Reduced brain amyloid burden in elderly patients with narcolepsy type 1

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Running Head: Amyloid load in narcolepsy

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Abstract

Objective: To determine whether brain amyloid burden in elderly patients with narcolepsy type 1 (NT1) is lower than in controls, and to assess in patients with NT1 the relationships between amyloid burden, cerebral spinal fluid (CSF) markers of Alzheimer's disease (AD), CSF orexin-A, and cognitive profile.

Methods: Cognitive and ^{18}F-florbetapir-positron emission tomography (PET) data were compared in patients with NT1 aged ≥65 years (n=23) and in age- and sex-matched controls free of clinical dementia selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI, n=69) and the Multi-domain Intervention Alzheimer's Prevention Trial (MAPT-AV45; n=23) cohorts. The standardized uptake values (SUV) of the cortical retention index for six regions of interest were computed and averaged to create a mean SUV ratio normalized to three subcortical reference regions (cerebellum, pons and a composite region). A cortical/cerebellum SUV ratio ≥1.17 defined positive PET amyloid.

Results: Lower cortical amyloid burden was observed in the NT1 than in the ADNI and MAPT-AV45 groups (mean cortical/cerebellum SUV ratios: 0.95±0.15, 1.11±0.18 ($p<0.0001$), and 1.14 ±0.17 ($p=0.0005$), respectively). Similar results were obtained with all subcortical reference regions and for all cortical regions of interest, except cingulum. Only one patient with NT1 (4.4%) had positive PET-amyloid compared with 27.5% in the ADNI and 30.4% in the MAPT group. In the NT1 group, cortical or regional amyloid load was not associated with CSF orexin-A, CSF AD biomarkers or neuropsychological profile.

Interpretation: Lower brain amyloid burden, assessed by ^{18}F-florbetapir-PET, in patients with NT1 suggests delayed appearance of amyloid plaques.

Key words: narcolepsy, orexin, amyloid, Alzheimer, biomarkers, sleep, amyloid-PET

Introduction

Positron emission tomography (PET) imaging with tracers that bind specifically to amyloid-β (Aβ) aggregates can be used to quantify the accumulation of amyloid plaques, many years before the clinical symptoms of Alzheimer's disease (AD)[1 2]. The dynamics of Aβ changes and the large variability in progressive cognitive decline remain mostly unclear in subjects at risk for AD[3 4]. Recent findings showed interactions between Aβ peptides and sleep/wake patterns with efficient convective clearance of Aβ during deep sleep and Aβ accumulation in brain interstitial fluid during wakefulness[5 6 7]. Increased neuronal activity during wakefulness might promote AD development, with a strong relationship with a wake-promoting peptide named orexin-A/hypocretin-1[8]. Specifically, in transgenic mice that overexpress amyloid precursor protein (APP), Aβ level increases during wakefulness and after orexin-A infusion and decreases during sleep and after infusion of an orexin-A receptor antagonist[8]. In APP/presenilin 1 (PS1) transgenic mice in which the orexin gene also is knocked out, Aβ brain load is decreased and sleep time is increased[9]. Moreover, sleep deprivation by rescue of orexinergic neurons in these mice increases the amount of brain Aβ[9].

Conversely, results on orexin-A levels in cerebrospinal fluid (CSF) samples from patients with AD are conflicting. In a post-mortem analysis, the number of orexin neurons in the hypothalamus and the concentration of orexin in ventricular CSF were reduced in patients with AD compared with controls [10]. However, higher CSF orexin-A levels were observed in patients with AD compared with controls [11-13]. Moreover, in one study, CSF orexin-A levels were correlated with tau protein levels and sleep-wake alterations in patients with AD. [13] Recently, an experimental study showed that suppression of slow-wave sleep increased CSF Aβ concentrations the following day [14]. Altogether, these data suggest that sleep-wake cycle abnormalities and orexin levels may influence amyloid clearance and brain amyloidosis.

Narcolepsy type 1 (NT1) is an orphan chronic disease characterized by excessive daytime sleepiness (EDS), cataplexy, and caused by the destruction of orexin neurons[15 16]. It represents an interesting model to improve our understanding of the relationship between Aβ and the orexin pathways. NT1 typically starts in the teens or twenties[17]. Therefore, these patients could be partially protected from AD, a disease that develops and progresses over several years prior to clinical symptoms. Only one post-mortem study addressed this hypothesis by analyzing the presence of neuropathological lesions consistent with AD in brain tissues from few patients with narcolepsy-cataplexy. It reported that 33% of patients had AD lesions, a proportion similar to what expected in the general population[18]. However, data on the narcolepsy phenotype, cerebrospinal fluid (CSF) orexin-A levels and orexinergic neurons quantification were not available, except for one patient.

Therefore, to determine whether elderly patients with NT1 have a lower brain amyloid burden and lower AD risk compared with age- and sex-matched controls free of clinical dementia, we used brain PET with ^{18}F-florbetapir, which binds to Aβ with high affinity and specificity. We also assessed in the NT1 group the relationships between Aβ load, and CSF-AD markers, CSF orexin-A level, and cognitive profile.

Methods

Patients

We recruited 23 consecutive patients with NT1 older than 65 years of age (14 men and 9 women; median age 71, range 65-86 years) at the Reference National Center for Narcolepsy of Montpellier, France. NT1 was diagnosed according to the ICSD-3 criteria[19]: EDS, clear-cut cataplexy and mean sleep latency on the Multiple Sleep Latency Test (MSLT) ≤8 minutes with ≥2 sleep onset rapid eye

movement sleep periods (SOREMPs) and/or CSF orexin-A level <110 pg/ml (in all 20 patients who underwent lumbar puncture). All patients had the HLA DQB1*06:02 genotype.

A standardized face-to-face clinical examination and interview evaluated the body mass index (BMI), the medical history, the age at NT1 onset and at diagnosis, EDS severity with the Epworth Sleepiness Scale (ESS)[20], cataplexy frequency, depressive symptoms using the Beck Depression Inventory scale [21] and health-related quality of life with the European Quality of Life Five Dimensions (EQ5D) scale [22]. The use of stimulants and anti-cataplectic drugs was recorded. A semi-structured interview of the patient and a reliable informant (e.g., family member) focused on six domains of cognitive and functional performance (i.e., Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care) was used to establish the 5-point Cognitive Dementia Rating (CDR™) scale score (i.e., 0= Normal; 0.5 = Very Mild Dementia; 1 = Mild Dementia; 2 = Moderate Dementia; 3 = Severe Dementia)[23]. The comprehensive neuropsychological evaluation included the presence of memory complaint based on clinical interview, the Mini Mental State Examination (MMSE), Free and Cued Selective Reminding Test (FCSRT-16 items), a verbal fluency test, a counting span test, Trail Making Test A and B (TMT-A and B), Frontal Assessment Battery (FAB) test, Rey-Osterrieth Complex Figure Test, and Praxis and Motor planning assessment. All patients underwent ^{18}F-florbetapir-PET brain imaging.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants gave their written informed consent to participate in this study that was approved by the Montpellier University Hospital ethics committee (www.clinicaltrials.gov NCT03378453).

Controls

Two age- and sex-matched control groups free of clinical dementia were selected from two different cohorts. The first group was selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI) after the scientific committee's agreement. Paired cases (three controls for each patient with NT1) were defined as cognitively normal subjects or with only subjective memory complaints (CDR = 0 or 0.5), and with available brain ^{18}F-florbetapir-PET data. Their MMSE score ranged from 24 to 30, and the subjective memory complaint score was 16 or higher for the first 12 questions of the Cognitive Complaint Index [24]. The second age- and sex-matched control sample was selected from the Multi-domain Intervention Alzheimer's Prevention Trial-AV45 PET ancillary study cohort (MAPT-AV45; www.clinicaltrials.gov NCT00672685)[25]. The selected participants (one control for each patient with NT1) were defined as cognitively normal or with subjective memory complaint (CDR = 0 or 0.5), and with available ^{18}F-florbetapir-PET data. Neuropsychological evaluations included the MMSE, FCSRT-16, Wechsler Adult Intelligence Scale-revised (WAIS-R) and Category Naming Test.

Main study outcome: Assessment of Aβ brain deposition by ^{18}F-florbetapir-PET imaging

The PET image acquisition procedure was similar in the NT1 and MAPT-AV45 groups. Imaging was performed for 15min at 50 min after injection of 370 MBq ^{18}F-florbetapir. Images were reconstructed using 3D OSEM (24 subsets, 12 iterations) followed by Gaussian post-filtering with 5mm Full Width at Half Maximum (FWHM). As concurrent structural MRI data were not available for most patients, PET images were spatially normalized to the standard Montreal Neurological Institute (MNI) space by co-registration to a generic T1-weighted MRI template using SPM12[26].

The ^{18}F-florbetapir-PET data for the ADNI group consisted of 4×5 min frames acquired at 50–70min after ^{18}F-florbetapir injection. They were realigned, averaged, resliced onto a common voxel size, and smoothened with an 8mm FWHM Gaussian kernel[27]. Structural MRI images acquired concurrently with the baseline ^{18}F-florbetapir-PET images were used as a structural template to spatially normalize

the PET images. Briefly, for each subject, the baseline ^{18}F-florbetapir-PET images were rigidly co-registered with the baseline structural T1-weighted MRI images by maximizing the normalized mutual information. The individual T1-weighted MRI images were non-linearly co-registered to the standard MNI-space MRI template using tissue probability maps delivered with SPM. Non-linear transformation was then used to spatially normalize the co-registered PET images to the MNI space. To compare PET data with consistent resolutions, images of the NT1 cohort were post-smoothened using a proper Gaussian kernel to adjust their final resolution to that of post-processed PET data for the ADNI group (8 mm). The final resolution of the available PET data for the MAPT-AV45 group was slightly lower (9.5 mm) due to systematic post-smoothing using SPM12.

For each subject, the ^{18}F-florbetapir-PET voxels were labeled according to the maximum probability atlas derived from the "MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling" and provided by Neuromorphometrics, Inc. (neuromorphometrics.com) under academic subscription. The standardized uptake values (SUV) of the cortical retention index were computed in six cortical regions of interest (i.e., frontal, parietal, temporal, precuneus, anterior and posterior cingulate cortices) and were averaged to create a mean cortical SUV that defines the amyloid load. Cortical SUV ratios (SUVr) were obtained by normalizing the cortical SUV with the mean uptake in a reference region. For the present study, subcortical reference regions were the whole cerebellum (for the three groups), and the pons, and a composite region (i.e., the whole cerebellum, pons, and eroded subcortical white matter) for the NT1 and ADNI groups[28]. Thus, the following SUVr were used: cerebellar (with the previously validated cut-off of 1.17)[25], pontine, and composite SUVr. PET images were also visually assessed by three observers and classified as Aβ positive or negative, as previously described[29].

CSF biomarker assessments

CSF samples were collected retrospectively in 20 patients with NT1, and aliquots frozen and stored immediately at -80°C at the Montpellier CSF-Neurobank (#DC-2008-417 of the certified NFS 96-900 CHU resource center BB-0033-00031, www.biobanques.eu). CSF $A\beta_{42}$, $A\beta_{40}$, total-tau and phosphorylated-tau (p-tau 181) levels were measured using the standardized, commercially available Innotest® sandwich ELISA (Fujirebio), as previously described[30]. CSF orexin-A level was determined in duplicate using the I^{125}-radioimmunoassay (RIA) kit from Phoenix Peptide, Inc, according to the manufacturer's recommendations.

Statistical analysis

Clinical and neuropsychological data, and amyloid load (based on SUVr values) were compared in the three groups (NT1, ADNI and MAPT-AV45) using the Wilcoxon matched-pairs signed-rank test for continuous variables, the McNemar's test for binary data, and the Bowker's test of symmetry for categorical data with more than two categories. Spearman's rank order correlations were used to determine associations between continuous variables. A correction for multiple comparisons for the SUVr values was applied using the False Discovery Rate (FDR) procedure. Significance level was set at $p<0.05$. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the different groups

Among the 23 patients with NT1, 4 (17.4%) were obese, 14 (66.6%) had persistent sleepiness (ESS>10) and 19 (82.6%) took psychostimulant medications (mainly modafinil, methylphenidate and sodium oxybate). Moreover, 17 (73.9%) had a history of cardiovascular disease (mainly hypertension),

and two (8.6%) reported depressive symptoms (Table 1). Thirteen patients had a cognitive complaint (56.5%), including seven patients with CDR = 0.5 and one with CDR = 1. Based on the neuropsychological evaluation, 21.7% of patients with NT1 had an episodic memory deficit (i.e., hippocampal syndrome), and 60.9% an executive dysfunction (Table 1). The median [range] scores were 29 [15-30] for the MMSE, 16 [12-18] for the FAB, and 35 [25-36] for the Rey-Osterrieth Complex Figure Test (with a median time to perform the test of 130 seconds [65-330]). No praxis alteration was observed. The only patient with mild dementia (CDR=1) had a past history of stroke and extrapyramidal signs potentially related to vascular damages (MRI Fasekas score equal to 3). Family history of dementia was reported by 13.6% of patients, and adulthood traumatic brain injury by 9%. APOE genotyping in 22 patients with NT1 showed that seven (31.8%) of them were APOEε4 carriers, but none was homozygous for the ε4 allele. CSF AD biomarker analysis (n=20 patients) showed normal CSF p-tau levels in 18 (90%) patients (only two with values >60pg/ml: 70 and 73 pg/ml, respectively), and normal Aβ42 concentration (>500pg/ml) in 17 (85%) patients (300, 309 and 438 pg/ml in the other three patients). These five patients with one AD abnormal biomarker/each did not have episodic memory deficits and their CDR score was 0. The median interval between the lumbar puncture and the PET scan was 1.05 years [0-16.49].

Comparison of the three groups showed that the MMSE score was lower and CDR scores >0 more frequent in the NT1 than in the ADNI control group. Conversely, no difference was found between the NT1 and the MAPT-AV45 groups (Table 2). No between-group difference was found for the presence of the APOE ε4 allele.

Amyloid burden in patients with NT1 and controls

The cortical/cerebellum SUVr values were lower in patients with NT1 than in the two control groups, when assessed as continuous variables ($p<0.0001$) (Table 3, Figure 1). Similar results were obtained for the cortical/pons and cortical/composite SUVr values between the NT1 and ADNI groups. Similarly, the SUVr values of the six cortical regions of interests, regardless of the reference subcortical area, were all lower in the NT1 group than in the ADNI ($p<0.001$) and MAPT-AV45 groups ($p<0.05$, but for the cingulum regions).

Using the validated cortical/cerebellum SUVr cut-off of 1.17, only one patient with NT1 (4.3%) had positive amyloid burden, compared with 27.5% of the ADNI and 30.4% of the MAPT-AV45 controls ($p<0.05$) (Table 3). PET image visual analysis (only for patients with NT1 and MAPT-AV45 controls) confirmed that only one patient with NT1 had an Aβ positive PET compared with six (26.1%) MAPT controls ($p<0.10$) (Table 3).

The only patient with NT1 and Aβ positive PET was a 68-year-old woman with late onset of EDS and cataplexy (i.e., at 60 years of age), normal cognitive profile (no cognitive complaint, amnesia, aphasia, apraxia or agnosia), CDR = 0, MMSE = 30 and FAB, TMT-A and B and FCSRT free and total recall scores in the normal range. Her CSF orexin-A level was 19 pg/ml, tau 148 pg/ml, p-tau 41 pg/ml, $A\beta_{40}$ 7861 pg/ml, and $A\beta_{42}$ 438 pg/ml. MRI imaging revealed no cortical atrophy, normal hippocampal volume (Scheltens score 0, right and left), but some minor white matter hyperintense lesions (Fazekas score of 1). Fluorodeoxyglucose-PET imaging highlighted a mild left parietal hypometabolism that did not reach the pathological threshold.

A sub-analysis after exclusion of all participants with CDR ≥0.5 (i.e., 8 patients with NT1, 6 ADNI and 11 MAPT-AV45 controls) confirmed lower cortical/cerebellum SUVr values in the NT1 than in the two control groups ($p<0.0006$). We performed another subanalysis in excluding all participants with abnormal CSF Aβ42 concentration from the NT1 and ADNI populations (i.e. 3 patients with NT1 and

28 subjects from ADNI; no CSF available in the MAPT-AV45 population) and confirmed lower cortical/cerebellum SUVr values in the NT1 than in the ADNI group (0.92 ± 0.10 vs 1.02 ± 0.10, p=0.0007). None of the 6 subjects from ADNI cohort with a CDR at 0.5 had abnormal CSF Aβ42 levels The SUVr values were lower in the NT1 than in the two control groups for the six cortical regions of interest, but for the cingulum regions when comparing the NT1 and MAPT-AV45 groups, and regardless of the subcortical reference area (cerebellum, pons, composite areas) for the comparison between the NT1 and ADNI groups.

Finally, in patients with NT1, no association was found between cortical or regional SUVr values and CSF orexin-A and AD biomarkers or neuropsychological assessment results. No correlation was found between NT1 duration and CSF levels of tau, p-tau and Aβ42.

Discussion

Using ^{18}F-florbetapir-PET and the semi-quantitative cortical SUVr method, we found lower levels of cortical amyloid burden in elderly patients with NT1 than in two age- and sex-matched control groups free of clinical dementia (ADNI and MAPT-AV45). Using the validated cortical/cerebellum SUVr cut-off, only one patient with NT1 (4.3%) had Aβ positive PET compared with 27.5% of the ADNI and 30.4% of the MAPT-AV45 controls. Finally, in patients with NT1, we did not find any association between cortical/regional amyloid load and CSF orexin-A levels, CSF Aβ42 or Aβ40 concentration or neuropsychological profile.

^{18}F-florbetapir-PET is a reliable tool to identify subjects at greatest risk of AD, because amyloid plaque deposition begins many years before the detection of cognitive and non-cognitive symptoms [31]. Several clinical-histopathological studies highlighted ^{18}F-florbetapir-PET high affinity and specificity for Aβ and the correlation with the amyloid burden at autopsy [31]. The low levels of cortical Aβ in elderly patients with NT1 suggest a reduced risk for progression to AD. The only patient with NT1 and Aβ positive PET was remarkable due to the late disease onset (60 years of age when normally is before the age of 30) and the normality of her neuropsychological profile. Conversely, among the ADNI and MAPT-AV45 controls, 27.5% and 30.4%, respectively had Aβ positive PET. These results are in agreement with most studies on healthy controls [32 33]. More than half of patients with NT1 reported cognitive complaints, in agreement with the literature [34]. We diagnosed mild dementia (CDR equal to 1) in one patient with NT1 and normal amyloid-PET, in a context of cerebrovascular and Parkinson's disease.

For this study, we used both a manual visual and a semi-quantitative (SUVr) approach to evaluate Aβ load and then compare the three groups. For the semi-quantitative approach, we focused on six cortical regions and used three reference subcortical regions (cerebellum, pons, and the most sensitive composite areas), when possible, and the validated cortical/cerebellum SUVr cut-off of 1.17 [25 29]. We obtained similar results (i.e., lower amyloid load in NT1, except for the cingulum between the NT1 and MAPT-AV45 groups) with the different approaches, although the manual visual analysis is a less accurate method[29]. As Aβ load could be influenced by cognitive status alterations, we performed additional analyses after exclusion of all people with a CDR score ≥0.5 to retain only people with normal cognitive status and confirmed the previous results. We also confirmed lower amyloid load in NT1 than in the ADNI group after exclusion of all participants with abnormal CSF Aβ42 levels (i.e. data available in the NT1 and ADNI populations).

To our knowledge, brain amyloid deposition has never been quantified by PET in patients with NT1. However, there are some data on post-mortem neuropathological AD lesions and CSF concentration of AD biomarkers in narcolepsy. The only study with post-mortem neuropathological confirmation evaluated a 75-year-old man with narcolepsy-cataplexy since the age of 12, and cognitive complaint for

8 years [18]. Post-mortem histological analysis showed loss of 85% of orexinergic neurons and extensive plaques and tangles in targeted regions, consistent with AD. The author extended the analysis to another 11 patients with narcolepsy-cataplexy and found that 33% had AD lesions (same prevalence as in the general population). However, in these additional patients, orexinergic neurons and CSF orexin-A levels were not quantified, the clinical records of narcolepsy and cognitive profiles were poorly reported, the cause of the autopsy request and related selection bias were missing, and the mean age at death was very old (81 years, range 75-94)[18]. Some differences between this work and the present study (i.e., detailed phenotype, orexin-A status, age at evaluation, post-mortem neuropathology vs in vivo analysis) could explain the different findings.

Previous studies assessed CSF Aβ levels in small groups of patients with narcolepsy. Discrepancies between their results [35 36 37 38 11 39] can be partially explained by differences in the populations under study (age, disease duration, type 1 vs type 2 narcolepsy, drug-free or not, and choice of controls), the sample size, and also the method used for orexin-A quantification (RIA vs enzyme immunoassays). Some studies reported lower levels of CSF Aβ42 in patients with NT1 and also in patients with NT2 (i.e., who have normal orexin levels) [37 39] , especially in younger patients and with short disease duration . Conversely, other works found normal, or even increased CSF Aβ42 levels [11] in patients with NT1 compared with controls, especially in patients with longer disease duration and with stable stimulants intake [40]. In our study, the long disease duration (median age at onset: 27 years, and median age at time of study: 71 years) and the high frequency of psychostimulant intake in the NT1 group could explain the absence of significant changes in CSF Aβ levels (i.e. normal CSF Aβ42 levels in 17/20 patients with NT1). Analysis of CSF Aβ42 and orexin levels in patients with AD has also led to discordant results[11 41]. We found higher CSF orexin-A levels, but not histamine, in patients with early and advanced AD than in those with other dementia types, with a negative correlation between $A\beta_{42}$ and orexin-A in AD[42]. Similarly, other studies reported increased CSF orexin-A levels in patients with AD at different stages of disease progression[10,11]. Conversely, two other studies showed normal or low CSF orexin-A levels in AD[10,43]. Again, these discrepancies could be explained by differences in methodology, population characteristics, small sample sizes, and the influence of uncontrolled factors, such as sleep-wake states. Altogether, these different findings suggest that orexin-A might influence amyloid clearance and aggregation in the brain. However, other factors could also be involved, such as immunological or neuroinflammatory mechanisms, neuronal activity levels, changes in the glymphatic pathway, and sleep-wake cycle abnormalities.

In the present study, CSF Aβ42 levels were abnormal in three patients with NT1, including the one with positive ^{18}F-florbetapir-PET. However, the neuropsychological test scores were normal in all of them (no hippocampal syndrome and CDR = 0), as well as the MRI images, and CSF tau and p-tau profiles. Although CSF and PET-based Aβ measurement are highly correlated in the literature, some discordances may exist especially in cognitively normal participants, where 15-20% of people have low CSF Aβ and normal amyloid PET[44]. In contrast to PET with tracers that bind to amyloid plaques, the CSF concentration of soluble Aβ could reflect different aspects of AD pathology and be influenced by neuro-inflammation and sleep-wake patterns. Recent studies confirmed that reduced CSF Aβ42 level is an earlier biomarker of AD compared with amyloid PET[45]; however semi-quantitative PET assessment is more powerful for accurate grading of early-stage AD and AD conversion prognosis[46]. The mechanism underlying abnormal amyloid-β metabolism in NT1 remains unclear, but orexin deficiency, neuroinflammation and abnormal sleep-wake patterns could be involved in brain amyloidosis. Although normal orexin-A levels are certainly not a prerequisite for AD pathogenesis, we could hypothesize that long-term loss of orexin signaling affects the balance between Aβ production and degradation/clearance and that in patients with NT1 the risk of developing AD could be reduced or the appearance of amyloid plaques and related disease symptoms delayed.

The present study has some strengths, particularly the well-defined phenotype of patients with NT1, all with clear-cut cataplexy (CSF orexin-A measurements for 87% of them to confirm the diagnosis) and a comprehensive neuropsychological evaluation. We assessed amyloid pathology by measuring CSF

Aβ42 and Aβ40 levels and also by using brain ^{18}F-florbetapir-PET. The method used to analyze the ^{18}F-florbetapir-PET images was the same for the three groups (NT1, ADNI and MAPT-AV45), and included the most sensitive and reliable quantification assessment to increase the diagnostic performance.

Some limitations also need to be acknowledged, particularly the limited number of patients with NT1. However, NT1 is an orphan disease and only subjects older than 65 years of age were included. As concurrent MRI brain imaging data were available only for four patients with NT1, with long time intervals between the MRI and the PET data acquisition (median interval of 1581 days [125 to 3089]), PET-amyloid in the NT1 group was calculated after spatial normalization with the standard MNI data from the MRI template, whereas the PET-amyloid in the control groups was calculated using the individual structural MRI, leading to a potential limitation bias. However, the analysis limited to the SUVr of the four patients NT1 with concurrent MRI data showed no difference between the results obtained after normalization using the MRI generic template and the MRI individual data. Similarly, the analysis in the 69 ADNI participants using the generic MRI template for normalization (like for the patients with NT1) did not highlight any difference with the SUVr values obtained using their MRI individual data (data not shown). Regarding the strong association reported between NT1 and HLA DQB1*06:02, and the evidences supporting the role of neuroinflammation in AD pathophysiology, we cannot exclude that this genotype might influence both amyloid metabolism and orexin-A levels via immunological or neuroinflammatory mechanisms. However, the limited data on HLA typing available in the ADNI group (less than 40%) and their absence in the MAPT group did not allow us to control our results for HLA. The two control groups included subjects free of clinical dementia at time of study but we cannot exclude that some of them may further develop AD or other dementias. However, sub-analysis after exclusion of participants with CDR ≥0.5 confirmed lower cortical/cerebellum SUVr values in the NT1 group than in the two control groups. In the same way, exclusion of participants with abnormal CSF Aβ42 concentration from both ADNI and NT1 populations confirmed lower cortical/cerebellum SUVr values in the NT1 group. None of the subjects from ADNI cohort with a CDR at 0.5 (n=6) had abnormal CSF Aβ42 levels. No differences in the median of CSF Aβ42 levels were found between subjects with CDR at 0 and those with CDR at 0.5 in the ADNI population. No CSF orexin-A levels were available for both control groups and no CSF AD biomarkers were available for the MAPT-AV45 population. The CSF procedure for patients with NT1 was decided for the diagnosis purpose to measure the concentration of orexin-A to validate the diagnosis of NT1. We did not perform a second lumbar puncture for this specific study. The variable interval between PET data acquisition and CSF sampling in the NT1 group remains an additional limitation that could explain the lack of correlation between AD markers and NT1 duration. Finally, we were unable to include a population of age- and sex-matched patients with AD with available PET with ^{18}F-florbetapir. However, the inclusion of such group of patients with AD with a range of 61% to 84.7% of PET-amyloid positive for diagnosed AD patients (i.e. diagnosis made with clinical signs only or with both positive clinical signs and biomarkers, respectively)[47,48] would have led to an even more significant difference with patients with NT1 ($p<0.0001$) than with the other control populations free of clinical dementia.

Our results highlight a lower brain amyloid-β burden, detected by ^{18}F-florbetapir-PET, in elderly patients with orexin-A-deficient narcolepsy, suggesting a lower risk of amyloidopathy related to AD in NT1. Longitudinal amyloid PET and cognitive studies in elderly patients with NT1 are required to confirm this result and to understand its implications. For instance, this could lead to reconsider the potential protective effect of orexin receptor antagonists on brain amyloid load in subjects at high risk of AD.

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Potential Conflicts of Interest:

Nothing to disclose relating to this study

Author contributions:

YD and AG contributed to the conception and design of the study; YD, AG, FBB, IJ , SL, RL, LB, CG, CP, DVD, SB, DMG, and BC contributed to the acquisition and analysis of data; YD, AG, FBB, IJ, RL, LB contributed to drafting the text and preparing the figures.

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Table 1: Clinical, neuropsychological and biological characteristics of the 23 patients with NT1.

	N	% or Median (Minimum value; Maximum value)
Clinical assessment		
Age at onset, *in years*	23	27.00 (11;61)
Age at diagnosis, *in years*	23	52 (34;73)
BMI, kg/m^2		
<25	5	21.7
25-30	14	60.9
≥30	4	17.4
Epworth Scale total Score	21	15 (6;24)
Epworth Scale total Score		
≤10	7	33.3
11-15	4	19.0
≥16	10	47.6
Psychostimulants drugs, Yes	19	82.6
Anti-cataplectic drugs, Yes	13	56.5
Cardiovascular events history,* Yes	17	73.9
Beck depressive inventory total score	23	9.00 (0;29)
Beck depressive inventory total score		
<12	12	52.2
12-19	9	39.1
20-27	1	4.3
≥28	1	4.3
EQ5D – Visual analog scale	23	70 (30;95)
EQ5D- utility	23	0.84 (0.34;1.00)
Neuropsychological assessment		
Mild cognitive impairment (CDR=0.5)	7	30.4
Mild dementia (CDR=1)	1	4.3
Memory episodic deficit (Hippocampal syndrome)	5	21.7
Executive dysfunction	14	60.9
Biology		
CSF Aβ42 levels, *pg/ml*	20	899.50 (300;1438)
Abnormal CSF Aβ42 levels <500 *pg/ml*	3	15.00
CSF Aβ40 levels, *pg/ml*	15	7751 (2657;11759)
CSF Tau levels, *pg/ml*	20	193.50 (58;407)
Abnormal CSF Tau levels >400 *pg/ml*	1	5.00
CSF p-Tau levels, *pg/ml*	20	38.50 (15;73)
Abnormal CSF p-Tau levels >60 *pg/ml*	2	10.00

CDR = Clinical Dementia Rating (0= Normal; 0.5 = Very Mild Dementia; 1 = Mild Dementia; 2 = Moderate Dementia; 3 = Severe Dementia); European Quality of Life Dimension; CSF = cerebrospinal fluid; p-Tau= phosphorylated Tau.

*Cardiovascular events defined as the presence of hypertension, diabetes, myocardial infarction, or stroke

Table 2: Demographical and cognitive characteristics of patients with NT1 and controls from the ADNI and MAPT-AV45 cohorts.

	NT1 patients N=23		ADNI controls N=69		MAPT controls N=23		ADNI controls vs NT1 patients	MAPT controls vs NT1 patients
Variables	*n*	*%*	*n*	*%*	*n*	*%*	*p*	
Sex								
Male	14	60.9	42	60.9	14	60.9	-	-
Female	9	39.1	27	39.1	9	39.1		
Age, in years								
<75	14	60.9	42	60.9	14	60.9	-	-
[75-80[	4	17.4	12	17.4	4	17.4		
≥80	5	21.7	15	21.7	5	21.7		
MMSE score[(1)]	29 (15;30)		29 (25;30)		28 (25;30)		0.006	0.92
MMSE score								
<26	2	8.7	1	1.5	1	4.4	0.03	0.56
≥26	21	91.3	68	98.5	22	95.6		
CDR scale								
Normal	15	65.22	63	91.30	12	52.17	0.0001	0.41
Very Mild/Mild Dementia	7/1	34.78	6/0	8.70	11/0	47.83		
Carrier of the APOE ε4 allele								
No	15	68.18	48	69.57	15	71.43	0.90	0.82
Yes	7	31.82	21	30.43	6	28.57		

[(1)] Continuous variables are expressed as median (minimum value;maximum value)

NT1 = narcolepsy type 1; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating

Table 3: Comparisons of brain amyloid burden measured by ^{18}F-florbetapir-PET between patients with narcolepsy type 1 (NT1) and controls from the ADNI and MAPT-AV45 cohorts

	NT1 patients N=23		ADNI controls N=69		MAPT-AV45 controls N=23		ADNI vs NT1	MAPT-AV45 vs NT1
Variables	*Mean (±SD)*		*Mean (±SD)*		*Mean (±SD)*		*p*	*p*
SUVr-cortical/cerebellum	0.95 (± 0.15)		1.11 (± 0.18)		1.14 (± 0.17)		<0.0001	0.0005
SUVr-cortical/pons	0.57 (± 0.09)		0.68 (± 0.11)		-		<0.0001	
SUVr-cortical/composite score	0.66 (± 0.09)		0.78 (± 0.11)		-		<0.0001	
SUVr-frontal/cerebellum	0.92 (± 0.16)		1.10 (± 0.20)		1.08 (± 0.13)		<0.0001	0.0006
SUVr-parietal/cerebellum	0.93 (± 0.17)		1.08 (± 0.19)		1.08 (± 0.16)		<0.0001	0.001
SUVr-temporal/cerebellum	0.98 (± 0.12)		1.08 (± 0.16)		1.18 (± 0.14)		<0.0001	0.0005
SUVr-precuneus/cerebellum	1.05 (± 0.22)		1.18 (± 0.23)		1.20 (± 0.25)		0.0003	0.02
SUVr-anterior cingulate/cerebellum	1.13 (± 0.21)		1.28 (± 0.23)		1.16 (± 0.18)		<0.0001	0.93
SUVr-posterior cingulate/cerebellum	1.10 (± 0.20)		1.22 (± 0.23)		1.16 (± 0.23)		0.0007	0.62
Variables	*n*	*%*	*n*	*%*	*n*	*%*		
SUVr-cortical/cerebellum								
≤1.17	22	95.7	50	72.5	16	69.6	0.0003	0.04
>1.17	1	4.3	19	27.5	7	30.4		
Positive PET-AV45 visual rating								
No	22	95.7	-	-	17	73.9	-	0.08
Yes	1	4.3	-	-	6	26.1	-	

ADNI = Alzheimer's disease Neuro-Imaging Initiative, MAPT-AV45= Multi-domain Intervention Alzheimer's Prevention Trial with PET-AV45 ancillary study, SUVr = Standard Uptake Value ratio

Figure 1. Mean ^{18}F-florbetapir tracer uptake in representative axial/coronal (A and B) slices showing less cortical amyloid load in patients with narcolepsy type 1 (NT1) than in ADNI and MAPT-AV45 controls.