LA MALADIE D'ALZHEIMER À L'ÈRE DES BIOMARQUEURS

LE POINT DE VUE DU CLINICIEN

DR MEYER FRANÇOIS (MD, PhD student)

FORMATION CONTINUE EN BIOLOGIE CLINIQUE (23/09/21)

PLAN

1. La maladie d'Alzheimer – Généralités

2. Le diagnostic « historique »

3. L'ère des biomarqueurs

4. En clinique

5. Take-home message

PLAN

1. La maladie d'Alzheimer – Généralités

2. Le diagnostic « historique »

3. L'ère des biomarqueurs

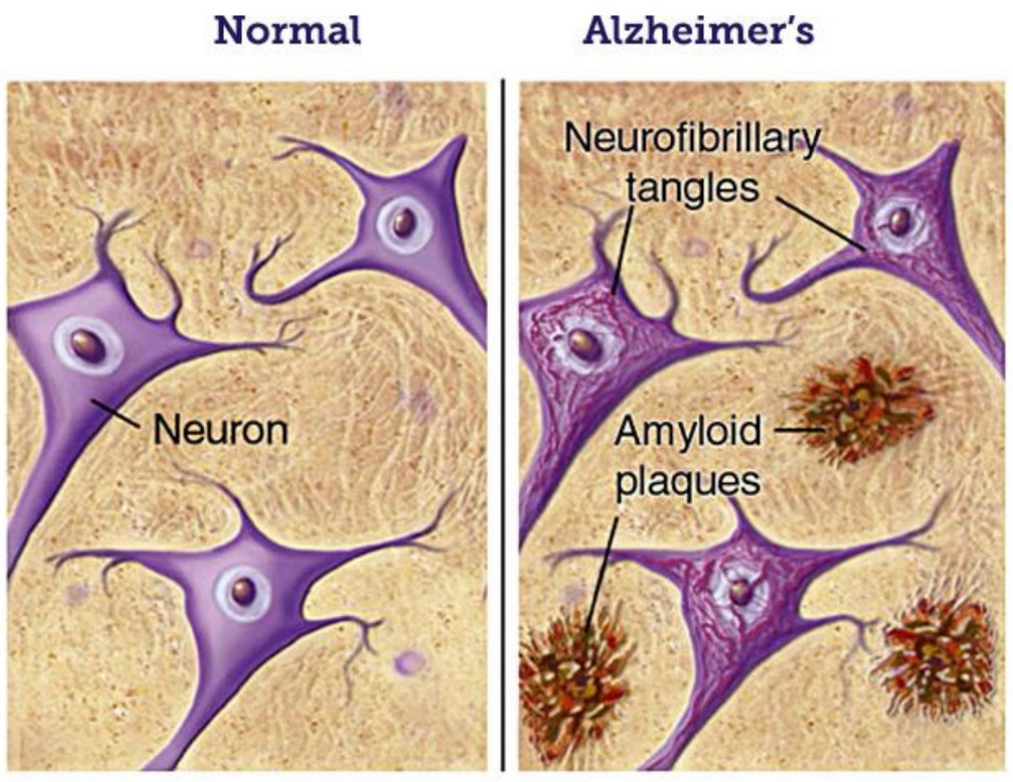
4. En clinique

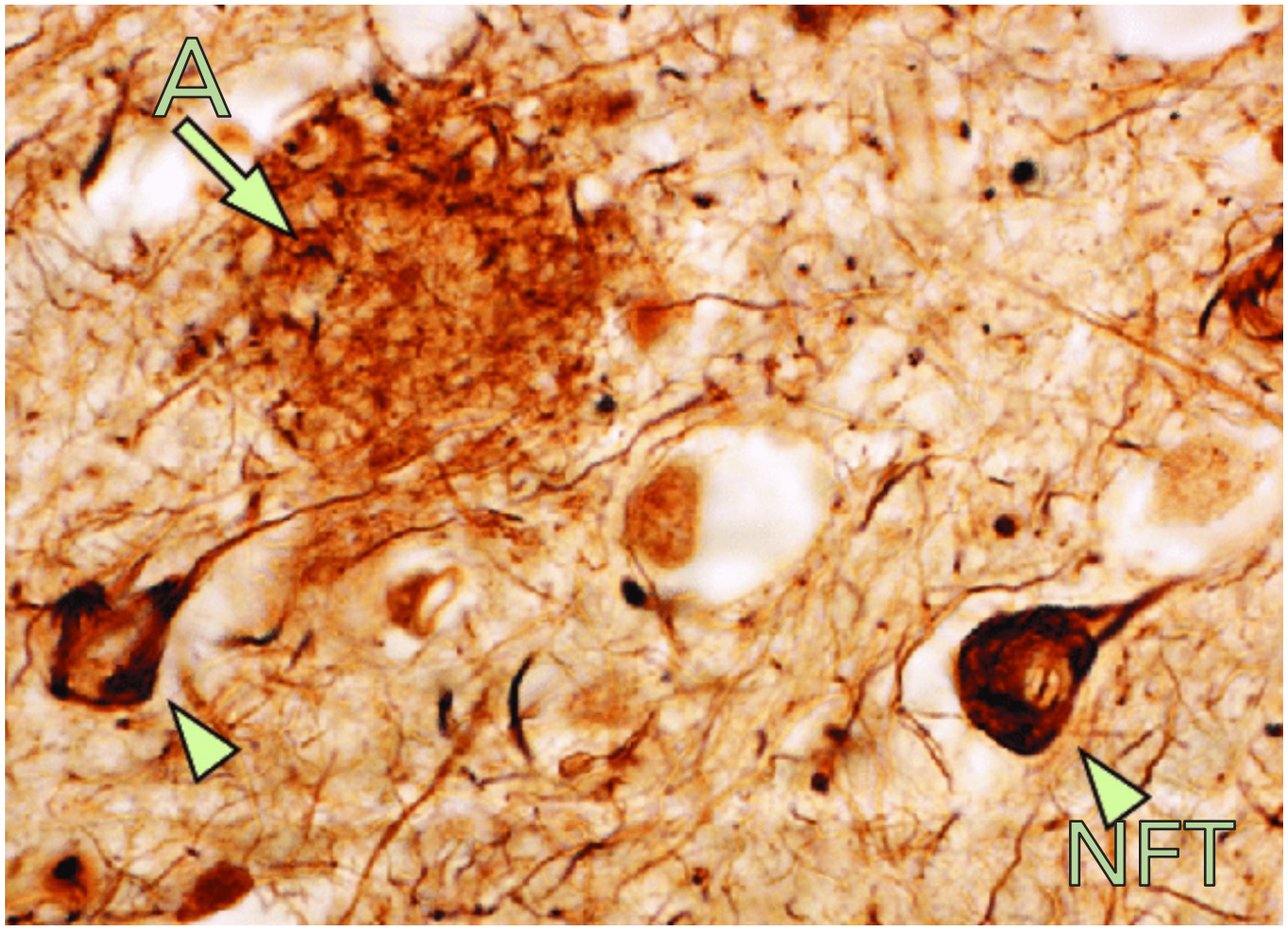
5. Take-home message

LA MALADIE D'ALZHEIMER

- Décrite en 1906 par Alois Alzheimer
- Pathologie neurodégénérative, évolutive, irréversible
- Syndrome amnésique évoluant vers syndrome démentiel
- 1st cause de démence dans le monde
- 2nd cause de mortalité en Occident

ANATOMOPATHOLOGIE – GOLD STANDARD

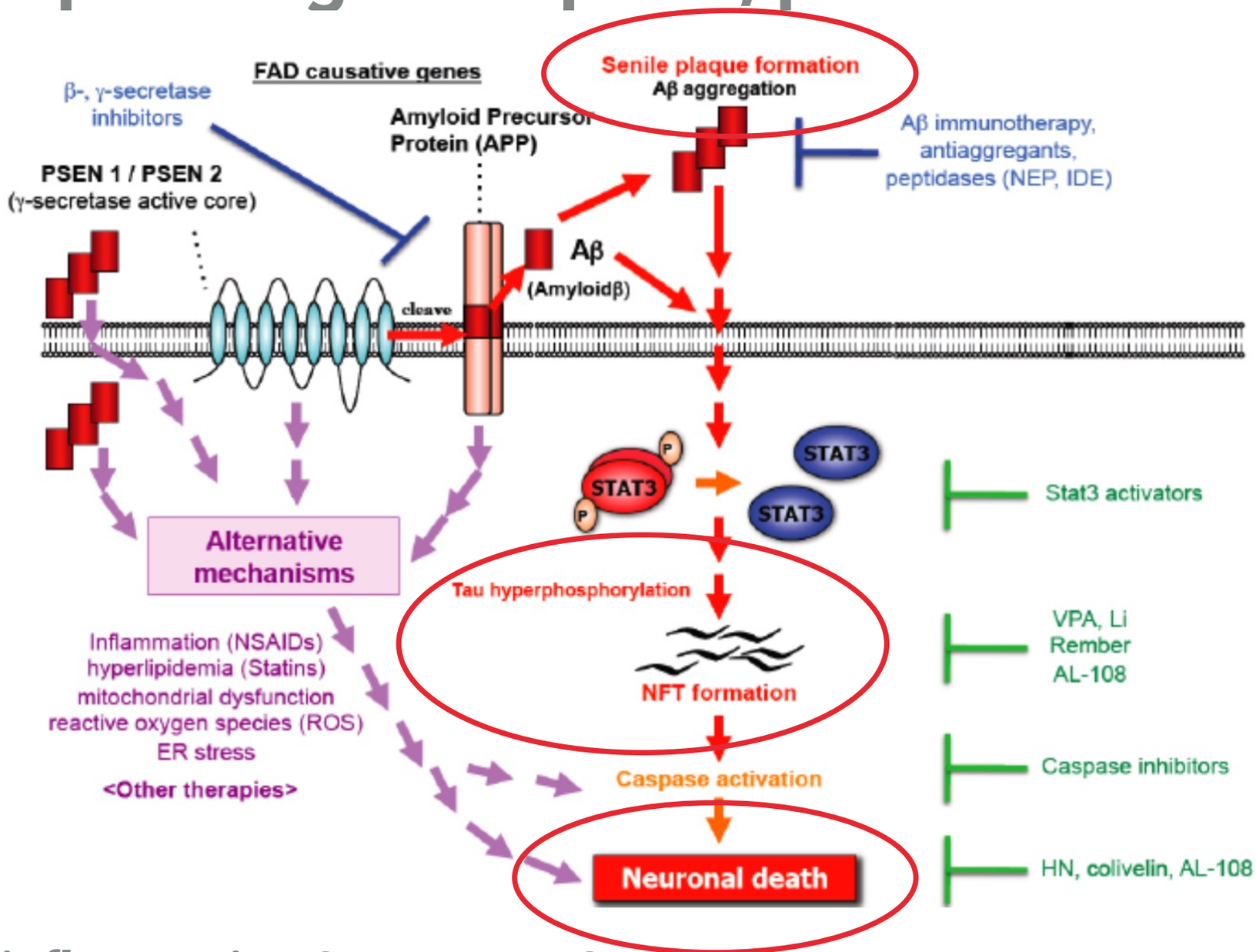




- Accumulation extra-cellulaire de plaques d'amyloïdes ß42
- Accumulation intra-cellulaire de protéine Tau hyperphosphorylée (p-Tau)
- Dégénérescence neuronale

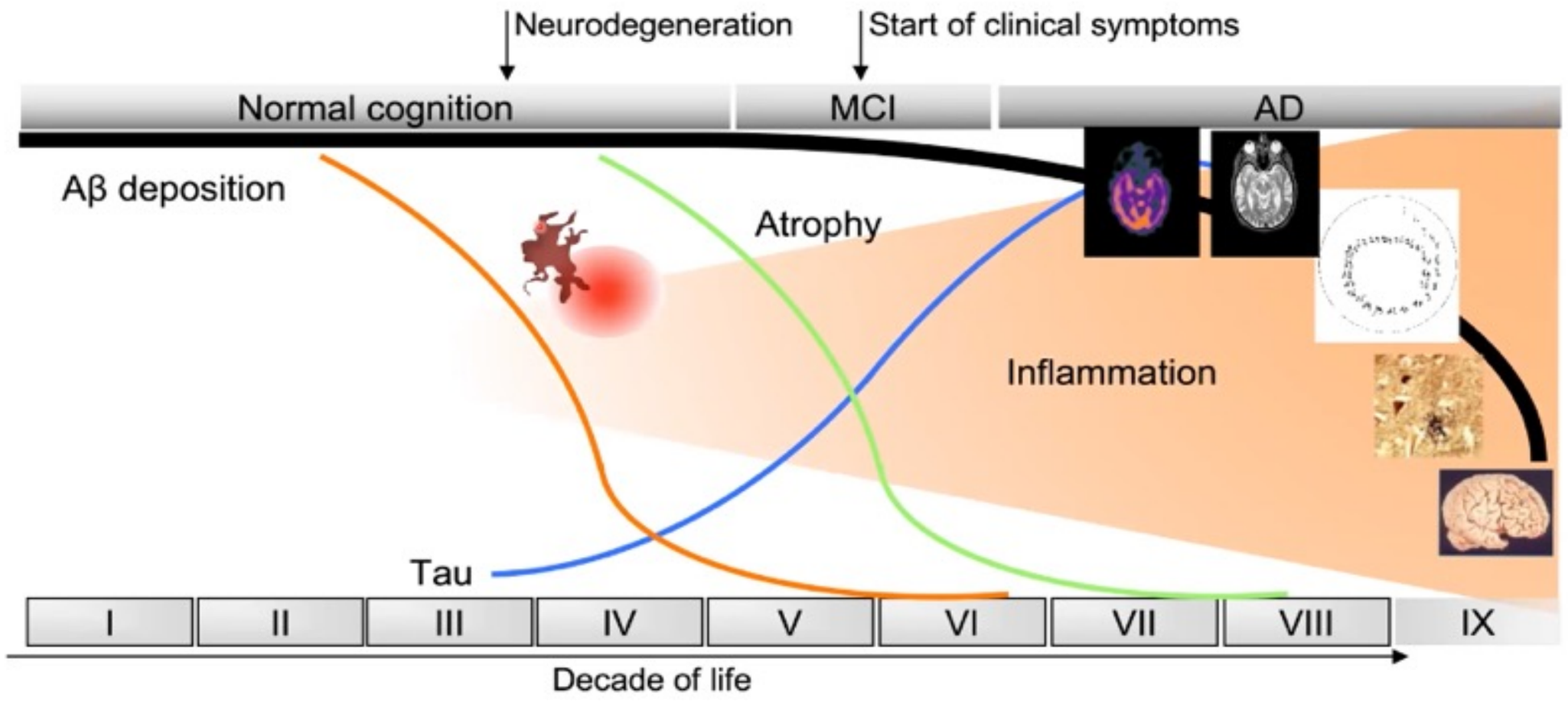
PHYSIOPATHOLOGIE – LA CASCADE AMYLOÏDE

- **Physiopathologie complexe, probablement non linéaire**



- **Neuro-inflammation ? Astrocyte ? …?**

PHYSIOPATHOLOGIE – EVOLUTION TEMPORELLE



- **MCI :** Altération de une ou plusieurs fonctions cognitives sans répercussion fonctionnelle dans la vie quotidienne
- **Démence :** Altération de plusieurs fonction cognitives avec répercussions fonctionnelles dans la vie quotidienne

PLAN

1. La maladie d'Alzheimer – Généralités

2. Le diagnostic « historique »

3. L'ère des biomarqueurs

4. En clinique

5. Take-home message

ALZHEIMER'S DISEASE – DIAGNOSTIC

- **Gold-standard = anatomopathologie (post-mortem)**

- **In vivo : Diagnostic de « probabilité »**

- **« Maladie d'Alzheimer » comme terme parapluie**

ALZHEIMER'S DISEASE – CRITERES 1984

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques;

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

ALZHEIMER'S DISEASE – CRITERES 2011

PROBABLE AD DEMENTIA

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
    a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
    b. Nonamnestic presentations:
        - Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
        - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
        - Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

ALZHEIMER'S DISEASE – CRITERES 2011

In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may **increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.**

- **Amyloid-beta deposition :** LCR Aß42, Amyloid PET
- **Neuronal degeneration :** LCR Tau, LCR p-Tau, FDG-PET, IRM

However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes

© McKhann G., *Alzheimers Dement.*, 2011

PLAN

1. La maladie d'Alzheimer – Généralités

2. Le diagnostic « historique »

3. L'ère des biomarqueurs

4. En clinique

5. Take-home message

Alzheimer's & Dementia 14 (2018) 535-562

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]**:** Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

L'ÈRE DES BIO MARQUEURS

AMYLOÏDE	P-TAU	NEURO - DÉGÉNÉRESCENCE
A	**T**	**N**
↓ Aß$_{42}$ (LCR) *Amyloïde – PET*	↑ P-tau (LCR) *Tau - PET*	↑ Tau (LCR) FDG – PET ; IRM

PROTEINES ALZHEIMER

Protéine Tau Totale	*	883	pg/ml	Normal si <400
Protéine Phospho-Tau (181)	*	127.5	pg/ml	Normal si <56.5
Protéine bêta-amyloïde 40		10164	pg/ml	
Protéine bêta-amyloïde 42	*	587	pg/ml	Normal si > 600
Rap. prot. bêta-amyl.1-42/1-40	*	0.058		Normal si >0.068
Rap. prot. Tau / bêta-amyl.1-42	*	1.504	ormal si <0.54 (selon Kaplow. Alzheimer's	

PROFIL DE BIOMARQUEURS

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

« COMBINED STAGING »

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	$A^- T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$ $A^+ T^+(N)^+$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^- T^+(N)^-$ $A^- T^-(N)^+$ $A^-T^+(N)^+$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia

SHIFT CONCEPTUEL

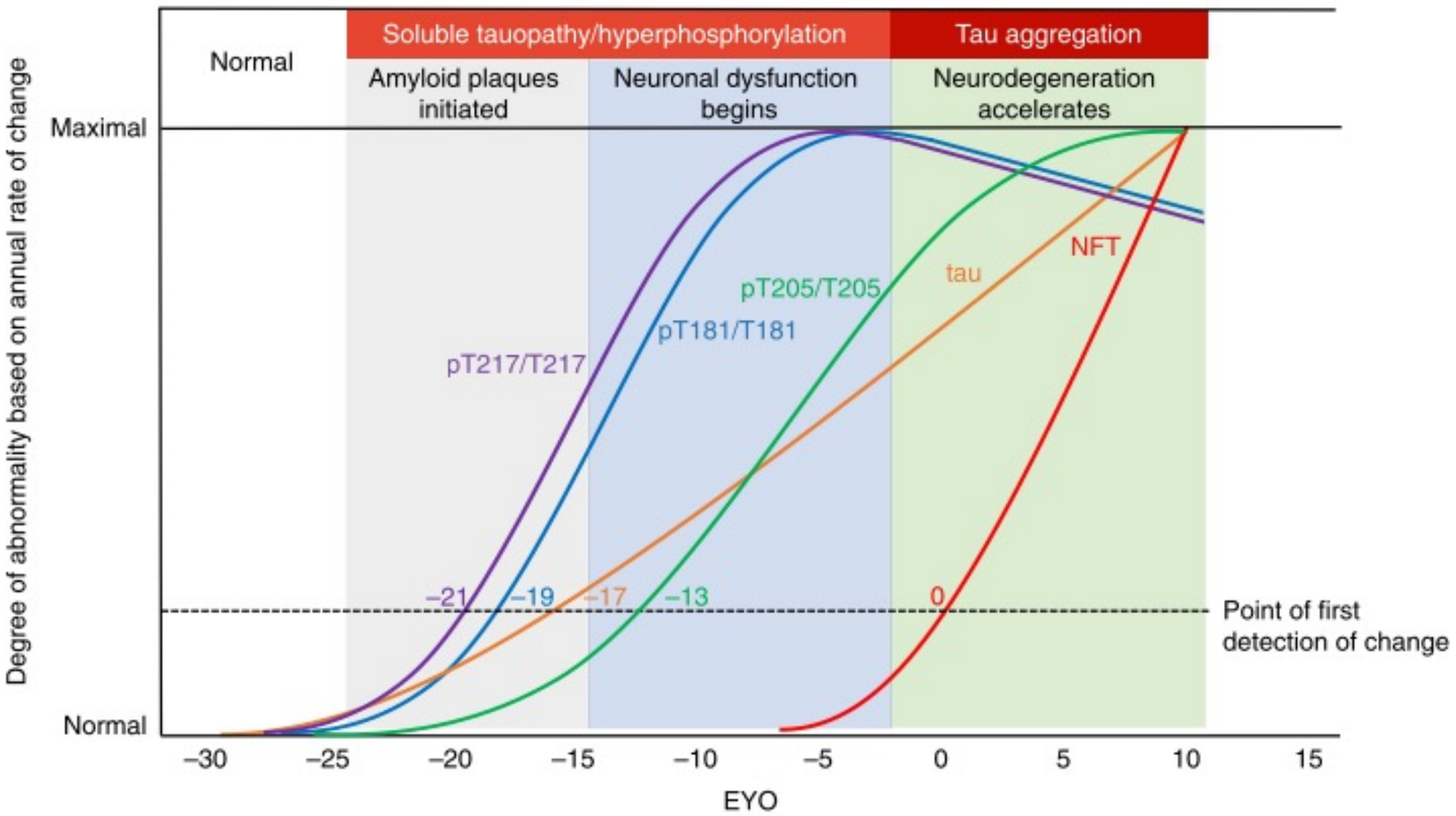
- **Définition biologique et étiologique**

- **« Démence » ≠ « maladie d'Azheimer »**
- Dissociation biologie (étiologie) / symptômes (répercussions)

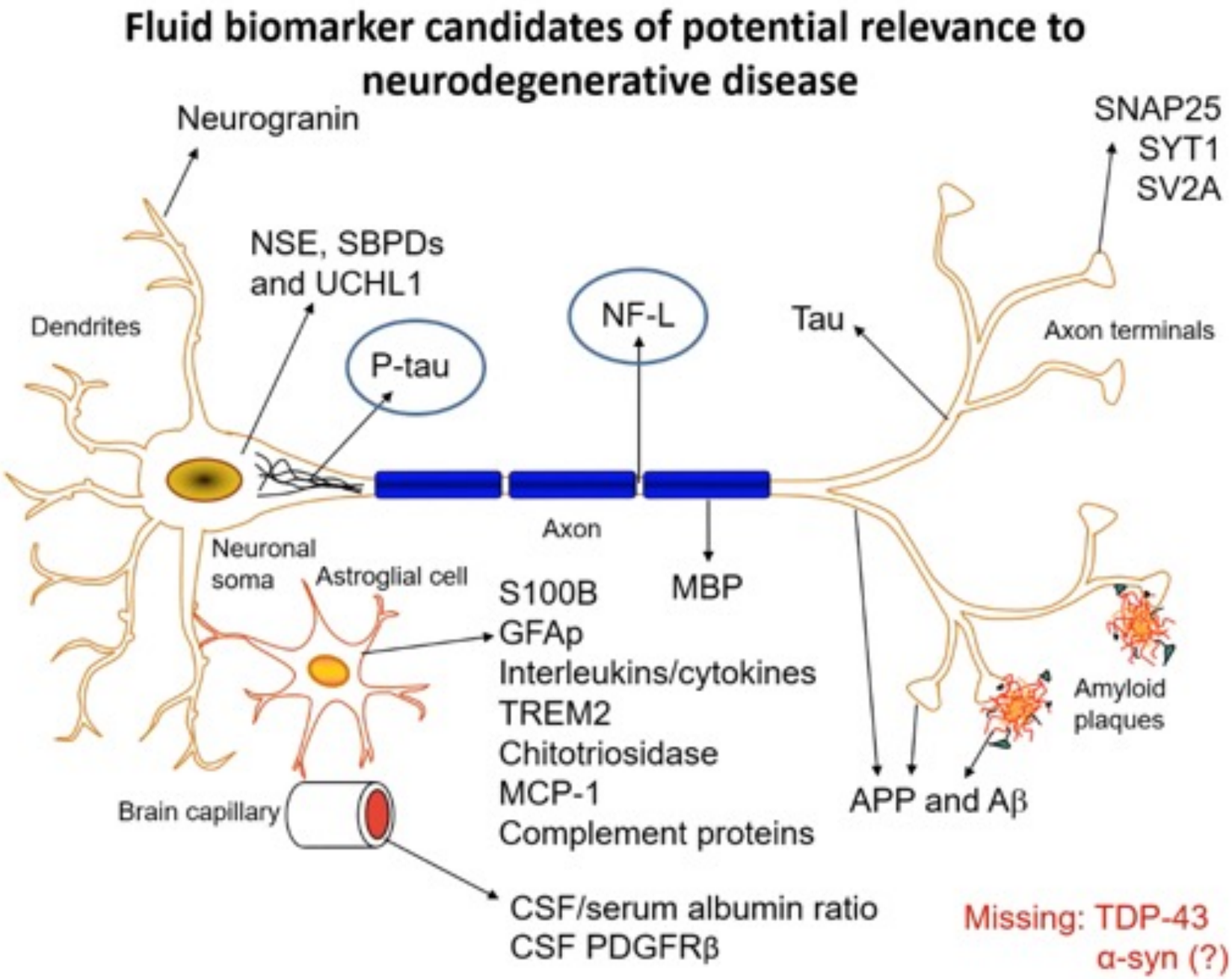
L'ÈRE DES BIO MARQUEURS : MARQUEURS PLASMATIQUES

	A	T	N
Imaging	*Amyloïde – PET*	*Tau - PET*	FDG – PET ; IRM
LCR	↓ Aß$_{42}$ ↓ Aß$_{42/40}$	↑ P-tau	↑ Tau ↑ Tau/Aß42
Plasma	↓ Aß42 ↓ Aß42/40	↑ P-tau 181, 217, 231,...	NFL

L'ÈRE DES BIO MARQUEURS : MARQUEURS PLASMATIQUES



L'ÈRE DES BIO MARQUEURS



PLAN

1. La maladie d'Alzheimer – Généralités

2. Le diagnostic « historique »

3. L'ère des biomarqueurs

4. En clinique

5. Take-home message

L'INTÉRÊT POUR LE CLINICIEN

- Intérêt d'abord **scientifique** (phénotypage population)

- Diagnostic différentiel des cas complexes

- « Première évaluation de dépistage »

- Patient jeune, peu symptomatique, atypique
- Rôle clé dans les futures options thérapeutiques
- Evolution vers l'ère du « pré-clinique »

LES LIMITATIONS EN CLINIQUE

- Patients A+T+ asymptomatiques ?

- Co-pathologies (asymétrie des biomarqueurs) ?

- « Continuum model » versus « At-risk model »

- Modèle prédictif à l'échelle individuelle ?

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

Bruno Dubois, Nicolas Villain*, Giovanni B Frisoni, Gil D Rabinovici, Marwan Sabbagh, Stefano Cappa, Alexandre Bejanin, Stéphanie Bombois, Stéphane Epelbaum, Marc Teichmann, Marie-Odile Habert, Agneta Nordberg, Kaj Blennow, Douglas Galasko, Yaakov Stern, Christopher C Rowe, Stephen Salloway, Lon S Schneider, Jeffrey L Cummings, Howard H Feldman*

Lancet Neurol 2021; 20: 484–96

Published Online
April 29, 2021
https://doi.org/10.1016/S1474-4422(21)00066-1

See Comment page 414

*Joint first authors

Assistance Publique-Hôpitaux de Paris (AP–HP) Department of Neurology (Prof B Dubois MD, N Villain MD, S Bombois MD, S Epelbaum MD, M Teichmann MD), **AP–HP Department of Nuclear**

In 2018, the US National Institute on Aging and the Alzheimer's Association proposed a purely biological definition of Alzheimer's disease that relies on biomarkers. Although the intended use of this framework was for research purposes, it has engendered debate and challenges regarding its use in everyday clinical practice. For instance, cognitively unimpaired individuals can have biomarker evidence of both amyloid β and tau pathology but will often not develop clinical manifestations in their lifetime. Furthermore, a positive Alzheimer's disease pattern of biomarkers can be observed in other brain diseases in which Alzheimer's disease pathology is present as a comorbidity. In this Personal View, the International Working Group presents what we consider to be the current limitations of biomarkers in the diagnosis of Alzheimer's disease and, on the basis of this evidence, we propose recommendations for how biomarkers should and should not be used for diagnosing Alzheimer's disease in a clinical setting. We recommend that Alzheimer's disease diagnosis be restricted to people who have positive biomarkers together with specific Alzheimer's disease phenotypes, whereas biomarker-positive cognitively unimpaired individuals should be considered only at-risk for progression to Alzheimer's disease.

INTERNATIONAL WORKING GROUP

- Diagnostic = Phénotype typique et A+T+

- Phénotype atypique : co-pathology ?

- Non-recommandé chez le sujet asymptomatique

- Importance du follow – up clinique

CAS CLINIQUE 1

- Monsieur C., 74 ans
- Plaintes cognitives subjectives depuis 2 ans
- Bilan neuropsychologique normal
- CT scan normal, PET-CT scan normal

LIQUIDE CEPHALO-RACHIDIEN
ANALYSES CHIMIQUES
PROTEINES ALZHEIMER

Protéine Tau Totale	*	635
Protéine Phospho-Tau (181)	*	82.7
Protéine bêta-amyloïde 40		21933
Protéine bêta-amyloïde 42		1162
Rap. prot. bêta-amyl.1-42/1-40	*	0.053
Rap. prot. Tau / bêta-amyl.1-42	*	0.546

CAS CLINIQUE 2

- Monsieur D., 73 ans
- Trouble cognitif modéré (MCI) depuis 2 ans
- IRM : Leucopathie vasculaire
- PET-CT : Hypométabolisme diffus aspécifique
- Antécédent familial d'AD

LIQUIDE CEPHALO-RACHIDIEN		
ANALYSES CHIMIQUES		
PROTEINES ALZHEIMER		
Protéine Tau Totale		261
Protéine Phospho-Tau (181)		40.8
Protéine bêta-amyloïde 40		6067
Protéine bêta-amyloïde 42	*	**321**
Rap. prot. bêta-amyl.1-42/1-40	*	0.053
Rap. prot. Tau / bêta-amyl.1-42	*	0.813

CAS CLINIQUE 3

- Madame J., 72 ans
- Asymptomatique
- Inquiétude de développer une maladie d'Alzheimer
- Pas d'antécédent familial

PLAN

1. La maladie d'Alzheimer – Généralités

2. Le diagnostic « historique »

3. L'ère des biomarqueurs

4. En clinique

5. Take-home message

TAKE – HOME MESSAGE

- Le « syndrome démentiel » n'est pas suffisant pour poser un diagnostic de maladie d'Alzheimer
- La maladie d'Alzheimer évolue d'une définition « anatomo-clinique » à une définition « biologique »
- Il faut distinguer le profil biologique du profil clinique
- L'intérêt primitif est le phénotypage pour les études cliniques
- En clinique, la place des biomarqueurs reste à définir
- Intérêt des biomarqueurs dans les traitements futurs ?