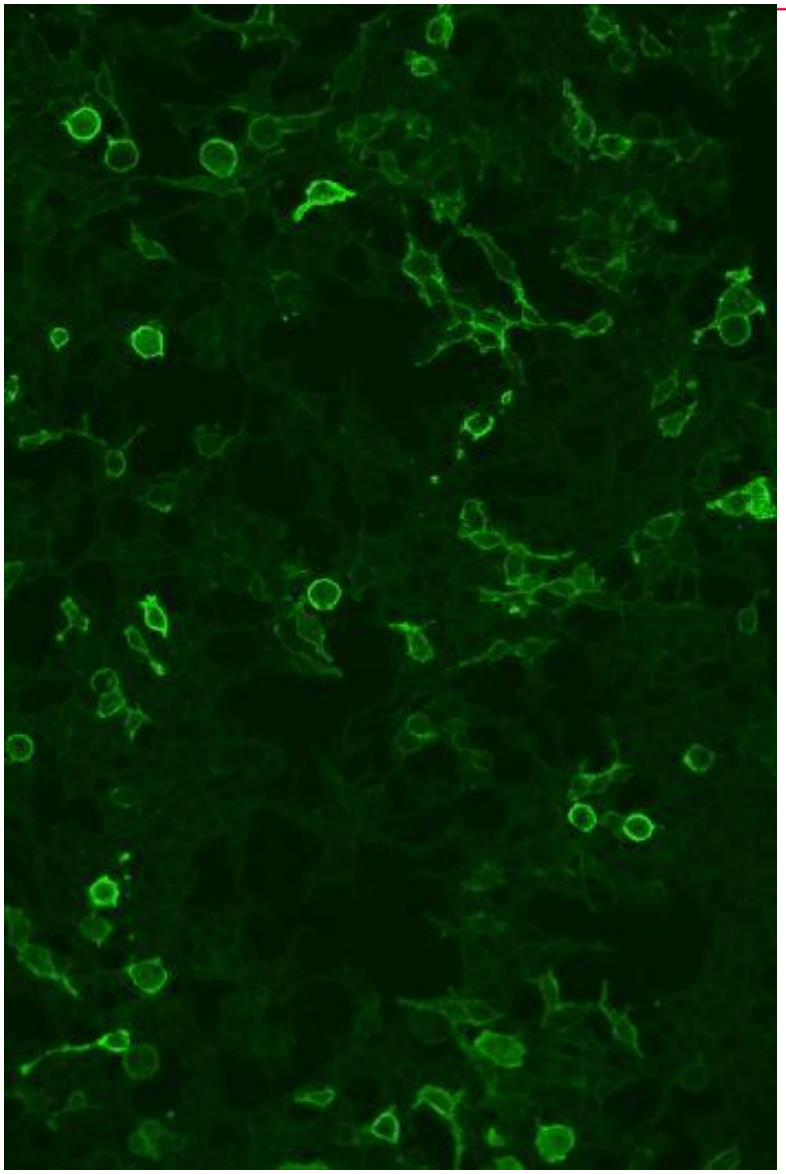
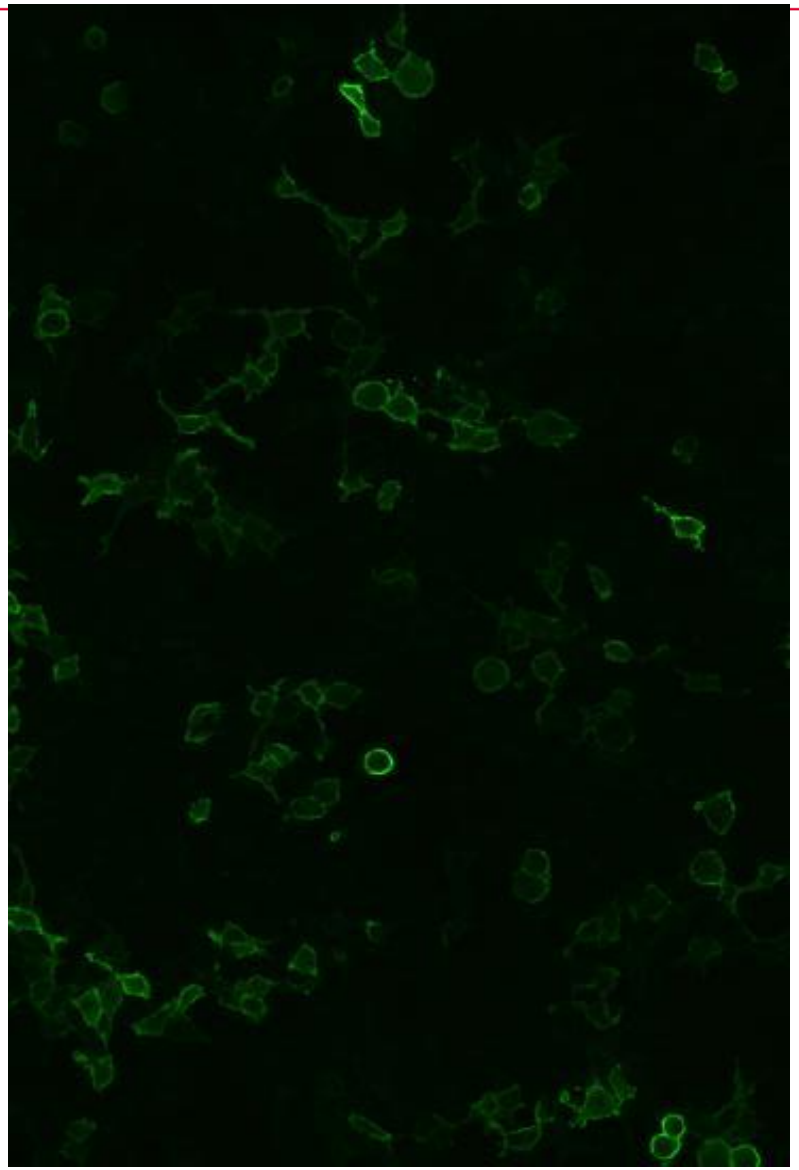


Anti-GlyR, Serum, 1/320



Anti-GlyR, CSF, 1/320

One patients with anti-GlyR antibody

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M. C. 1950

Summary

Persistent hyperthermia > 38.2°C, significant diaphoresis

Disoriented T + E, severe attention deficit disorder, aggressivity

Generalized, predominantly axial stiffness

Diffuse myoclonia at the 4 extremities

Signs of brainstem and medulla damage

Highly positive anti-GlyR in serum and CSF

Diagnosis

PERM
Progressive Encephalomyelitis
with Rigidity and Myoclony

One patients with anti-GlyR antibody

M. C. 1950

Treatment

Plasma exchanges

Solu-Medrol iv high doses, 5 d, then **Prednisone** 1mg/kg

Rituximab 1g 2x

Slow improvement : curare stopped on April 20th
extubation on April 21

Persistence of rigidity and complications related to ICU

M. C. 1950

Long-term evolution

Out-patient follow-up

Not able to walk alone

No more improvement of rigidity

A new course of plasmapheresis did not result in any improvement

Anti-GlyR : associated diseases

PERM : Progressive Encephalomyelitis with Rigidity and Myoclony

Rare pathology, remitting relapsing at the beginning

Always fatal without treatment after some months / years

Disorders of consciousness, dysautonomy and signs of brainstem damages

+

A combination of the following symptoms :

- rigidity of the extremities and trunk
- myoclony
- hyperekplexia, ataxia
- signs of spinal cord injury

Characterized by the presence of anti-GlyR antibodies (50% of cases...)

Hyperekplexity (exaggerated startle reflex) is caused by disinhibition of neurons in the brainstem, an area rich in glycinergic synapses

Congenital Hyperekplexity ("startle's disease")

Hyperekplexity **throughout life**

Massive hypertonia at birth (risk of sudden death), Regression during infancy (delayed motor acquisition, normal intellect)

Caused by a mutations in the glycine receptor

(mostly subunit α1) and associated structures

This stimulates the discovery of anti-GlyR antibodies
Hutchinson M, Waters P, McHugh J. 2008

SPS : stiff person syndrome

Rare disease, characterized by a progression phase and then a stabilization phase

With : progressive muscular hyperactivity, rigidity and spasms
axial muscles are the most involved
no encephalomyelitis (no state of confusion)
rarely associated with tumors

SPS is often associated with anti-GAD antibodies
and with type 1 diabetes (HLA)

«Incomplete PERM …» → and PERM is called «SPS Plus»…

Other antibodies found in SPS : anti-amphiphysine, anti-GlyR, anti-DPPX

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Redefining progressive encephalomyelitis with rigidity and myoclonus after the discovery of antibodies to glycine receptors

Sarah J. Crisp[a], *Bettina Balint*[a,b], *and Angela Vincent*[c]

100 patients described in 2017

The strongest association is with PERM

other possible clinical manifestations exist (SPS)

Anti-GlyR is associated with better response to treatment (marker of good prognosis) compared to anti-GAD for example

Curr Opin Neurol. 2017 Jun;30(3):310-316

Prospective study of 52 patients with anti-GlyR

75% of patients have a PERM

25% of patients have a more limited form (SPS)

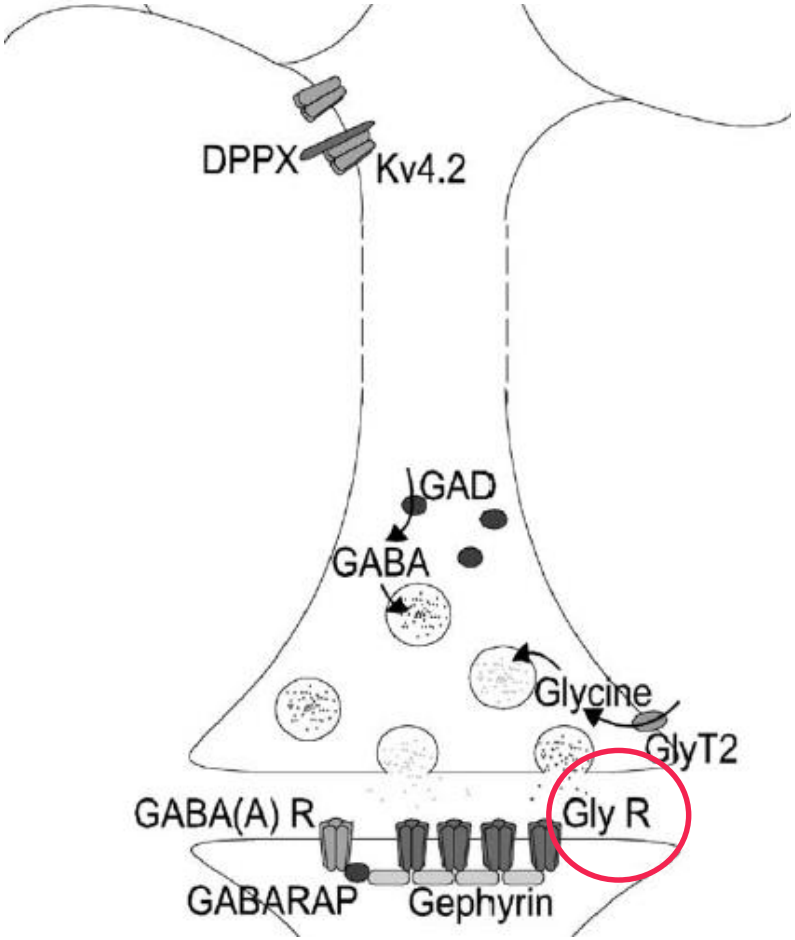
or other diseases (limbic encephalitis, epilepsy, …)

Presence of another autoimmune disease in approx. 20% of cases

A tumor is diagnosed after anti-GlyR detection in 10-12%

Anti-GlyR is associated with better response to treatment (marker of good prognosis) compared to anti-GAD for example

The symptoms are linked to an alteration in the function of the inhibitory receptor

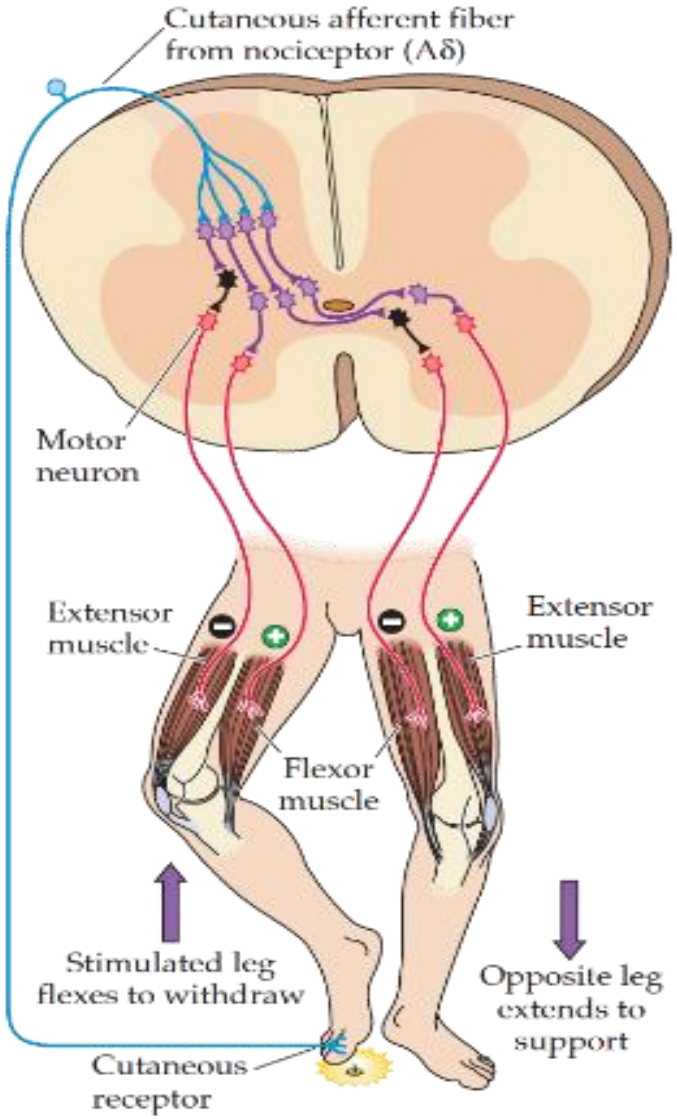


Glycine is secreted by **inhibitory** interneurons of the **spinal cord** and **the brainstem**

Gly- R are members of the superfamily of ligand gated ion channels. Glycine activation leads to an influx of Cl- in the neurons

50% of the inhibitory receptors are Gly-R
50% are GABA-R

Anti-GlyR : associated diseases



In the spinal chord, GlyRs play an important role for reciprocal muscle inhibition

GlyR blocking => simultaneous contraction of flexors and extensors

Strychnine specifically inhibits GlyR

At low-dose :

is stimulant (Olympic games, 1900)

At higher dose, it induces :

generalized muscular hypertonicity, myoclonias with opisthotonos

rhabdomyolysis followed by acute renal failure

respiratory distress due to rigidity of the thoracic musculature and laryngeal spasm

A PERM-like disease…

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Mrs. P. 1965

CAS 2

Anti-NMDA Receptor encephalitis

Cas 2 : movement disorders, anti-NMDA

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Mrs. P. 1965

This woman, generally in good health, was hospitalized due to confusion and abnormal movements.

History :

- since April 2019
  onset of a progressive left superior arm tremor
  progressive asthenia, with hypersomnia

- then :
  psychomotor decline
  spatio-temporal disorientation
  sadness, "depressive" state...
- since June, a marked worsening of abnormal movements

film

Cas 2 : movement disorders, anti-NMDA

Mrs. P. 1965

Brain MRI :
Suspicion of meningitis
Hypersignals on both sides and around the hippocampus on the right.
No intracerebral abscess.

Whole body 18F-FDG PET-CT : no hypermetabolic lesion

Brain MRI after 2 weeks
Decrease of the hypersignal and hippocampal swelling

and a marked reduction of the suspected meningitis

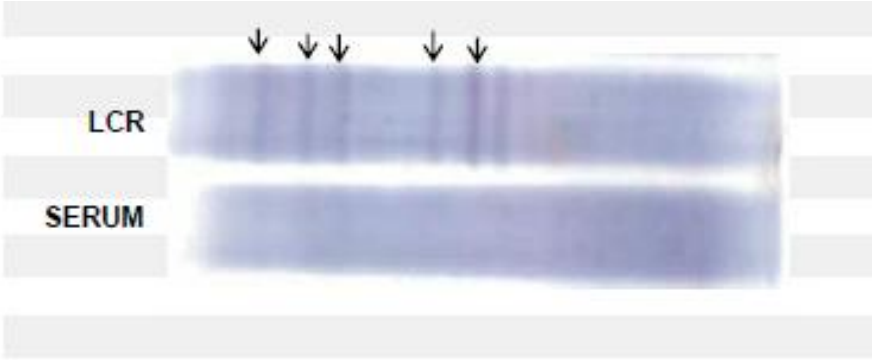
EEG : signs of mild cerebral encephalopathy

Cas 2 : movement disorders, anti-NMDA

Mrs. P. 1965

LIQUIDE CEPHALO-RACHIDIEN (LCR)		
Aspect	Clair	
Aspect après centrifugation	Clair	
Cellules		
Erythrocytes	1	*
Leucocytes	22	*
Neutrophiles (totaux)	0,0	
Monocytes	1,0	
Lymphocytes	99,0	
Autres cellules	0,0	
Chimie		
Chlorure	129	
Glucose	3,1	
Lactate	1,5	
Protéines	460	*
Albumine	305	
IgA	4,9	
IgG	49,7	
IgM	0,6	
Albumine (sérum)	33,3	*
^IgA (sérum)	0,87	
^IgG (sérum)	6,0	*
^IgM (sérum)	0,56	*
Quotient albumine	9,2	*
Quotient IgA	5,6	
Quotient IgG	8,3	
Quotient IgM	1,1	
^Index d'IgG	0,90	*
Isoélectrofocalisation	Oligo T2	*①

Lumbar puncture



Cas 2 : movement disorders, anti-NMDA

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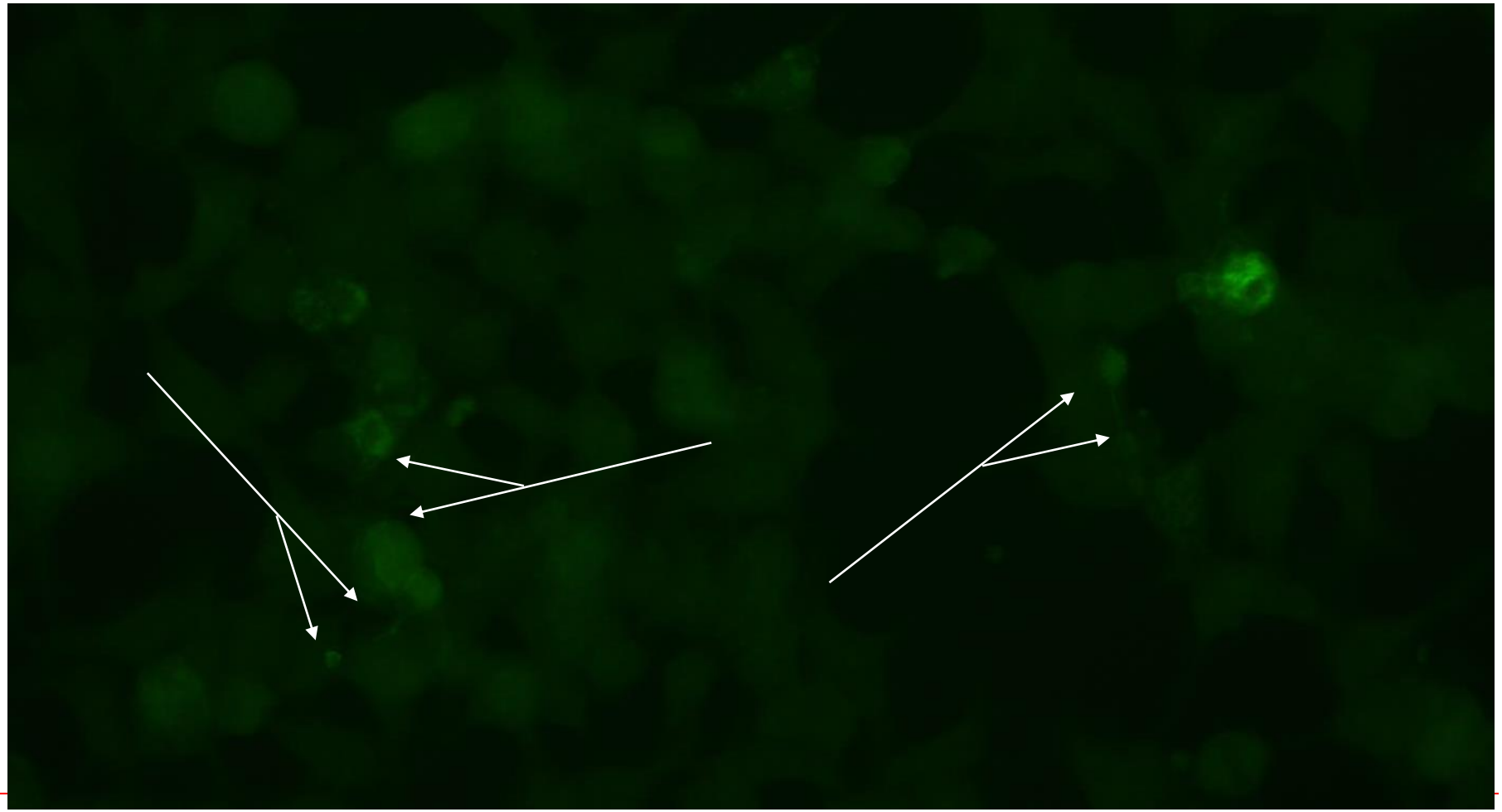
CSF Immunofluorescence NMDAR transfected cells, titre 1:1



Cas 2 : movement disorders, anti-NMDA

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Mrs. P. 1965

Diagnosing autoimmune encephalitis based on clinical features and autoantibody findings

Christian G. Bien

Expert Rev Clin Immunol. 2019 May;15(5):511-527.

Box 4. Criteria for 'anti-NMDA receptor encephalitis' (Panel 4 in [25]).

All 3 criteria must be met:

1		Rapid onset (<3 months) of ≥4 of the 6 following major groups of symptoms:
	V	• Abnormal (psychiatric) behavior or cognitive dysfunction
	V	• Speech dysfunction (pressured speech, verbal reduction, mutism)
		• Seizures
	V	• Movement disorder, dyskinesias or rigidity/abnormal postures
		• Decreased level of consciousness
	V	• Autonomic dysfunction or central hypoventilation
2		≥1 of the following laboratory study results:
	V	• Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
	V	• CSF with pleocytosis or oligoclonal bands
3	V	Reasonable exclusion of other disorders*

*New onset psychosis, malignant neuroleptic syndrome, drugs (e.g. phencyclidine), viral encephalitis, encephalitis lethargica [32].

Diagnosis

Autoimmune NMDA receptor encephalitis

Cas 2 : movement disorders, anti-NMDA

Mrs. P. 1965

Pelvic MRI and whole body PET-CT are normal

Implementation of immunosuppressive therapy

- Solu-Medrol 1g x 3d then Prednisone
- IVIG at immunomodulatory doses (2g/kg) 1x/month
- Rituximab (anti-CD20) 2x1g in 15 days then at 6 months

Progressive improvement of the clinic,
The patient returned home mid-July (after 6 weeks)
Outpatient follow-up in neurology

film

Described by Dalmau 2007

Severe, but potentially reversible neurological disease
evolving with stages of symptoms progression and resolution,
associated with anti-NMDA R1 antibodies,

begin with	-psychiatric symptoms
	-memory deficits
	-epilepsy, language disorders
progress to	-movements abnormalities, dysautonomia, breathing difficulties, catatonic comatose state

Anti-NMDAR encephalitis

Women 81% / men 19%

Affects young people : 37% before age 18 and 95% before age 45

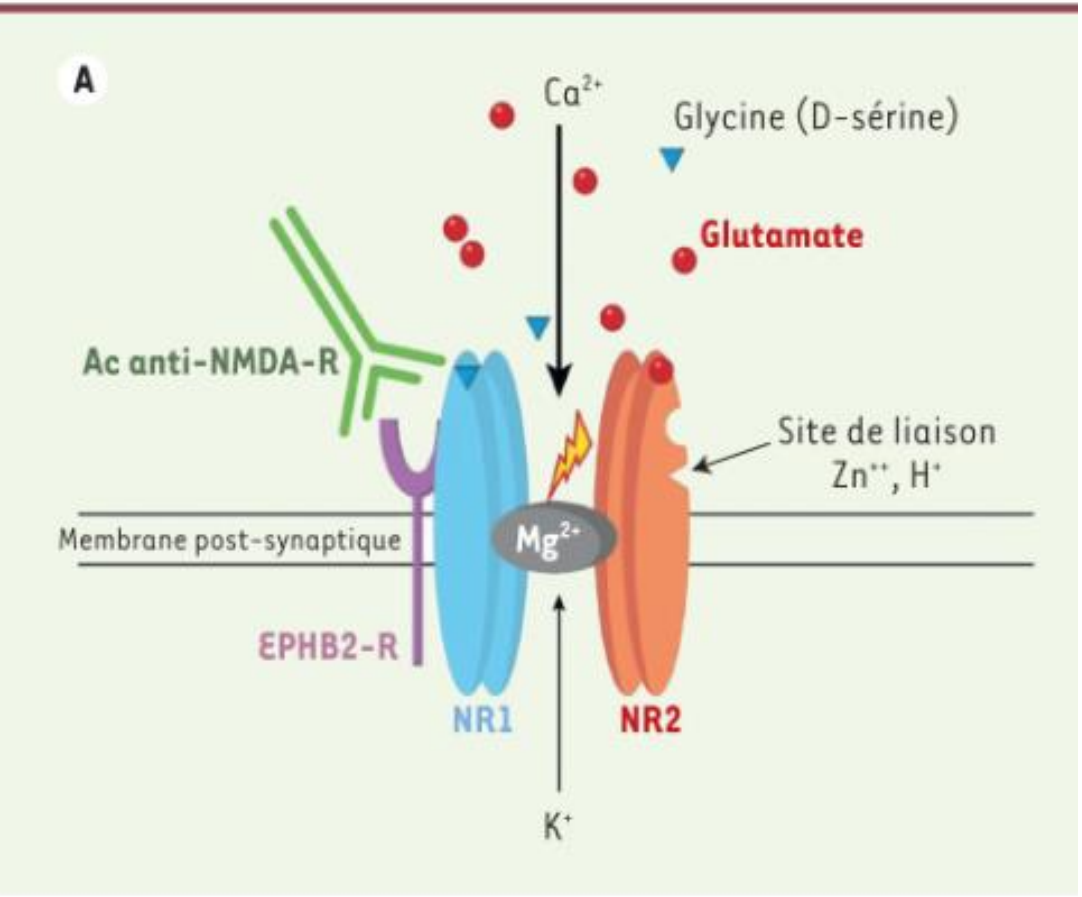
50% of men among “extreme” ages: <12 years and > 45 years old

Cancer Frequency : about 40% in total
up to 60% in women between 18 - 45 years

Types of cancers : ovarian teratoma: women 18 - 45 years old

other: Hodgkin's lymphoma, SCLC,
neuroblastoma and testicular teratoma
(>45 years old, men)

Anti-NMDAR encephalitis



Anti-NMDA NR1 destabilizes the receptor of the membrane, NMDAR leaves the synapse and then is internalized

IgG anti-NMDA-r are specific
IgA and IgM are non specific

NMDA-Rs are involved in CNS plasticity

Med Sci (Paris) 2015 ; 31 : 60–67

Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

Maarten J Titulaer, Lindsey McCracken, Iñigo Gabilondo, Thaís Armangué, Carol Glaser, Takahiro Iizuka, Lawrence S Honig, Susanne M Benseler, Izumi Kawachi, Eugenia Martinez-Hernandez, Esther Aguilar, Núria Gresa-Arribas, Nicole Ryan-Florance, Abiguei Torrents, Albert Saiz, Myrna R Rosenfeld, Rita Balice-Gordon, Francesc Graus, Josep Dalmau

577 included Pts	-> 501 patients assessed (response to ttt) median 24-month follow-up (4-186)
At 4 months	-> improvement after first-line treatment (53%) (steroids, IVIG, plasmapheresis) or tumor resection
At 24 months	-> good clinical outcome for 394/501 (79%) -> 30 deaths (6%)

Improvement continues >18 months after the start of treatment

Lancet Neurol 2013; 12: 157–65

Anti-NMDAR encephalitis

Criteria for a good prognosis :

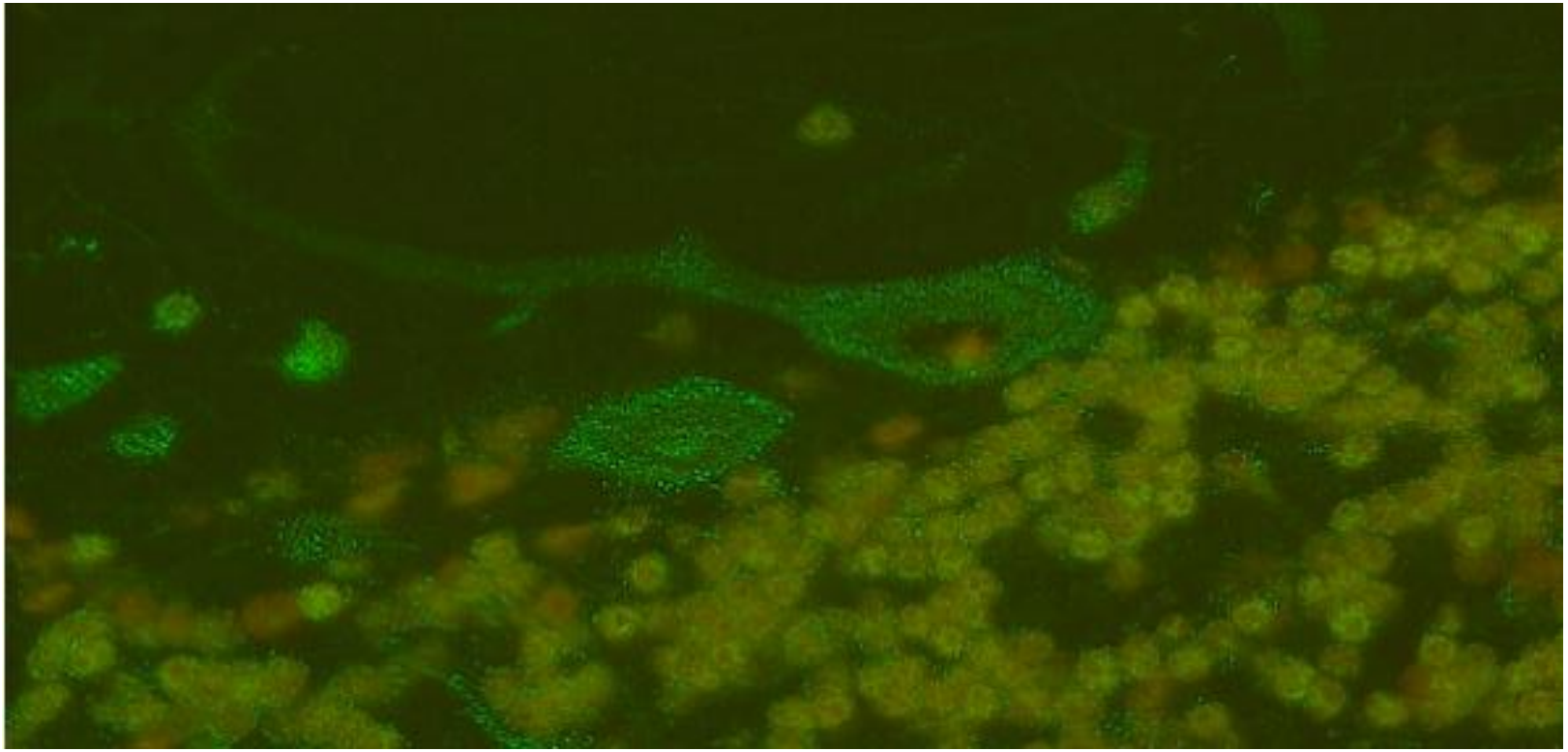
-early diagnosis with early treatment

-no need for intensive care

Long-term follow-up is needed because recurrences are not rare.

A disease to recognize and to treat as fast as possible

«Anti-neuronal antibodies» : diagnostic approach in the lab



Challenges for laboratory diagnosis of antineurals antibodies

1. Paraneoplastic neurologic syndromes are rare pathologies

-must be recognized

-not always associated with an antibody

-some antibodies have yet to be discovered...

who to test, when to test, what to test ?

Exemple

Challenges for laboratory diagnosis of antineurals antibodies

2. Different methods must be used
depending on the type of antibody being sought

Exemple

Challenges for laboratory diagnosis of antineurals antibodies

3.1 The tests available on the market are not perfect…

Especially Immuno-DOTS :

-sensitivities and specificities are not the same for all antigens

-the labs must know their own tests

Challenges for laboratory diagnosis of antineurals antibodies

3.2 The tests available on the market are not perfect…

Immuno-DOTS and Cell Based assay :

-only known (and commercially available) antibodies are tested !

Immunofluorescence :

-differences according to the substrate (mice or primate)

-several antibodies are difficult to recognize (lab dependency)

-the presence of other antibodies (ANA, M2, …) can hide a specific anti-neuronal antibody

Exemple

Challenges for laboratory diagnosis of antineurals antibodies

4. The labs should combine different test to increase Sp and Se

Immuno-DOTS results must be interpreted in comparison with immunofluorescence results

Exemple