ASAP SYNTAU:

ALIGNMENT AND STANDARDIZATION OF NEUROIMAGING METHODS IN ATYPICAL PARKINSONISM, SPECIFICALLY SYNUCLEINOPATHIES AND TAUOPATHIES

Report of a JPND Working Group on Harmonisation and Alignment in Brain Imaging Methods

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ASAP SynTau: Alignment and Standardization of Neuroimaging Methods in Atypical Parkinsonism, specifically Synucleinopathies and Tauopathies

Report of a JPND *Working Group for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration*

Content

1. Introduction

Parkinsonism is the most common neurodegenerative syndrome after the syndrome of dementia (Alzheimer's disease and other dementias). In ~20% of patients, parkinsonism is not due to Parkinson's disease (PD) pathology, which is commonly referred to as atypical parkinsonism (AP).[1,2] The most frequent forms of underlying pathological entities in AP are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA). Neuronal degeneration is generally much more rapid and widespread and symptomatic therapy is much less effective in these disorders than in PD.[3] However, great hope currently stems from the development of therapies directed at the underlying pathological substrates, such as Tau for PSP/CBD.[4] Further development of these therapeutic strategies depends on large multi-centre trials, which face two major obstacles: i) low initial diagnostic accuracy for pathological entities using symptom-based differentiation; ii) a lack of sensitive objective progression markers.[5,6] Neuroimaging methods, such as transcranial sonography (TCS), ^{18}F-Fludeoxyglucose (FDG) PET, 1.5T and 3T MRI are recommended to increase diagnostic accuracy and to provide objective progression markers in AP.[7] In addition, new imaging techniques provide exciting opportunities in this domain, such as ultra-high field MRI (UHF MRI) and molecular PET markers of Tau pathology (TAU PET). However, community-based consensus on technical standards for imaging biomarkers for diagnosis and progression as required for the necessary scale of multi-centre trials in AP, are currently missing. The ASAP SynTau working group set out to formulate and address key challenges for the application of new and innovative brain imaging techniques by establishing a methodological framework to overcome barriers in AP, specifically in PSP and MSA.

2. Vision Statement of Advisory Group

2.1. General information

2.1.1. Advisory Group Members

Günter Höglinger, MD PhD, Technical University Munich and DZNE, Munich, Germany
Gregor K. Wenning, MD PhD MSc, Medical University of Innsbruck, Austria
Matej Ondruš, MD, MSc, Medical Director at AXON Neuroscience SE, Bratislava, Slovakia

2.1.2. Role of Advisory Group

Providing external reference on the desired applicability of the project outcomes through expert input via statements and participation at the workshops. Advisory group members acted as representatives of the MDS Study Groups for MSA (Wenning) and PSP/CBD (Höglinger), or of potential future trial sponsors (Ondruš).

2.2. Background Information

2.2.1. Clinical vs. pathological entities

Even though some clinical entities (e.g. PSP-Richardson Syndrome) highly correlate with the underlying pathological entity (PSP-tauopathy), we recognize that in AP, the clinical entity (e.g. Cortico-basal syndrome or parkinsonism with orthostatic hypotension) can have poor overlap with a pathological entity (CBD-tauopathy / MSA) and vice versa.

2.2.2. Role of imaging biomarkers in AP

Imaging biomarkers may be instrumental to overcome the following major challenges for therapeutic trials in AP:

1) low initial diagnostic accuracy for clinical entities, valid on the level of individual patients rather than groups (markers for clinical diagnosis)
2) low diagnostic accuracy for pathological entities, valid on the level of individual patients rather than groups (markers for pathological diagnosis)
3) lack of sensitive objective markers of disease progression (monitoring markers)

We also see some potential for imaging biomarkers to serve as

4) target verification markers for tau- or synuclein-targeting interventions (diagnostic target markers)
5) target quantification markers for tau- or synuclein-targeting interventions (target monitoring markers)
6) markers accurately predicting the clinical or pathological diagnosis earlier than clinical diagnostic criteria (pre-clinical diagnostic markers)

2.2.3. Definition and Characteristics of Imaging Biomarkers

In line with the FDA/NIH BEST Resource (2016) propositions, a biomarker is a defined characteristic that is measured as an indicator of a biological (pathogenic) processes. With regard to the above-mentioned context, most valuable biomarkers would be:

Diagnostic biomarkers in AP

Applicable to increase diagnostic accuracy for pathological entities or clinical entities in comparison to clinical judgement alone. In agreement with this definition, an imaging characteristic may also serve to enhance patient stratification (resulting in a more homogenous sample) in a specific study or trial (for example as a target verification tool in case of Tau PET).

Monitoring biomarkers for AP

Measured serially and used to detect a change in the degree / extent of a disease process. In agreement with this definition, an imaging characteristic may serve as a more proximal surrogate endpoint expected to highly correlate with or predict clinical outcomes, - or - may serve as a predictor of efficacy without necessarily correlating with clinical outcomes.

2.3. Recommendations of the Advisory Group

Anticipating the use of imaging biomarkers in future multi-centre studies, the ASAP SynTau Working Group should aim to deliver detailed descriptions of technical procedures and data processing pipelines to produce comparable minimum data sets at different sites (possibly using different equipment, e.g. Philips vs. Siemens MRI or ligands, e.g. AV-1451 vs. THK-5351).

We specifically encourage you to develop standardized technical guidelines for a (potentially vendor independent or multimodal) minimal dataset that can be validated in a multi-centre study as

diagnostic markers

- to increase early diagnostic accuracy for clinical entities in AP
- to increase early diagnostic accuracy for pathological entities in AP
- to serve as a target validation instrument for tau-targeting interventions

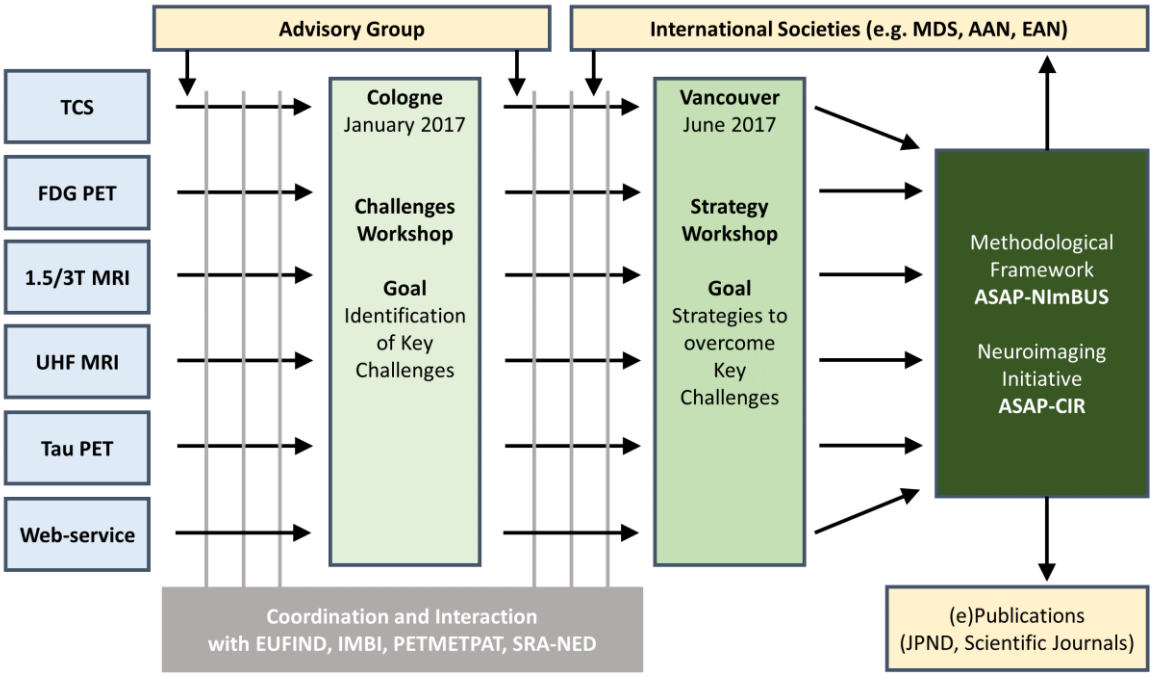
monitoring markers

- to detect changes, which are predictive of clinically meaningful outcome measures
- to detect changes in the degree of disease pathology predictive of clinical outcomes
- to detect changes that are predictive of the efficacy of a therapeutic intervention
- to potentially serve as a target quantification instrument for tau-targeting interventions

We encourage you to develop the conceptual design for a web-based service that may serve in a multi-centre study aiming at above-mentioned goals, particularly delineating the means of including postmortem pathological information on individual patients.

3. Activities of ASAP SynTau

The figure below summarizes main activities of the Working Group ASAP SynTau:



The ASAP SynTau group consisted of specialists for TCS, FDG PET, 1.5/3T MRI, UHF MRI, and Tau PET. In addition, the conceptual design for a web-based service that may serve in a multi-centre study for the goals of ASAP SynTau was discussed. During the whole process, the group coordinated activities and exchanged ideas with Working Groups of overlapping interests: EUFIND (UHF MRI), IMBI (PET), PETMETPAT (FDG PET), SRA-NED (PET and MRI).

The timeline of activities was as follows:

November 2016: Start of the project

December 2016: A Vision Statement (see above) was issued by the Advisory Board

December 2016 to January 2017: Remote discussions of Vision Statement and initial steps

January 2017: The Working Group held a workshop in Cologne, Germany to identify the key challenges and barriers in the field and to initiate processes to address these challenges

January 2017 to June 2017: Telephone conferences to finalize outcome of 1st workshop

June 2017: The Working Group held a workshop in Vancouver, Canada to initiate strategies to overcome the key challenges and barriers in the field

June 2017 to October 2017: Telephone conferences to finalize outcome of 2nd workshop

October 2017: End of the project

4. Results of ASAP SynTau

4.1. Key Challenges

A consensus was achieved regarding the key challenges in the field of brain imaging in AP:

Working together with other experts in the field, this Working Group has summarized new and innovative brain imaging techniques that may provide highly useful biomarkers, e.g. in multi-centre cohort studies and treatment trials in AP. [8-11]

However, there currently is no well-defined reference frame for the development and testing of new biomarkers. Benchmarking, for example, is currently difficult, because there is no consensus in the field, which imaging biomarkers are most favourable in transnational multi-centre trials in AP. This consensus is hindered by

- a lack of comparability of studies, mainly due to a lack of:
  1. Operational definitions for various possible applications of biomarkers
  2. Technical acquisition and processing standards
  3. Reporting standards for „usefulness“ (e.g. sensitivity/specificity, positive/negative predictive value)
- a lack of generalizability of studies, mainly due to:
  4. Focus on specific phenotypes (e.g. PSP with Richardson Syndrome, PSP-RS)
  5. Use of convenience samples
  6. Small sample sizes
- a lack of proven validity of studies, mainly due to lack of:
  7. Confirmatory studies
  8. Confirmation of type and distribution of pathology (post mortem)

A consensus was also achieved that the ASAP SynTau Working Group will aim to address the need of operational definitions for „usefulness“ (utility) of biomarkers integrating ability to be helpful early in the course of disease, to be highly specific, and to track progression. In agreement with the Vision Statement, most relevant areas of application will include diagnostic biomarkers for early clinical diagnosis, diagnostic biomarkers for a specific pathology, monitoring biomarkers for clinical progression and monitoring biomarkers for the progression of a specific pathology.

4.2. Strategies

It was agreed that the ASAP SynTau group will address above-mentioned key challenges by two strategies: i) a consensus paper on operational definitions for the utility of neuroimaging biomarkers in AP (see ASAP-NImBUS); ii) a Neuroimaging Initiative (see ASAP-CIR) to provide the best obtainable quantitative imaging biomarkers for diagnosis and progression for AP based on standardized procedures for acquisition and analysis.

4.2.1. ASAP - Neuro-Imaging Biomarker Utility System (NImBUS)

Following the Vision Statement of the Advisory Board, the ASAP SynTau Working Group considered these biomarkers categories as most relevant:

Diagnostic Biomarker: A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease. This sort of biomarker should typically provide a binary (yes/no) answer.

The Working Group agreed that the assessment of utility of a diagnostic biomarker should take into account:

a) superiority to the utility of clinical examination at the time of imaging
b) accuracy in relation to the time course of disease (the earlier, the better)
c) differences in utility with respect to pathological and clinical entities, as determined by histopathological examination or long-term clinical follow up, respectively

d) preference for accuracy measures, such as predictive value (PPV, NPV), and/or ROC-AUC for sensitivity/specificity

Monitoring Biomarker: A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

The Working Group agreed that the assessment of utility of a monitoring biomarker should take into account:

a) usability as a surrogate endpoint in clinical trials. Since a mechanistic rationale favors a biomarker to be considered as a surrogate endpoint (e.g. by FDA/EMA), one may want to distinguish biomarkers according to their proximity to the (assumed) initial pathological process
b) preference for effect size as a measure. For meaningful utility, the effect size of the biomarker should be superior to the effect size of clinical measures
c) difference in utility with respect to the clinical phase: preclinical phase (clinical criteria not yet met), early clinical phase (mild to moderate disease, physically independent), advanced clinical phase (physically dependent, severe deficits in activities of daily living)

The Working Groups aims to publish a paper summarizing these positions until mid 2018.

4.2.2. ASAP – Central Imaging Repository (CIR)

The ASAP SynTau Working Group decided to form a Neuroimaging Initiative.

4.2.2.1. Overarching Aim

The ASAP Neuroimaging Initiative is dedicated to engage in a benchmarking process using multi-centric neuroimaging data to provide the best obtainable quantitative imaging biomarkers for diagnosis and progression for AP based on standardized procedures for acquisition and analysis.

4.2.2.2. Main Projects

The ASAP Neuroimaging Initiative will mainly engage in two projects, which will overlap in terms of time and objectives:

ASAP-CIR retro: Comparative Benchmarking using a Retrospective Data Collection
In the first phase of activities, the ASAP Neuroimaging Initiative will merge multiple collections of high-resolution T1 3T/1.5T MRI data and ^{18}F-FDG PET data obtained in patients with PD, PSP, or MSA and HC by collecting the data in a Central Imaging Repository (CIR). Retrospectively acquired data will be analysed following a standardized processing pipeline with the aim of a head-to-head comparison of multiple published procedures for diagnostic purposes to produce a benchmark. ASAP-CIR retro members committed to share >2000 MRI data sets of patients with PSP, MSA and PD. As proof of principle, the group already shared >75 anonymized T1 data sets which were analysed in a fully automated process. While we expect to produce the first meaningful outcome within 1 year after provisional completion of the data collection, the entire project including subsidiary and complimentary analyses is expected to produce highly relevant results for at least five years.

ASAP-CIR pro: Prospective Validation of Neuroimaging Biomarkers
In the second phase of activities, the ASAP Neuroimaging Initiative aims to prospectively validate the benchmark diagnostic biomarkers based on the latest criteria for PSP [12], MSA [13], CBD [14], and DLB [15]. In addition, we aim to develop MRI-based biomarkers for disease progression based on longitudinal data. Initiation and duration of this phase largely depends on anticipated funding.

5. Contributors

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