Sleep Breath (2016) 20:277–283
DOI 10.1007/s11325-015-1305-9

NEUROLOGY • ORIGINAL ARTICLE

Beta-amyloid and phosphorylated tau metabolism changes in narcolepsy over time

Claudio Liguori[1] · Fabio Placidi[1] · Francesca Izzi[1] · Marzia Nuccetelli[2] · Sergio Bernardini[2] · Maria Giovanna Sarpa[1] · Fabrizio Cum[1] · Maria Grazia Marciani[3] · Nicola Biagio Mercuri[1,4] · Andrea Romigi[1,5]

Received: 18 July 2015 / Revised: 26 November 2015 / Accepted: 23 December 2015 / Published online: 23 January 2016

Abstract
Purpose The aim od this study is to test whether metabolism of beta-amyloid and tau proteins changes in narcolepsy along with the disease course.
Methods We analyzed a population of narcoleptic drug-naïve patients compared to a sample of healthy controls. Patients and controls underwent lumbar puncture for assessment of cerebrospinal fluid (CSF) beta-amyloid$_{1–42}$ (Aβ_{42}), total tau (t-tau), and phosphorylated tau (p-tau) levels. Moreover, based on the median disease duration of the whole narcolepsy group, the patients were divided into two subgroups: patients with a short disease duration (SdN, <5 years) and patients with a long disease duration (LdN, >5 years).
Results We found significantly lower CSF Aβ_{42} levels in the whole narcolepsy group with respect to controls. Taking into account the patient subgroups, we documented reduced CSF Aβ_{42} levels in SdN compared to both LdN and controls. Even LdN patients showed lower CSF Aβ_{42} levels with respect to controls. Moreover, we documented higher CSF p-tau levels in LdN patients compared to both SdN and controls. Finally, a significant positive correlation between CSF Aβ_{42} levels and disease duration was evident.
Conclusions We hypothesize that beta-amyloid metabolism and cascade may be impaired in narcolepsy not only at the onset but also along with the disease course, although they show a compensatory profile over time. Concurrently, also CSF biomarkers indicative of neural structure (p-tau) appear to be altered in narcolepsy patients with a long disease duration. However, the mechanism underlying beta-amyloid and tau metabolism impairment in narcolepsy remains still unclear and deserves to be better elucidated.

Keywords Narcolepsy · Beta-amyloid$_{1–42}$ · Tau protein · Orexin · CSF

✉ Andrea Romigi
a_romigi@inwind.it

[1] Department of Systems Medicine, Neurophysiopathology Unit, Sleep Medicine Centre, University of Rome 'Tor Vergata', Viale Oxford 81, 00133 Rome, Italy

[2] Clinical Biochemistry and Molecular Biology, University of Rome 'Tor Vergata', Rome, Italy

[3] Department of Systems Medicine, Neurology Unit, University of Rome 'Tor Vergata', Rome, Italy

[4] Fondazione Santa Lucia IRCCS, Rome, Italy

[5] IRCCS Neuromed, Via Atinense 18, 86077 Pozzilli, IS, Italy

Introduction

Narcolepsy is a disabling sleep disorder clinically characterized by sleep manifestations such as excessive daytime sleepiness and abnormal rapid eye movements (REMs), including cataplexy, sleep paralysis, and hypnagogic hallucination [1–3]. Narcolepsy is caused by the selective lack of orexin signaling due to loss of the hypothalamic neurons normally producing this neuropeptide [4, 5]. The striking precision of the attack on orexin neurons is hypothesized to be due to autoimmune/inflammatory processes [6]. In this line, several recent observations of narcolepsy related to H1N1 virus infection and vaccination supported the hypothesis of an immunologic trigger of this sleep disorder in genetically predisposed individuals [7]. To elucidate its pathogenesis, several cerebrospinal fluid (CSF) biomarkers have been investigated, such as beta-amyloid, tau proteins, and neuron-specific enolase (NSE) [8–12]. However, conflicting results emerged from the literature regarding the assessment of CSF biomarkers in

narcoleptic patients, probably due to confounding factors such as small and heterogeneous samples of patients [8–12]. In fact, whereas reduced CSF beta-amyloid and normal tau protein levels have been described in narcoleptic drug-naïve patients [8, 9, 12], on the contrary, increased CSF levels of beta-amyloid, tau proteins, and NSE were documented in patients with long disease duration receiving central stimulant medication [10].

To determine whether CSF biomarkers involved in inflammatory and neurodegenerative processes (beta-amyloid and tau proteins) change in narcolepsy over time, we evaluated these biomarkers in a population of narcoleptic drug-naïve patients ranging from early to late phases of the disease.

Methods

Participants and study design

We consecutively recruited drug-naïve patients admitted to the Sleep Center of the University of Rome "Tor Vergata" from September 2011 to December 2014. All patients underwent a standard screening including physical and neurological examination, laboratory tests, HLA-DQB1*06:02 haplotype determination, full laboratory polysomnography followed by the multiple sleep latency test, brain MRI, and lumbar puncture (LP) for analysis of CSF biomarkers, including orexin, beta-amyloid$_{1–42}$ ($A\beta_{42}$), total tau (t-tau), and phosphorylated tau (p-tau) proteins. All of them were diagnosed as narcolepsy type 1 (N1) or narcolepsy type 2 (N2) according to the International Classification of Sleep Disorders, 3rd edition (2014) [1].

We also enrolled controls of similar age and sex with narcolepsy patients. All of them were patients at the same neurology clinic, which underwent neurological examination, brain MRI, and LP for diagnostic purposes, who were considered healthy at the end of the diagnostic investigations which resulted negative.

Narcoleptic eligible patients and controls were required to meet the following inclusion criteria: no concomitant neurological or psychiatric diseases, no use of drugs active on the CNS, and no use of caffeine, tobacco, and/or alcohol at the time of the investigations. Exclusion criteria for patients and controls were the following: neoplastic or thyroid illness, inflammatory/infectious conditions, anti-inflammatory or corticosteroid therapies, and abnormal cell count (>4 cells/μl) at the CSF sample analysis. Additional exclusion criterion for controls was the presence of sleep complaints investigated by means of a structured interview performed by certified sleep medicine experts (AR, FI, and FP).

Narcoleptic patients were divided into two groups based on the estimated disease duration. Disease duration was defined as the elapsed time from the onset of the first symptom (i.e., sleepiness or cataplexy, including "cataplectic facies") to clinical observation. Based on the median length of the disease duration in the whole group, a cutoff to define two subgroups of equal size was chosen. Therefore, we considered two subgroups: patients with a short disease duration (SdN) and patients with a long disease duration (LdN).

The study protocol was approved by the internal review board of the local ethical committee. Written informed consent was obtained from all participating in the study.

CSF collection and analysis

All the CSF samples were obtained by LP performed in decubitus position between 8:00 and 9:00 AM using an atraumatic needle. Blood specimens were also obtained at the same time of LP procedure. CSF samples were collected in polypropylene tubes using standard sterile techniques [13]. The first 4-ml CSF sample was used for biochemistry routine analysis including total cell count. The second 4-ml CSF sample was centrifuged to eliminate cells and cellular debris and immediately frozen at −80 °C until the analysis to assess orexin, t-tau, p-tau, and $A\beta_{42}$ amount.

The CSF $A\beta_{1–42}$, t-tau, and p-tau levels were determined according to previously published standard procedures, using commercially available sandwich enzyme-linked immunosorbent assays (ELISAs) (Innotest β-Amyloid 1–42, Innotest h-T-tau, Innotest Phospho-T-tau 181; Innogenetics, Ghent, Belgium) [13].

The CSF orexin levels were detected according to previously published standard procedures with commercially available ELISA kit (Orexin A/Hypocretin-1 EIA Kit; Phoenix Pharmaceuticals, Burlingame, CA, USA), based on the principle of competitive enzyme immunoassay [9, 14]. The unknown sample concentrations were calculated on the corresponding standard sigmoid curve equation (peptide standards ranging from 0 to 1000 pg/ml); pathological cutoff was set at ≤50 pg/ml [9, 14]. The intra-assay and inter-assay coefficients of variation were 2.5 and 3.9 %, respectively [14]. The minimum detectable concentration found was 26.2 pg/ml [14]. All the samples were analyzed each time on the same ELISA plate, in duplicate and in random order. The experiments were replicated three times to confirm the values and to demonstrate the reliability of the assay. Researchers (MN and SB) completely blinded to the study participants' clinical status performed the analysis.

Data and statistical analysis

The Kolmogorov-Smirnov test was used to check for normal distribution of data. Student's *t* test was used in order to compare demographic and CSF data between the two groups (narcolepsy versus controls; SdN versus LdN). The one-way ANOVA was used to compare CSF results between SdN,

LdN, and controls. The post hoc analysis was performed using Tukey's HSD test.

Within the narcolepsy group, correlations between levels of CSF biomarkers (orexin, $A\beta_{42}$, t-tau, p-tau) and clinical data were separately performed by utilizing the Pearson correlation test. An additional multiple regression analysis between demographic, clinical, and CSF data was also performed. *P* value <0.05 was considered to be statistically significant.

Results

Demographic and clinical data

Twenty-six consecutive drug-naïve narcolepsy patients were enrolled from September 2011 to December 2014. Based on the median length of the disease duration of the whole group, a cutoff of 5 years was chosen to define two subgroups of equal size: SdN patients reporting a disease duration ≤5 years and LdN patients reporting a disease duration >5 years. Therefore, 13 narcolepsy patients were included in the SdN group whereas the remaining 13 narcolepsy patients constituted the LdN group. The control group consisted of 17 healthy subjects of similar age and sex with narcolepsy patients. Considering narcolepsy diagnosis, 12 patients were included in the N1 group (7 SdN and 5 LdN) whereas 14 patients were counted in the N2 group (5 SdN and 7 LdN).

Demographic and clinical features of patients and controls are summarized in Tables 1, 2, and 3.

Between-group analysis

By comparing CSF $A\beta_{42}$ levels between the whole narcolepsy population and the control group, we found significantly lower CSF $A\beta_{42}$ levels in narcolepsy patients than controls (see Table 1). On the other hand, we did not find differences in CSF t-tau and p-tau levels between patients and controls (see Table 1). As expected, narcolepsy patients showed lower CSF orexin levels with respect to controls (see Table 1).

We next compared CSF biomarkers between SdN, LdN, and controls. Statistical analysis documented reduced CSF $A\beta_{42}$ levels in the SdN group compared to both LdN and control groups (see Table 2 and Fig. 1). Furthermore, LdN narcoleptic patients showed lower CSF $A\beta_{42}$ levels with respect to controls (see Fig. 1).

Considering t-tau and p-tau levels, the statistical analysis between the three groups showed an increase of p-tau levels in LdN patients compared to both SdN and controls (see Table 2 and Fig. 2).

Comparing N1 and N2 patient groups, we did not find differences in CSF t-tau, p-tau, and $A\beta_{42}$ levels. Consistently, N1 patients showed reduced CSF orexin levels compared to N2 patients (Table 3).

Correlations in patients and control groups

In the whole narcoleptic group, the Pearson correlation test proved a significantly positive correlation between CSF $A\beta_{42}$ levels and disease duration ($R = 0.54$, $P = 0.005$; Fig. 3). On the other hand, we did not find correlations

Table 1 Demographic, clinic, MSLT, and CSF data of narcoleptic patients and controls

Demographic data	Narcoleptic patients ($n = 26$) (mean value ± SD)	Controls ($n = 17$) (mean value ± SD)	*P* value
Age	33.72 ± 11.58	33.29 ± 8.39	NS
Sex (M:F)	14:12	10:7	NS
Disease duration (years)	8.29 ± 9.46	NA	NA
Cataplexy (%positive)	46	NA	NA
Sleep paralysis (%positive)	77	NA	NA
Hypnagogic hallucinations (%positive)	69	NA	NA
MSLT data			
Sleep latency	3.99 ± 1.81	NA	NA
SOREMp	3.58 ± 1.06	NA	NA
CSF data (expressed in pg/ml)			
Orexin A	79.12 ± 36.73	186.42 ± 22.29	<0.001
t-tau	172.2 ± 69.68	212.41 ± 62.08	NS
p-tau	28.52 ± 11.28	23.88 ± 2.95	NS
$A\beta_{42}$	623.24 ± 252.63	1039 ± 105.05	<0.001

P values <0.05 were statistically significant

SD standard deviation, *F* female, *M* male, *CSF* cerebrospinal fluid, *t-tau* total tau proteins, *p-tau* phosphorylated tau proteins, $A\beta_{42}$ beta-amyloid$_{1-42}$, *MSLT* multiple sleep latency test, *SOREMp* sleep onset rapid eye movement period, *NS* not significant, *NA* not applicable

Table 2 Demographic, clinic, MSLT, and CSF data of narcoleptic patient subgroups

Demographic data	SdN ($n=13$) (mean value ± SD)	LdN ($n=13$) (mean value ± SD)	*P* value
Age	29.15 ± 10.24	38.67 ± 11.28	NS
Sex (M:F)	8:5	6:7	NS
Disease duration (years)	2.84 ± 1.58	14.21 ± 10.92	<0.001
Cataplexy (%positive)	53	38	NS
Sleep paralysis (%positive)	84	69	NS
Hypnagogic hallucinations (%positive)	77	61	NS
MSLT data			
Sleep latency	3.93 ± 1.85	4.06 ± 1.84	NS
SOREMp	3.77 ± 1.01	3.38 ± 1.12	NS
CSF data (expressed in pg/ml)			
Orexin A	64.69 ± 36.88	92.19 ± 33.84	NS
t-tau	168.84 ± 76.03	175.83 ± 65.28	NS
p-tau	22.69 ± 8.58	30.67 ± 5.09	<0.01
$A\beta_{42}$	496.54 ± 180.91	760.5 ± 253.02	<0.001

P values <0.05 were statistically significant

SdN narcoleptic patients with a short disease duration (≤5 years), *LdN* narcoleptic patients with a long disease duration (>5 years), *SD* standard deviation, *F* female, *M* male, *CSF* cerebrospinal fluid, *t-tau* total tau proteins, *p-tau* phosphorylated tau proteins, $A\beta_{42}$ beta-amyloid$_{1–42}$, *MSLT* multiple sleep latency test, *SOREMp* sleep onset rapid eye movement period, *NS* not significant

between CSF and clinical data. Moreover, we found no correlations between all the parameters analyzed in control groups.

We also performed in the narcolepsy group an additional multivariate regression analysis among demographic, clinical, and CSF data revealing the significant interplay between CSF $A\beta_{42}$ levels and disease duration ($\beta = 0.39$ and $P < 0.05$).

Discussion

In this paper, we investigated the CSF beta-amyloid and tau protein levels in a large clinically based cohort of narcoleptic drug-naïve patients. Dividing narcoleptic patients into two subsets on the basis of the median disease duration of the

Table 3 Demographic, clinic, MSLT, and CSF data of N1 and N2 patients

Demographic data	N1 ($n=12$) (mean value ± SD)	N2 ($n=14$) (mean value ± SD)	P value
Age	27.45 ± 9.47	38.64 ± 10.93	NS
Sex (M:F)	7:5	7:7	NS
Disease duration (years)	4.63 ± 4.37	11.18 ± 11.41	<0.001
Disease duration (years)	8.29 ± 9.46	NA	NA
Cataplexy (%positive)	100	0	<0.0001
Sleep paralysis (%positive)	92	64	NS
Hypnagogic hallucinations (%positive)	75	64	NS
MSLT data			
Sleep latency	3.91 ± 1.89	4.06 ± 1.82	NS
SOREMp	3.75 ± 1.05	3.43 ± 1.09	NS
CSF data (expressed in pg/ml)			
Orexin A	45.53 ± 13.11	105.53 ± 25.56	<0.001
t-tau	177 ± 58.79	168.43 ± 79.19	NS
p-tau	25.64 ± 7.66	30.78 ± 13.31	NS
$A\beta_{42}$	574.82 ± 195.06	661.28 ± 291.57	NS

P values <0.05 were statistically significant

SD standard deviation, *F* female, *M* male, *CSF* cerebrospinal fluid, *t-tau* total tau proteins, *p-tau* phosphorylated tau proteins, $A\beta_{42}$ beta-amyloid$_{1–42}$, *MSLT* multiple sleep latency test, *SOREMp* sleep onset rapid eye movement period, *NS* not significant

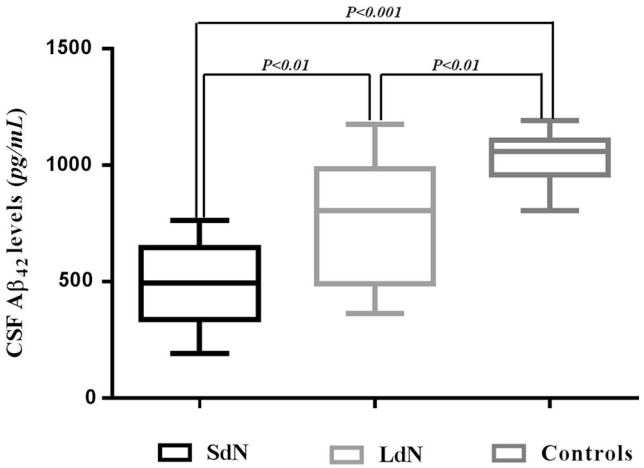

Fig. 1 Cerebrospinal fluid (*CSF*) beta-amyloid$_{1–42}$ ($A\beta_{42}$) levels in narcoleptic patients with short disease duration (*SdN*) and long disease duration (*LdN*) and controls (expressed in pg/ml)

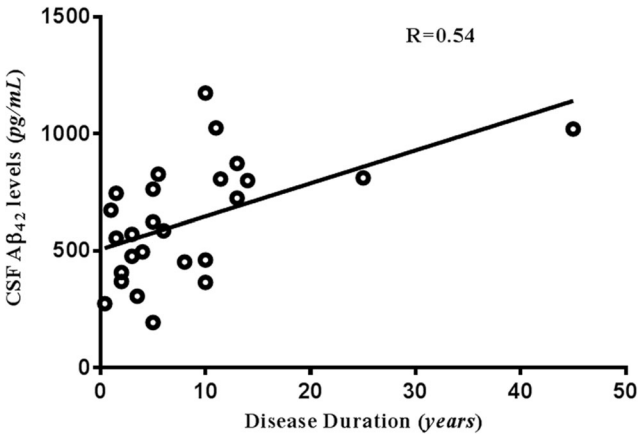

Fig. 3 Correlation between cerebrospinal fluid (*CSF*) beta-amyloid$_{1–42}$ ($A\beta_{42}$) levels (pg/ml) and disease duration (years) in narcoleptic patients

whole group, we documented lower CSF beta-amyloid levels in patients near to disease onset compared to patients with long disease duration. In this way, it is conceivable to highlight the impairment of beta-amyloid metabolism and clearance, manifesting with reduced CSF Aβ_{42} levels, in narcoleptic patients near to disease onset. On the other hand, we found in patients with a long disease duration higher CSF Aβ_{42} concentrations than SdN, documenting the trend in restoring the beta-amyloid metabolism to physiological conditions along with the disease course. Consistently, we also documented the significant positive correlation, associated with the significant mutual interplay in the multiple regression analysis, between Aβ_{42} levels and disease duration, corroborating the hypothesis that the beta-amyloid metabolism is more altered near to the disease onset and progressively increases to normal levels. However, we documented that both SdN and LdN patients showed lower CSF Aβ_{42} concentrations with respect to controls, confirming in an enlarged group of patients

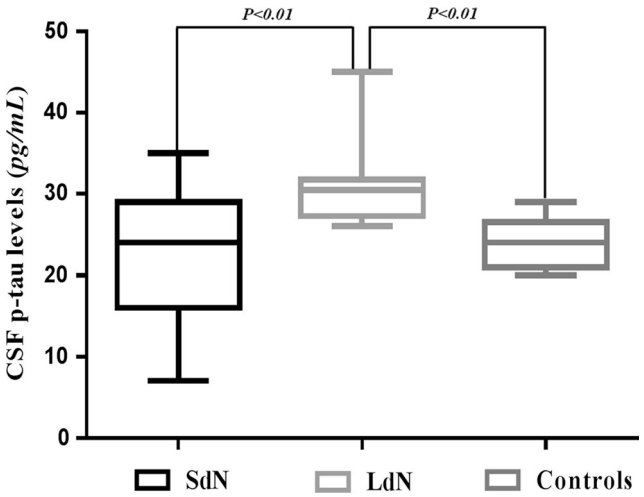

Fig. 2 Cerebrospinal fluid (*CSF*) phosphorylated tau (*p-tau*) levels in narcoleptic patients with short disease duration (*SdN*) and long disease duration (*LdN*) and controls (expressed in pg/ml)

previous findings regarding the alteration of the beta-amyloid cascade in narcolepsy [9]. The cause of the beta-amyloid metabolism dysregulation in narcolepsy is still unidentified. In our previous study, we hypothesized that both inflammatory conditions present at disease onset—related to the immunopathogenesis of narcolepsy—and the presence of an "amyloidogenic" pathway of beta-amyloid catabolism—owing to alpha-secretase enzyme deficiency—may be involved [4, 9, 15–18]. In keeping with this hypothesis, the present data allow to suppose two different phases of beta-amyloid metabolism dysregulation in narcolepsy.

The first phase, probably acute or subacute, near to disease onset, is characterized by transient inflammatory processes well known in narcolepsy [6, 8, 15, 19], which may dramatically alter the beta-amyloid cascade producing the marked reduction of CSF Aβ_{42} levels evident in SdN patients. In fact, it has been demonstrated that the beta-amyloid metabolism could be affected by inflammatory processes [20]; moreover, the activation of the immune system may alter the beta-amyloid metabolism [21]. Indeed, narcolepsy is considered an inflammatory/autoimmune disease, since it has been associated with HLA-DQB1*06:02 allele and it has been considered to be triggered by environmental factors such as streptococcal and influenza A H1N1 infection and vaccination [7, 15, 22, 23]. Furthermore, taking into account that in narcolepsy the inflammatory responses are confined to the lateral hypothalamus, thus reducing the opportunity to find detectable levels of inflammatory markers such as cytokines diffusing to the CSF [24, 25], we could speculate that the alteration of beta-amyloid metabolism may be a detectable evidence of the immune processes present in narcoleptic brains.

The second phase, evident along with the disease course, in which inflammatory triggers are lowered and beta-amyloid metabolism could be mainly affected by the underlying deficiency of alpha-secretase enzymes, was recently documented in narcolepsy patients [16–18]. In fact, a reduced activity of alpha-secretase enzymes may be responsible for an incomplete catabolism of beta-amyloid proteins, thus causing the

reduction of CSF $A\beta_{42}$ concentrations [16, 26]. These effects could result in a less severe reduction of CSF $A\beta_{42}$ levels evident in LdN patients.

Therefore, we hypothesize that SdN patients show lower CSF $A\beta_{42}$ concentrations than LdN patients since they are co-affected by inflammatory processes and alpha-secretase enzyme deficiency. On the other hand, LdN patients present a less severe impairment of the beta-amyloid metabolism, because the inflammatory drives are less evident in the chronic phase of the disease, and then the patients suffer predominantly from the deficiency of alpha-secretase enzymes. However, we are aware that $A\beta_{42}$ changes in narcolepsy could be more informative if assessed over time within the same patient.

Recently, it has been described that narcoleptic patients with a long disease duration and under stable treatment with psychostimulants showed increased t-tau, p-tau, and $A\beta_{42}$ levels [10]. Authors postulated that these findings may be the expression of an altered cell metabolism, featured by changing in plasticity and regenerative capacity of the neuronal networks of the brain [10]. In agreement with this observation, we found higher CSF p-tau levels in LdN patients than in both SdN patients and controls. Taking into account that narcoleptic patients included in our study were drug naïve, these data may encourage the emerging hypothesis of an altered neuronal plasticity, involving the phosphorylated tau proteins, evident in narcolepsy along with the disease course. However, few studies showed that narcolepsy seems to not predispose to Alzheimer's dementia (AD) [11, 27, 28], thus proving that beta-amyloid and tau protein metabolism dysregulation does not take part in prearranging to AD pathology.

We next found no differences in the levels of CSF biomarkers between N1 and N2 patients. We may hypothesize that both types of narcolepsy show similar pathological pathways of beta-amyloid and tau protein metabolism alteration, disregarding orexin signaling.

In conclusion, beta-amyloid metabolism seems to be impaired in narcolepsy not only at the onset but also along the disease course although it shows a compensatory profile over time. At the same time, also CSF biomarkers regulating the neuron dynamic and structure appear to be altered in narcolepsy, as documented by the trend in an increase of CSF p-tau levels after a long disease duration. However, the mechanism by which beta-amyloid is reduced and tau metabolism is dysregulated during narcolepsy, although largely hypothesized, remains still unclear and deserve to be better elucidated in larger groups of narcolepsy patients.

Study limitations

Few limitations of this study should be considered when interpreting the results. First, the sample size is small although similar to other *single-center* studies on narcolepsy. Second, the mechanism by which beta-amyloid and tau metabolism is dysregulated is still unclear and should be better evaluated in larger multicenter prospective trial in order to clarify the role of these markers in narcolepsy. Therefore, this can be considered as a pilot study to determine a sample size and optimization for a future multicenter trial.

Compliance of ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. International Classification of Sleep Disorders (2014) Darien, Ill.: American Academy of Sleep Medicine
2. Dauvilliers Y, Billiard M, Montplaisir J (2003) Clinical aspects and pathophysiology of narcolepsy. Clin Neurophysiol 114:2000–2017
3. Overeem S, Mignot E, van Dijk JG, Lammers GJ (2001) Narcolepsy: clinical features, new pathophysiologic insights, and future perspectives. J Clin Neurophysiol 18:78–105
4. Thannickal TC, Moore RY, Nienhuis R et al (2000) Reduced number of hypocretin neurons in human narcolepsy. Neuron 27:469–474
5. Mignot E, Lammers GJ, Ripley B et al (2002) The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 59:1553–1562
6. Kornum BR, Faraco J, Mignot E (2011) Narcolepsy with hypocretin/orexin deficiency, infections and autoimmunity of the brain. Curr Opin Neurobiol 21(6):897–903
7. Partinen M, Kornum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O (2014) Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet Neurol 13(6):600–613
8. Kallweit U, Hidalgo H, Engel A, Baumann CR, Bassetti CL, Dahmen N (2012) Post H1N1 vaccination narcolepsy-cataplexy with decreased CSF beta-amyloid. Sleep Med 13(3):323
9. Liguori C, Placidi F, Albanese M et al (2014) CSF beta-amyloid are altered in narcolepsy: a link with the inflammatory hypothesis? Sleep Res 23(4):420–424
10. Heier MS, Skinningsrud A, Paus E, Gautvik KM (2014) Increased cerebrospinal fluid levels of nerve cell biomarkers in narcolepsy with cataplexy. Sleep Med 15(6):614–618
11. Dauvilliers YA, Lehmann S, Jaussent I, Gabelle A (2014) Hypocretin and brain β-amyloid peptide interactions in cognitive disorders and narcolepsy. Front Aging Neurosci 6:119
12. Liguori C, Placidi F, Izzi F et al (2014) May CSF beta-amyloid and tau proteins levels be influenced by long treatment duration and stable medication in narcolepsy? Sleep Med 15(11):1424
13. Sancesario GM, Esposito Z, Nuccetelli M et al (2010) Abeta1-42 detection in CSF of Alzheimer's disease is influenced by

temperature: indication of reversible Abeta1-42 aggregation? Exp Neurol 223(2):371–376
14. Liguori C, Romigi A, Mercuri NB et al (2014) Cerebrospinal-fluid orexin levels and daytime somnolence in frontotemporal dementia. J Neurol 261(9):1832–1836
15. Fontana A, Gast H, Reith W, Recher M, Birchler T, Bassetti CL (2010) Narcolepsy: autoimmunity, effector T cell activation due to infection, or T cell independent, major histocompatibility complex class II induced neuronal loss? Brain 133:1300–1311
16. Miyagawa T, Miyadera H, Tanaka S et al (2011) Abnormally low serum acylcarnitine levels in narcolepsy patients. Sleep 34:349–353
17. Miyagawa T, Kawamura H, Obuchi M et al (2013) Effects of oral L-carnitine administration in narcolepsy patients: a randomized, double-blind, cross-over and placebo-controlled trial. PLoS One 8:e53707
18. Romigi A, Liguori C, Izzi F et al (2015) Oral l-carnitine as treatment for narcolepsy without cataplexy during pregnancy: a case report. J Neurol Sci 348(1–2):282–283
19. Liguori C, Dinallo V, Pieri M, et al. (2015) MicroRNA expression is dysregulated in narcolepsy: a new evidence? Sleep Med 16(8): 1027–1028
20. Hickman SE, Allison EK, El Khoury J (2008) Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. J Neurosci 28(33):8354–8360
21. Soscia SJ, Kirby JE, Washicosky KJ et al (2010) The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One 5(3):e9505
22. Aran A, Lin L, Nevsimalova S et al (2009) Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. Sleep 32(8):979–983
23. Han F, Lin L, Li J et al (2012) TCRA, P2RY11, and CPT1B/CHKB associations in Chinese narcolepsy. Sleep Med 13(3):269–272
24. Kornum BR, Pizza F, Knudsen S, Plazzi G, Jennum P, Mignot E (2015) Cerebrospinal fluid cytokine levels in type 1 narcolepsy patients very close to onset. Brain Behav Immun 49:54–58
25. Dauvilliers Y, Jaussent I, Lecendreux M et al (2014) Cerebrospinal fluid and serum cytokine profiles in narcolepsy with cataplexy: a case–control study. Brain Behav Immun 37:260–266
26. De Strooper B, Vassar R, Golde T (2010) The secretases: enzymes with therapeutic potential in Alzheimer disease. Nat Rev Neurol 6: 99–107
27. Honda M, Arai T, Fukazawa M et al (2009) Absence of ubiquitinated inclusions in hypocretin neurons of patients with narcolepsy. Neurology 73:511–517
28. Economou NT, Manconi M, Ghika J, Raimondi M, Bassetti CL (2012) Development of Parkinson and Alzheimer diseases in two cases of narcolepsy-cataplexy. Eur Neurol 67(1):48–50

Comments

In this manuscript, the authors evaluated the levels of CSF biomarkers in drug-naïve narcoleptic patients using enzyme-linked immunosorbent assays. The CSF samples were collected from 26 narcoleptic patients (SDN < 5 years, n = 13; and LDN < 5 years, n = 13) and 17 healthy controls. The results demonstrated that while CSF levels of Aβ42 were significantly decreased in SDN and LDN compared to the control, its levels were lower in SDN compared to LDN. They also reported a significant positive correlation between the CSF levels of Aβ42 and disease duration. Further, they detected an increase in the level of p-tau in LDN compared to SDN and control, and no differences in the level of t-tau across the three groups. The authors concluded impairment in Aβ42 metabolism at the onset and along the disease course.

Overall, the aim of this study is clear and addressing an important clinical point in narcolepsy.

Sausan Azzam
Ohio, USA