Altered age-linked regulation of plasma DYRK1A in elderly cognitive complainers (INSIGHT-preAD study) with high brain amyloid load

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Abstract
Introduction: An effective therapy has not yet been developed for Alzheimer’s disease (AD), in part because pathological changes occur years before clinical symptoms manifest. We recently showed that decreased plasma DYRK1A identifies individuals with mild cognitive impairment (MCI) or AD, and that aged mice have higher DYRK1A levels.

Methods: We assessed DYRK1A in plasma in young/aged controls and in elderly cognitive complainers with low (L) and high (H) brain amyloid load.

Results: DYRK1A level increases with age in humans. However, plasma from elderly individuals reporting cognitive complaints showed that the H group had the same DYRK1A level as young adults, suggesting that the age-associated DYRK1A increase is blocked in this group. L and H groups had similar levels of clusterin.

Discussion: These results are reflective of early changes in the brain. These observations suggest that plasma DYRK1A and not clusterin could be used to classify elderly memory complainers for risk for amyloid beta pathology.

KEYWORDS
aging, Alzheimer’s disease, blood marker, immunometric test

1 INTRODUCTION

Current clinical diagnosis of Alzheimer’s disease (AD)-type dementia relies on experienced clinicians using a battery of cognitive tests combined with various structural and functional imaging and cerebrospinal fluid (CSF) biomarkers to inform a judgment-based decision. A definitive AD-type dementia diagnosis is possible only post-mortem, with histologic examination of AD brain tissue during autopsy showing significant evidence of extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau. However, deposition of Aβ plaques can start up to 20 years before the onset of symptoms.1,2
Numerous AD drug candidates have failed clinical trials because they have been unsuccessful in reversing symptoms or slowing progression of the disease in symptomatic patients. One reason for the failure of these candidates may be that they were not administered during the preclinical phase of disease. However, it is a challenge to diagnose individuals during the preclinical phase, when they are cognitively normal. Therefore, biomarkers that can identify individuals at high risk of developing clinical AD are needed.

Along with a number of collaborators, we are participating in the INSIGHT-preAD Study. This study is designed to identify risk factors for and markers of progression to clinical AD in asymptomatic at-risk individuals. In this study, participants received follow-up, clinical, cognitive, and psychobehavioral assessments every 6 months; neuropsychological assessments, electroencephalography (EEG), and actigraphy every 12 months; and magnetic resonance imaging (MRI) and 18F-FDG (fluorodeoxyglucose) and 18F-florbetapir positron emission tomography (PET) every 24 months.

We recently showed in a well-characterized cohort of AD and age-matched controls that plasma DYRK1A levels are reduced in individuals with oligosymptomatic AD and with dementia due to AD. Additional validation of DYRK1A levels in two unrelated AD patient cohorts with age-matched controls showed that decreased levels of plasma DYRK1A are associated with AD, and decreased DYRK1A is already observed in individuals with mild cognitive impairment.

Other factors associated with AD are of potential interest for relationships to DYRK1A. Many studies have reported an association between plasma homocysteine level and AD-related cognitive decline: A landmark study including 1092 elderly participants in the Framingham cohort who were free from cognitive impairment at baseline revealed a strong concentration-related effect of baseline tHcy (total homocysteine), with no obvious threshold, with the risk of incident dementia up to 11 years later. In a mouse model of hyperhomocysteinemia with decreased liver DYRK1A and treated with an adeno-Dyrk1a construct, we showed an association between DYRK1A and levels of apolipoproteins, including ApoJ (clusterin) (another apolipoprotein, apoe, is a primary genetic determinant of AD risk). Plasma proteomic studies associated with CSF and PET measures of AD pathology show that clusterin is nominally yet significantly associated with CSF Ap42, which is associated with early brain atrophy in AD. A longitudinal follow-up of patients with AD established that plasma clusterin could serve as a biomarker for severity of cognitive decline. However, the link between plasma DYRK1A and plasma clusterin has not been fully explored.

These results suggest two questions: is there already a visible decrease in DYRK1A in memory complainers with no dementia, and when does this difference appear in the general population? To address these questions, in this study we first compared plasma DYRK1A levels between young adults and older individuals. We then analyzed plasma samples from elderly cognitive complainers from the INSIGHT cohort to assess levels of DYRK1A and clusterin proteins in comparison with imaging biomarkers for Aβ load.
TABLE 1  Demographic data

| Demographic and clinical data of studied groups | Controls | AD |
|-----------------------------------------------|----------|----|
| Cohort I                                       |          |    |
| Number of subjects                            | 20       | 20 |
| Female-male                                   | 16f/4m   | 16f/4m |
| Age (years)                                   | 75,3     | 58 |
| MMSE                                         | 28,7     | 21,6 |
| DYRK1A                                       | 1065     | 573 |
| Cohort II                                     |          |    |
| Number of subjects                            | 20       | 20 |
| Female-male                                   | 6f/14m   | 10f/10m |
| Age (years)                                   | 24,5     | 76 |
| DYRK1A                                       | 747      | 1156 |
| CLU                                           | 103,2    | 104,5 |
| Cohort INSIGHT                                |          |    |
| Number of subjects                            | 230      | 88 |
| Female-male                                   | 145f/85m | 56f/32m |
| Age (years)                                   | 75,7     | 76,8 |
| MMSE                                         | 28,74    | 28,48 |
| APOE ε4                                       | 29 (13%) | 33 (38%) |
| DYRK1A                                       | 1063     | 723 |
| CLU                                           | 98,6     | 99,1 |

Abbreviations: DYRK1A, pg/mL; CLU, ng/mL; MMSE, Mini-Mental State Examination.

2.2  Blood sampling and storage

For new proteomics studies in blood, plasma is recommended because of the variable nature of coagulation processes. For each participant, 10 mL of venous blood in BD Vacutainer lithium heparin tubes (BD Biosciences, Franklin Lakes, NJ, USA) was collected and used for all subsequent immunological analyses. Blood samples were taken in the morning after a 12-hour fast, handled per standard protocols, and centrifuged for 15 minutes at 2000 x g at 4°C. For each sample, the plasma fraction was collected, homogenized, aliquoted into multiple 0.5-mL sterilized cryovial tubes, and stored at −80°C within 2 hours of collection.

2.3  Immunometric tests

Immuoassay plates were obtained by spotting biotinylated AC4 (from a set of seven monoclonal antibodies raised against a short form of DYRK1A, 1-502 aa) on MSD GOLD Small Spot Streptavidin 96-well plates (Meso Scale Diagnostics, Rockville, MD, USA). After incubation with plasma samples or calibrator samples (serial dilution of DYRK1A protein) MSD GOLD SULFO-TAG conjugated detection antibody (AC6) was used to quantify DYRK1A protein levels on a Meso QuickPlex SQ120 instrument (Meso Scale Diagnostics) using electrochemiluminescence detection. Plasma samples underwent a single freeze-thaw cycle before analyses, and all samples were analyzed in duplicate with a coefficient of variability acceptance criteria of <20%.

2.4  Statistical analysis

Data are presented as mean ± standard deviation (SD) or median with interquartile range (IQR). D’Agostino and Pearson omnibus normality test was used for all data and Mann-Whitney U-test was chosen for comparisons between groups. Correlations between DYRK1A levels and SUVR were assessed for each marker using Spearman’s (non-parametric) test. P-values of < .05 for intergroup comparisons and < .01 for correlations were considered statistically significant. Graphs were prepared with GraphPad Prism software (version 6, La Jolla, CA, USA).

3  RESULTS

3.1  DYRK1A differences in AD patients

Using a sandwich enzyme-linked immunosorbent assay (ELISA) and seven monoclonal antibodies previously described, we assessed the best combination of capture and detection antibodies to maximize signal and decrease background noise. The selected sandwich (AC4 as a capture antibody and AC6 as a detection antibody) was used to analyze DYRK1A levels in Cohort I of AD patients characterized with PET amyloid-positive signals and decreased MMSE as well as in controls.
3.2 Age effect on plasma DYRK1A and clusterin levels

We also compared plasma DYRK1A levels of a group of 20 young individuals (mean age: 24.5 years) and a group of 20 older individuals chosen randomly among memory complainers with low SUVR (mean age: 76 years) in cohorts II and III. DYRK1A levels were significantly higher in older individuals than young individuals (Figure 2A). However, clusterin levels did not significantly differ between age groups (Figure 2B). Furthermore, linear regression analysis did not show any correlation between DYRK1A level and age within either age group (data not shown).

3.3 Plasma DYRK1A is decreased in Aβ-positive individuals

We further assessed DYRK1A levels in human plasma from elderly cognitive complainers in the INSIGHT cohort. Results were stratified by Aβ status, with high SUVR (SUVRH; >0.7918) considered Aβ-positive and SUVR low (SUVRL; >0.7918) considered Aβ-negative.4 The SUVRH group had significantly decreased DYRK1A levels compared to the SUVRL group at both 0 and 36 months (Figure 3A,B). Results were the same when stratified by sex (data not shown). Diagnostic accuracy (area under the curve) of DYRK1A levels in differentiating SUVRL and SUVRH individuals showed a significant relationship between DYRK1A and Aβ load with \( P < .0001 \) and area under curve of 0.66.

Results were also stratified by neurodegeneration status from \( ^{18} \text{F}-\text{FDG} \) SUVR, with SUVR >2.2 indicating a negative status (N−) and SUVR <2.2 indicating a positive status (N+). Both N− and N+ groups had similar levels of DYRK1A (Figure 3C). When stratified by APOE genotype, groups without or with APOE ε4 also had similar DYRK1A levels (Figure 3D). Furthermore, linear regression analysis between SUVR values and DYRK1A levels did not reveal a significant correlation (data not shown).

3.4 Clusterin is not modified in cognitive complainers with amyloid load

We also assessed clusterin levels in human plasma from elderly cognitive complainers in the INSIGHT cohort. Stratified by Aβ status/SUVR, results for SUVRH and SUVRL groups showed similar plasma levels of clusterin at 0 and 36 months (Figure 4A,B). When stratified by neurodegeneration status, both N− and N+ groups also presented similar levels of clusterin (Figure 4C).

4 DISCUSSION

We have established an ELISA-based technique to quantify DYRK1A levels in human plasma. Use of this technique confirmed our preliminary observations obtained with two different techniques, slot blot and solid-phase immobilized epitope immunoassay, on two other cohorts of controls and AD patients showing that DYRK1A levels are lower in plasma of AD patients than controls.5,6 AD starts silently and develops several years before clinical symptoms appear. Until recently, it has...
be difficult for physicians to predict which individuals with memory problems will eventually develop AD and which will not. Furthermore, even when clinical symptoms of dementia are present, clinical diagnosis of AD is reported to be correct only 65% to 96% of the time. Accuracy rates tend to be especially low in earlier stages of AD. Memory complaints can result from several causes and may be reversible, but it is especially difficult to discriminate AD in early stages from other types of dementia, depression, or even normal aging. Therefore, new diagnostic tools to help detect AD as early as possible with the highest level of certainty are of fundamental importance for physicians, patients, and families involved.

We have applied our technique to the INSIGHT cohort of memory complainers. A $^{18}$F-florbetapir-PET SUVR threshold of 0.7918 was used because imaging shows that a fraction of this population has an Aβ-positive signal, suggesting that plaque loads are present in this group. Stratifying the cohort with imaging results by SUVR values

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**Figure 3** DYRK1A protein levels in plasma from 318 cognitively normal individuals with subjective memory complaints in the INSIGHT cohort. DYRK1A protein levels stratified by amyloid status [SUVR low (SUVR L) or standardized uptake value ratio (SUVR) high (SUVR H)] at time 0 months (A) or 36 months (B). DYRK1A protein levels stratified by neurodegeneration status [SUVR > 2.2 negative status (N−) or SUVR < 2.2 positive status (N+)] (C) or APOE genotype (D). Bars indicate mean ± standard error of the mean (SEM). **P < .01, ***P < .001

**Figure 4** Clusterin protein levels in plasma from 318 cognitively normal individuals with subjective memory complaints in the INSIGHT cohort. Clusterin protein levels stratified according to amyloid status [SUVR low (SUVR L) or SUVR high (SUVR H)] at time 0 (A) or 36 months (B). (C) Clusterin protein levels stratified by neurodegeneration status [SUVR > 2.2 (N−) or SUVR < 2.2 (N+)]. Bars indicate mean ± SEM.
showed that lower plasma DYRK1A levels were observed among memory complainers with increased Aβ load, and these values were similar at 0 and 36 months. Neurodegeneration status of the INSIGHT cohort was characterized by assessing 18F-FDG PET brain metabolism in AD-signature regions—subjects were considered N+ if mean 18F-FDG PET of the four AD-signature regions had SUVR < 2.27. However, plasma DYRK1A level was similar for N− and N+ individuals, indicating that the difference is not linked to neurodegeneration status.

Because we previously observed a relationship between DYRK1A and clusterin levels in mouse models and many reports have investigated a possible relationship between clusterin plasma levels and risk of dementia,12 we also analyzed clusterin levels in memory complainers with SUVRH or SUVRL. No significant variation was detected. Nonetheless, this result agrees with a large study concluding that clusterin level is only positively associated with risk of dementia and AD in individuals >80-years-old and is probably a response to brain injury.16 Therefore, clusterin level does not seem to be modified in early stages of neuronal changes with Aβ positivity and/or in N+ individuals.

The observation of low DYRK1A levels in Aβ-positive brains suggest three possibilities: (1) a specific factor of environmental or genetic modification induces decreased DYRK1A in the group with increased Aβ load. (2) genetic variability induces constitutional variability for DYRK1A level, or (3) there is a normal increase of DYRK1A level during aging, and this increase is not observed in the part of the population that is at risk of developing Aβ pathology. We previously observed a DYRK1A increase in the brain of wild-type mice when comparing 4-month-old mice with 12 and 17-month-old mice.7 In mice this increase appears progressive with age: compared to the level at 4 months, DYRK1A level is increased 120% at 12 months and 140% at 17 months. This increase is also associated with increased GFAP (Glial fibrillary acidic protein), which is indicative of gliosis, a process highly related to brain damage and aging.18

Comparison of plasma from young adults to SUVRL individuals from the INSIGHT cohort shows that, as observed in mice, DYRK1A levels increase with aging in the normal population. Thus, we hypothesize that dysregulation of the regulatory mechanisms that induce this increase in normal individuals maintains DYRK1A levels of the SUVRH group at the level observed in younger individuals. Increased DYRK1A in aged individuals without high Aβ load might be indirectly associated with aging or directly caused by aging. Furthermore, the variation due to aging is similar in mice (140%) and in humans (130%). During aging, various molecular alterations take place, so increased DYRK1A could be a protective mechanism for aging.

Among the many functions proposed for DYRK1A, three are related to such a potential protective role. First, DYRK1A controls activation of NFκB and IKK levels and thus may be considered an anti-inflammatory protein, and numerous reports show a link between aging and increased inflammation. During aging, activation of neuroinflammation is largely redox-mediated through redox sensitivity of key inflammatory components such as NFκB and the inflammasome.19 A genetically modified mouse model has established a link between DYRK1A levels and NFκB.20,21 Moreover, through participation in the regulatory circuit DYRK1A/Ca2+/NFAT, DYRK1A contributes to fine-tuning of angiogenesis, deregulation of which participates in inflammation.22 Furthermore, neuroinflammation is widely recognized as a crucial process that participates in AD pathogenesis,23 and in AD there are also peripheral traces of this inflammatory status.24

The second protective role of DYRK1A is linked with DNA damage at two different levels. First, decreased endogenous DYRK1A leads to hypophosphorylation of SIRT1, thereby sensitizing cells to DNA damage–induced cell death.25 Second, DYRK1A phosphorylates the ubiquitin ligase RNF169 and modifies its ability to displace 53BP1, a mediator of non-homologous end joining, from sites of DNA damage, so DYRK1A depletion increases cell sensitivity to ionizing irradiation.26,27 Further genomic analysis of APOE e4 non-carriers have identified AD-associated genophenotypes of SIRT128 and SIRT2.29

The third protective role of DYRK1A is linked to a relationship with telomere shortening, as increased DYRK1A is associated with increased sirtuin activity and thus should protect against telomere shortening. Furthermore, telomere length and stability have been associated with pathology in histopathological studies of AD patients.30,31 Altogether, these potential roles indicate that impairment of the protective role of DYRK1A might contribute to Aβ plaque formation.

Similar to results in mice, our results in humans also indicate that there is an age-induced progressive increase of plasma DYRK1A, which might have a protective role. Modified environmental and/or genetic factors might dysregulate this age-related increase, thereby exposing individuals with low DYRK1A to more inflammation, DNA damage, and telomere shortening. However, increasing DYRK1A levels may be sufficient to delay or protect against these alterations. Our observations also reinforce the link between DYRK1A levels with formation of Aβ plaques and AD onset. These results suggest that DYRK1A-targeted intervention may lead to novel preventive treatments. However, to exclude the possibility of confounding factors such as ethnicity and socioeconomic status interacting with our results supporting an age-related hypothesis, further comparison of other larger age groups (20-80 years) is needed to determine the profile of DYRK1A increase in the normal population and to establish if low plasma DYRK1A levels in aged people might be a risk factor for Aβ plaque formation long before development of dementia.

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CONFLICTS OF INTEREST
Bruno Dubois has received consultancy fees from Biogen, Boehringer Ingelheim and Eli Lilly, and grants for his institution from Merck, Pfizer, and Roche. The other authors declare no competing interests.

ETHICS STATEMENT
Written informed consent was obtained from all participants before inclusion in the study. The medical ethics committee at each site approved the study.
AUTHOR CONTRIBUTIONS

Jean M. Delabar and Marie-Claude Portier contributed to study concept and design. Bruno Dubois initiated INSIGHT study. Marion Ortnerr and INSIGHT preAD study group contributed to sample collection/selection. Stephanie Simon, Cecile Feraudet-Tarisse, and Anne Wijhhusien produced and characterized antibodies. Jonathan Pegon, Emma Vidal, and Yael Hirschberg participated in data collection. Jean M. Delabar and Marie-Claude Portier carried out data analysis and interpretation.

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