BIOLOGICAL EVIDENCE OF MULTIPLE PATHOLOGIES IN DIFFERENT NEURODEGENERATIVE DISEASES: CLINICAL-BIOLOGICAL CORRELATION

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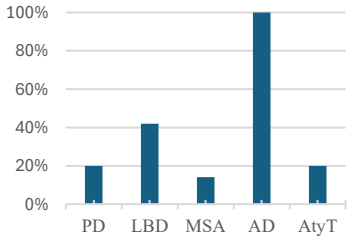
Objectives: Real Time - Quaking-Induced Conversion (RT-QuIC) has demonstrated high sensitivity and specificity in detecting misfolded α-synuclein (α-syn) strain in patients with α-synucleinopathies [1]. The possibility of detecting α-syn alongside with pathological biomarkers of Alzheimer's Disease (AD) make it possible to demonstrate the highly prevalent co-existence of several co-pathologies in same individuals. Here we present the results of an analysis of co-pathologies prevalence in patients affected by different parkinsonian syndromes.

Materials: we performed RT-QuIC for a-syn on olfactory mucosa (OM) samples and analyzed cerebrospinal fluid of 12 patients with Parkinson disease (PD), 12 with Lewy Body Dementia (LBD), 7 with Multiple System Atrophy (MSA), 5 with AD and 10 with other tauopathic parkinsonian syndromes (AtyT).

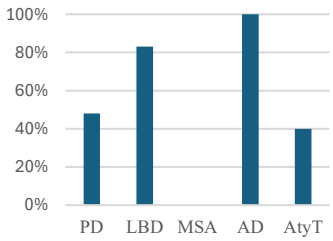
Methods: diagnosis was based on clinical criteria. Biomarker of AD pathological changes (Ab42, Ab40, Ab42/Ab40, total tau (t-tau), phosphorylated tau (p-tau181)) were sought on CSF. Two OM samples through fibroscopic guide were collected with FLOQBrushes® (Copan, Italia) [1] and sent to Neuropathology Laboratory of Verona for RT-QuIC analysis.

Results: Amyloid Ab42/Ab40 ratio was altered in 100% AD subjects (who also all had high levels of p-tau, as expected), and also in 41% LBD, 20% AtyT, 19% PD and 14% MSA patients. Increased p-tau was found in 40% AtyT, 8% LBD, 4% PD and 0% MSA patients. RT-QuIC analysis of α-syn was positive result in 81% PD, 75% AD, 67% LBD, 57% MSA and 20% AtyT subjects. When considering each protein and clinical diagnoses, these variables showed a statistical association when performing Chi-square tests or Fisher exact test (Ab42/40: p=0.007, p-tau: p<0.001, a-syn: p=0.018). We also considered the presence of one or more-than-one co-pathologies: co-pathologies were in 80% of AD, 42% of LBD, 19% of PD, 14% of MSA and 0% of AtyT. We found a significant association between co-pathologies and clinical diagnoses (p=0.006); a significant association was also detected between AD and AtyT.

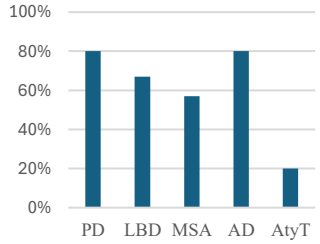
Decreased αB42/αB40 ratio



Increased P-tau

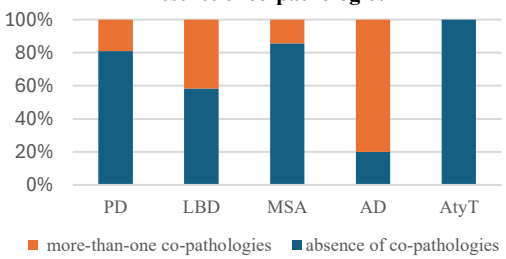


α-syn RT-QuIC positive test



Discussion: Measuring different biomarkers allow both a more accurate differential diagnosis and the detection of co-pathologies in different clinical phenotypes. Patients with α-synucleinopathies have a high frequency of concurrent amyloidopathy. Patients with primary AD have high rate of α-syn positivity, as high as 80% in our series, probably an overestimation due to atypical AD phenotypes herein considered [2,3].

Presence of co-pathologies



Conclusion: The presence of co-pathology varies in different clinical diagnoses. Implementing the sample of patients tested will be necessary to correctly estimate the number of patients displaying several co-pathologies, and to understand how all co-pathologies influence clinical manifestations.

1. Bongianni M, Catalan M, Perra D, et al. Olfactory swab sampling optimization for α-synuclein aggregate detection in patients with Parkinson's disease [published correction appears in Transl Neurodegener. 2022 Aug 12;11(1):38. doi: 10.1186/s40035-022-00312-2.].
2. Moda F et al.. Secondary Protein Aggregates in Neurodegenerative Diseases: Almost the Rule Rather than the Exception. Front Biosci (Landmark Ed). 2023 Oct 20;28(10):255.doi:10.31083/j.fbl2810255. PMID: 37919089.
3. Bellomo G et al. Investigating alpha-synuclein co-pathology in Alzheimer's disease by means of cerebrospinal fluid alpha-synuclein seed amplification assay. Alzheimers Dement. 2024 Apr;20(4):2444-2452. doi: 10.1002/alz.13658. Epub 2024 Feb 7.