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Supporting Data

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and it is unknown if these patients developed PD in between scans or presented PD with low dopaminergic degeneration.

α-synuclein seed amplification assays (α-S-SAA) detect α-synuclein (αSyn) aggregates in the cerebrospinal fluid (CSF) of PD, dementia with Lewy bodies (DLB), and isolated rapid eye movement (REM) sleep behavior disorder (iRBD) patients of PD, dementia with Lewy bodies (DLB), and isolated rapid eye movement (REM) sleep behavior disorder (iRBD) patients. We used an optimized high-throughput α-S-SAA (based on a previously described α-Syn protein misfolding cyclic amplification (PMCA) assay) that detects αSyn aggregates in CSF, to evaluate 140 fluid (CSF) samples and DaTscan images of α-S-SAA-positive scans without evidence of dopaminergic deficit (SWEDD) patients. The assay performed with 96.2% sensitivity (95% CI: 80.4%–99.9%) and 96.7% specificity (95% CI: 82.8%–99.9%) for PD versus HC at BL, and 96.4% sensitivity (95% CI: 81.7%–99.9%) and 93.8% specificity (95% CI: 79.2%–99.2%) at V08. After α-S-SAA analysis, PPMI reclassified two of the three α-S-SAA-negative subjects in the PD cohort as non-PD, therefore they were excluded from the above calculation. There were three false-positive samples: #3112-V08 and both samples from patient #3264. The latter was found to be a probable RBD case based on their RBD questionnaire score. Unfortunately, confirmatory polysomnography is not available and both samples from this patient were considered to be false-positives. Two BL-PD samples were inconclusive. Retest was not possible due to lack of sample and they were excluded from analysis.

Of the 20 BL-SWEDD samples, we found 4 positive, 15 negative, and 1 inconclusive. Second DaTscans available at V10 (4 years from BL) of the negatives were normal. Interestingly, two of the four α-S-SAA-positive SWEDD subjects (#3050 and #3101) showed a substantial increase in dopaminergic degeneration by DaTscans at 42 and 46 months after enrollment, with substantial putamen deficits consistent with a PD diagnosis (Fig. 1B). After α-S-SAA analysis and after reviewing all longitudinal, clinical, and imaging data, the PPMI analytic cohort consensus committee decided to change the enrollment diagnosis of #3050 and #3101 from SWEDD to PD.

Our results indicate that the optimized α-S-SAA is highly accurate compared to the gold standard (longitudinal, clinical, and imaging data). The potential value of unbiased α-S-SAA results in a clinical setting can be appreciated in cases with disputable diagnosis, such as the two α-S-SAA-negative clinical PD patients (reclassified as non-PD) and the two α-S-SAA-positive SWEDD cases (reclassified as PD). The α-S-SAA-positive HC with probable RBD is in agreement with recent reports showing prodromal PD diagnosis.

FIG. 1. α-Synuclein seed amplification assay (α-S-SAA) results of the 140 cerebrospinal fluid (CSF) samples and DaTscan images of α-S-SAA-positive scans without evidence of dopaminergic deficit (SWEDD) patients. (A) The data analysis algorithm produced a trinary qualitative outcome (positive, inconclusive, and negative), which was graphed for all 60 healthy control (HC), 60 Parkinson’s disease (PD) and 20 SWEDD CSF samples. Each bar represents the α-S-SAA result for a sample from a patient collected at a given time point (BL for baseline and V08 for visit 08). Reclassified PD patients are shown in grey; one was reclassified as multiple system atrophy (MSA) confirmed by postmortem pathological examination and the other one as unknown non-PD clinically. SWEDD patients whose abnormal brain scans were predicted by the optimized α-S-SAA 42 and 46 months (mo) before the abnormal DaTscans are indicated with an asterisk (*). (B) Transverse DaTscan from patient #3050 at BL was considered borderline normal by visual inspection and abnormal 42 months later at visit 10 (V10). BL scan (2010/09/23) showed slightly asymmetric uptake with heterogenous appearance left striatum with specific binding ratio (SBR) lowest putamen equal to 1.04. V10 scan (2014/03/05) shows significant bilateral reduction, with the greatest changes in the left striatum. Within 4 years, there was a significant 25% SBR reduction (SBR-V10 = 0.78). Transverse DaTscan from patient #3101 at BL was considered borderline normal by visual inspection and abnormal 46 months later. BL scan (2010/10/21) was read borderline normal with rotation effect creating a faux reduction in the left putamen (BL-SBR lowest putamen = 1.02). V10 scan (2014/08/22) shows decided asymmetric signal loss, bilateral, with greatest involvement of signal loss on the left, with relatively preserved right caudate. Within 4 years, there was a significant 47% SBR reduction (SBR-V10 = 0.54).

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A Role of Aging in the Progression of Cortical Excitability in Benign Adult Familial Myoclonus Epilepsy type 1 Patients

Recent molecular genetic studies have revealed that abnormal intronic TTTTA and TTTCA repeat expansion in sterile alpha motif domain containing 12 (SAMD12) causes benign adult familial myoclonus epilepsy (BAFME) type 1. This provides evidence of an inverse correlation between the expanded repeat sizes and seizure onset age. However, the effect of non-coding expanded repeat length on symptom progression during the late lifetime stage remains obscure. This knowledge gap is of interest given that cortical excitability gradually worsens during late-stage BAFME.

We evaluated 18 patients with genetically diagnosed BAFME type 1 and previously identified abnormal TTTTA and TTTCA repeat lengths (Table S1). Partial correlation analyses were conducted for internal correlations among cortical excitability (amplitudes of early components of cortical somatosensory-evoked potential [SEP], ie, N20, P25, and N33),3 aging (current age at SEP examination), and genotype (sum of the expanded TTTTA and TTTCA repeat sizes).3 We also investigated the associations among patients’ age, genotype, and an enhanced long-loop reflex (C-reflex).

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.