Distinguere la demenza di Alzheimer dalla demenza a corpi di Lewy

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What’s on in DLB?

- Challenge 1: sensitivity of diagnostic criteria
- Challenge 2: diagnostic specificity and pathological comoribidity
- Challenge 3: Definition of prodromal DLB
- ...and hence need of biomarkers
Lewy bodies pathology is common: community dwelling older subjects: **18% of cases** dementia patients: **15-20%**

Alzheimer’s disease comorbidity in half cases

Prevalence (clinical diagnosis)
- Community setting: **4.2%**
- Secondary care setting: **7.5%**

Schneider et al, Brain 2012, Jellinger; 2011; Vann Jones, Psychol Med 2014
But...

Clinical prevalence of Lewy body dementia

4.6% of all diagnoses (ranging 2.5-6%)

More frequently diagnosed in young subjects

O’ Brien 2018
Why revised diagnostic criteria?

Low sensitivity in clinical setting (Nelson, 2014)

Atypical DLB is now recognized

Some core features may never be present (25% no motor signs)

More weight on “indicative” biomarkers
# Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

## Essential

**Dementia (visual-spatial/attention)**

## Core clinical features

<table>
<thead>
<tr>
<th>Fluctuations</th>
<th>Visual Hallucinations</th>
<th>RBD</th>
<th>Parkinsonism</th>
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</table>

## Indicative Biomarkers

- ↓ DA uptake in the basal ganglia (SPECT o PET)
- Polysomnography (confirmed REM without atonia)
- ↓ Uptake $^{123}$I-MIBG (cardiac scintigraphy)

### PROBABLE DLB=
- 2 core features
- 1 core feature + 1 indicative biomarker

### POSSIBLE DLB=
- 1 core feature
- 1 indicative biomarker

McKeith 2017
3 minutes to make diagnosis of DLB

Lewy body composite risk score (≥3)

Motor

Sleep/wake, fluctuation, RBD, VH

Galvin, Alz&Dementia 2015
EXTRAPYRAMIDAL SIGNS IN DLB

98 DLB patients
130 PD patients

68 % EPS +

- Body bradykinesia
- Action tremor
- Facial expression
- Gait instability

- Rest tremor
- Rigidity

Severity did not correlate with age, disease duration, cognition

AARSLAND, 2001
Sleep-wake/fluctuation cluster

RBD upgraded to core feature
Hypersomnolence
Transient episodes of unconsciousness added among suggestive features

Polysomnography added as indicative biomarker
Sleep

frequent RBD-like symptoms (70%)

Wake

increased somnolence

increased number of daytime naps

daytime dysfunction due to somnolence

fluctuation of attention (associated with RBD+)

Cagnin et al, JAD 2017
FLUCTUATIONS

Spontaneous alterations in
  – Cognition
  – Attention
  – Arousal
• Behavioural inconsistency
• Disorganized speech
• Altered consciousness-lethargy
**Brain 2019**

**EEG (Wake)**
Intermittent slowing of local and global populations of neurons - worsening with sleep pressure

**PSG**
Dysfunctional transitions between sleep stages
Poor dissipation of delta power in sleep

**Pupillometry**
Altered pupil dynamics
- e.g. loss of phasic dilatation during task

**Circadian markers**
Altered timing/amplitude of circadian markers

**Pathways regulating brain states**
- Cortico-cortical connections (green)
- Thalamo-cortical connections (orange)
- Neuromodulatory pathways (red)

**Sleep Pressure**
Sleep Pressure over time of day

**Hours of sleep**
- Awake
- REM
- N1
- N2
- N3

**Loss of topological flexibility**
and altered dynamical switching of large scale brain networks

**Brainstem nuclei**
- Thalamus
- LH
- BF
EEG nella DLB

Analisi degli spettri:
- frequenza dominante: pre- alfa / theta (5,6- 7,9 Hz) prevalente nelle derivazioni posteriori
- fluttuazioni delta- theta/pre- alfa o theta- pre- alfa/alfa
- correlazioni con fluttuazioni cognitive

Studio delle sorgenti di attività elettrica cerebrale:
- attività diminuite nelle derivazioni occipitali e sensori- motorie.
- correlazioni con peggiori funzioni cognitive.

Studio di complessità:
Nessuno studio a disposizione nella DLB

Open issues

- PSG *versus* RBD questionnaires?
- Diagnosis of RBD *versus* NON REM sleep behavioural disorder (i.e. confusional awakenings, .....
- ESS *versus* other scales dedicated to dementia
- Definition of outcomes for interventional treatments?
Anatomical correlates of VH

• Associated with poor visual attention

• Long fibers tracts dysconnection mainly in the right hemisphere

• Imbalance between attentional functional networks
**FUNCTIONAL CORRELATES OF VH**

**Ventral Attention Network**
- Superior Frontal
- Anterior Insula
- Temporo Parietal Junction
- Mediate activation of other networks
- Engages attention to salient stimuli

**Dorsal Attention Network**
- Frontal Eye Fields
- Superior Parietal
- Extra Visual
- Voluntary orienting
- Cognitive information processing

**Default Mode Network**
- Posterior Cingulate
- Medial Prefrontal
- Hippocampus
- Task-independent thought
- Mind wandering

**Diagram:**
- Impaired Visual Processing
- Ambiguous Percept
- Basal Ganglia
- DMN
- Episodic Memory Recall: "I don’t remember leaving a hose here"
- Misperception
- Correct perception
- SALIENCE: "That could be a snake"
- Misperception
What’s on in DLB?

- Challenge 1: sensitivity of diagnostic criteria
- Challenge 2: diagnostic specificity and pathological comorbidity
- Challenge 3: Definition of prodromal DLB
- ...and hence need of biomarkers
Brain comorbidity in real life

Rabinovici, 2017
Person-specific contribution of neuropathologies to cognitive loss in old age

Patricia A. Boyle¹,², Lei Yu¹,³, Robert S. Wilson¹,²,³, Sue E. Leurgans¹,³, Julie A. Schneider¹,³,⁴, and David A. Bennett¹,³

✓ Comorbidity is the rule: 3/4 has 2 or more co-pathologies

✓ 230 combinations

✓ AD is the most virulent accounting for an average of 50% cognitive loss but individual contribution is variable

Ann Neurol, 2018
Heterogeneity of presentations

- Additional pathology
- Age
- Genetic variability of α-synuclein
- Different route of entry

Figure 3: Examples of presenting symptoms of dementia with Lewy bodies. REM, rapid eye movement.
Additional pathology

66% of DLB brains will have AD pathology

DLB phenotype is driven by alpha synuclein and neuritic plaques

AD pathology has an additive effect on clinical variables
Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies

<table>
<thead>
<tr>
<th>NPI&lt;sup&gt;d&lt;/sup&gt;</th>
<th>DLB/AD+</th>
<th>DLB/AD-</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>12.0 (6.5–21.5)</td>
<td>10 (5.0–16.0)</td>
<td>0.421</td>
</tr>
<tr>
<td>Delusions</td>
<td>7/31 (23%)</td>
<td>4/59 (7%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>17/31 (55%)</td>
<td>17/59 (29%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

<sup>d</sup> NPI: Neuropsychiatric Inventory.
Specific Verbal Memory Measures May Distinguish Alzheimer’s Disease from Dementia with Lewy Bodies

Bussè et al, JAD 2018
AD-like CSF biomarkers
Cortical thinning

A Control vs Aβ-negative DLB (n=15 vs 21)

B Control vs Aβ-positive DLB (n=15 vs 15)

C Aβ-negative DLB vs Aβ-positive DLB (n=21 vs 15)

Seok, Neurobiol Aging 2018
Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies

**Figure 3** Effect of the dementia with Lewy bodies (DLB)/Alzheimer’s disease (AD) positive cerebrospinal fluid (CSF) biomarker profile on admittance to nursing home. Kaplan-Meier curve of admittance to nursing home of DLB patients with the AD CSF profile and DLB/AD–CSF profile.
What’s on in DLB?

- **Challenge 1:** Sensitivity of diagnostic criteria
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...and hence need of biomarkers
Prodromal DLB

iRBD population followed for 14 years

Postuma et al, Brain 2019
Retinal thinning in DLB

Optical Coherence tomography

Papilla

Macula

A

B

Fragiacomo, Cagnin, Mov Dis 2019
Prodromal / pre-dementia DLB

may present as

DLB- mild cognitive impairment onset
   *DLB-mci*

DLB-delirium onset
   *DLB-del*

DLB-psychiatric onset
   *DLB-psych*

McKeith et al, 2017
Cognitive impairment in prodromal DLB

Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies

PROGRESSION RATE
incidence/100 person-years

✓ naMCI: 20% DLB, 1.6% AD
✓ aMCI: 17% AD, 1.5% DLB

Ferman et al, Neurology 2013
High specificity of MMSE pentagon scoring for diagnosis of prodromal dementia with Lewy bodies

Annachiara Cagnin a,b,*, Cinzia Bussè a,1, Nela Jelcic b,1, Francesca Gnoato a, Micaela Mitolo c, Paolo Caffarra d

IMPAIRED NUMBER OF ANGLES

MCI-DLB: 45.1% versus MCI-AD: 8.3%, p = 0.005

SENSITIVITY = 41.4% PPV: 86%
SPECIFICITY = 91%  NPV: 54%
Neurotransmission in visuospatial performance

2-month time

MMSE: 22/30

MMSE: 30/30

Tryclic antidepressant
Conventional antipsychotic
Benzodiazepine

SSRI
ChEI

• M; 72 yrs
• RBD
Delirium in the spectrum of DLB

- Clinical similarities

- Delirium more common in predementia phase of DLB than AD (Vardy, 2014)

- Severe cholinergic dysfunction

- Higher frequency of APOE4 (?)

- Therapeutic implications (no haloperidol)
core feature
✓ Complex recurrent visual hallucinations

DLB-psychiatric onset

Supportive features
✓ .......... 
✓ Hallucinations in other modalities
✓ Sistematized delusions
✓ Depression-apathy
✓ .......... 

Late-onset Affective disorder
Late-onset psychosis
Treatment refractory
Neuroleptic adverse sensitivity
Sea-monster with 50 tentacles?
What’s on in DLB?

✓ New revised diagnostic criteria
✓ Heterogeneity of presentation
✓ Definition of prodromal DLB
✓ ...and hence need of biomarkers
Biomarkers

- Dat scan has well established utility (Se 78%, Sp 90%) Only in cases of no or uncertain parkinsonism

- PSG: high likeliwood of synucleopathy but difficult to perform in older demented patients

- MIBG: high specificity

- Need of biomarkers mirroring the molecular pathology (CSF RTQuic?)
BRIEF COMMUNICATION

α-Synuclein RT-QuIC assay in cerebrospinal fluid of patients with dementia with Lewy bodies

Matilde Bongianni¹, Anna Ladogana², Stefano Capaldi³, Sigrid Klotz⁴, Simone Baiardi⁵,⁶, Annachiara Cagnin⁷, Daniela Perra¹, Michele Fiorini¹, D, Anna Poleggi², Giuseppe Legname⁸, D, Tatiana Cattaruzza⁹, Francesco Janes¹⁰, Massimo Tabaton¹¹, Bernardino Ghetti¹², Salvatore Monaco¹, Gabor G. Kovacs⁴,¹³,¹⁴,¹⁵, Piero Parchi⁶,¹⁶ D, Maurizio Pocchiari² & Gianluigi Zanusso¹ D
Future scenario

Cohort of at risk patients

- RBD
- IPOSMIA
- Pentagon copy-MMSE
- DELIRIUM

Possible prodromal DLB

Screening for core/suggestive features

- TCS
- DAT-SCAN
- Markers α-syn?

Probable prodromal DLB

Search for
- α syn pathology
- Neuronal dysfunction
Sea-monster with 50 tentacles
Autopsy validation of $^{123}$I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB

"False negative": 10%  
"False positive": FTD-parkinsonism

DAT SPECT: SE 80%, SP 92%  
CLINICAL DIAGNOSIS: SE 87%, SP 72%
Fig. 1. Representative cases of $^{123}I$-MIBG myocardial scintigraphy. A: normal control (HM ratio 2.84), B: a case of abnormal low accumulation (HM ratio 1.41). MIBG: metaiodobenzylguanidine The HM ratio: the heart to mediastinum ratio The cut-off value of delayed MIBG images (4 h after injection of 111 MBq MIBG, depending on uptake-1 [neuronal uptake], reflecting cardiac sympathetic nerve activity) of the HM ratio was 2.0. A reduced HM ratio indicates peripheral noradrenergic depletion.
(123) I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography and (123) I-metaiodobenzylguanidine myocardial scintigraphy in differentiating dementia with Lewy bodies from other dementias: A comparative study.

Tiraboschi P¹, Corso A², Guerra UP³, Nobili F⁴, Piccardo A⁵, Calcagni ML⁶, Volt terrani D⁷, Cecchin D⁸, Tettamanti M⁹, Antelmi L¹⁰, Vidale S¹¹, Sacco L¹¹,¹², Merello M¹³, Stefanini S¹³, Micheli A¹⁴, Vai P¹⁵, Capitanio S¹⁵, Gabanelli SV¹⁵, Riva R¹⁶, Pinto P¹⁶, Biffi AM¹⁷, Muscio G¹, SCILLA Working Group.

### Table 3 – Visual assessment findings for myocardial imaging in the differential diagnosis of DBL

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<tr>
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<th>[(123)I]-MIBG myocardial scintigraphy</th>
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<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
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</tr>
<tr>
<td></td>
<td>Baseline Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Rater A</td>
<td>87%</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td>Rater B</td>
<td>84%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Rater C</td>
<td>87%</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Overall rating #</strong></td>
<td><strong>87% 93%</strong></td>
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# There was complete agreement among the three raters for 56/59 cases. In the remaining three cases, scan assignment to normality or abnormality was based on the opinion of the majority of the raters.

### Table 4 – Visual assessment findings for striatal imaging in the differential diagnosis of DBL

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# There was complete agreement among the three raters for 52/59 cases. In the remaining seven cases, scan assignment to normality or abnormality was based on the opinion of the majority of the raters.
Cingulate Island Sign

Figure 1. Box plots of the cingulate island sign ratio among the patient groups.
Accuracy of transcranial brain parenchyma sonography in the diagnosis of dementia with Lewy bodies

S. Favaretto, U. Walter, C. Baracchini, S. Pompanin, C. Busse, G. Zorzi, M. Ermani, and A. Cagnin
Motor cluster

✓ “One of the motor signs of Parkinson disease among bradykinesia, rigidity, rest tremor.”
What’s on in DLB?

✓ New revised diagnostic criteria
✓ Heterogeneity of presentation
✓ Definition of prodromal DLB
✓ ...and hence need of biomarkers
Visual Hallucinations

- Recurrent complex VH (human faces, animals)
- Preserved environment
- Poor/lack insight
- Coping strategies

- Pre-hallucinatory episodes:
  - Feeling of presence or of passage
  - Visual illusions

- Secondary related delusions
Anatomical correlates of VH

Cagnin et al, submitted
In PD the lateral part of SN always degenerates first

= Preferential loss in putamen relative to caudate

"From comma to full stop!"
$^{18}$F-DOPA PET
Acquisizione 5 min!
Differentiation of dementia with Lewy bodies from Alzheimer’s disease using a dopaminergic presynaptic ligand

Z Walker, D C Costa, R W H Walker, K Show, S Gacinovic, T Stevens, G Livingston, P Ince, I G McKeith, C L E Katona

Walker, Neurology 2004
“INDICATIVE BIOMARKER”

$^{123}$I-MIBG
TRACERS USED FOR CARDIAC SYNAPTIC TARGETS FOR DOPAMINERGIC LIGANDS RECEPTORS

L-tyrosine ➔ dopa ➔ Dopamine ➔ Noradrenaline

DOPAMINE

$^{11}\text{C-CGP12177}$
$^{11}\text{C-carazolol}$
$^{11}\text{C-MQNB}$

$^{11}\text{C-Hydroxyephedrine}$
$^{11}\text{C-epinephrine}$
$^{123}\text{I-MIBG}$

MYOCITE

$^{18}\text{F-FDOPA}$
Atypical pattern of tau deposition

DLB

Temporo-parietal regions

Amy +

AV 1451 TAU +

Amy -

AV 1451 TAU +

Kantarci, Ann Neurol 2017
a-synuclein strains

Cross seed with other proteins
### Supportive features

- Severe sensitivity to antipsychotics
- Postural instability
- Falls/syncope
- Transient episodes unconsciousness
- Autonomic dysfunction
- Hypersomnolence
- Hyposmia
- Hallucinations in other modalities
- Systematized delusions
- Apathy-anxiety-depression

### Supportive biomarkers

- Relative preservation MTL
- General low PET uptake with reduced occipital activity +/- cingulate island sign
- Posterior slow-wave activity on EEG with periodic fluctuations