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RESEARCH PAPER

CSF lactate levels, τ proteins, cognitive decline: a dynamic relationship in Alzheimer's disease

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ABSTRACT

Objectives To investigate, in patients with Alzheimer's Disease (AD), the possible interplay linking alteration of neuronal energy metabolism, as measured via cerebrospinal fluid (CSF) lactate concentration, to severity of AD neurodegenerative processes and impairment of cognitive abilities.

Methods In this study we measured and correlated CSF lactate concentrations, AD biomarker levels (τ-proteins and β-amyloid) and Mini-Mental State Examination (MMSE) score in a population of drug-naïve patients with AD ranging from mild (MMSE≥21/30) to moderate-severe (MMSE<21/30) cognitive decline. They were compared to healthy controls and patients with vascular dementia (VaD).

Results Patients with AD (n=145) showed a significant increase of CSF lactate concentration compared to controls (n=80) and patients with VaD (n=44), which was higher in mild (n=67) than in patients with moderate–severe AD (n=78). Moreover, we found, in either the whole AD population or both subgroups, a CSF profile in which higher CSF levels of t-τ and p-τ proteins corresponded to lower concentrations of lactate.

Conclusions We verified the occurrence of high CSF lactate levels in patients with AD, which may be ascribed to mitochondria impairment. Hypothesising that τ proteins may exert a detrimental effect on the entire cellular energy metabolism, the negative correlation found between lactate and τ-protein levels may allow speculation that τ toxicity, already demonstrated to have affected mitochondria, could also impair glycolytic metabolism with a less evident increase of lactate levels in more severe AD. Thus, we suggest a dynamic relationship between neuronal energy metabolism, τ proteins and cognitive decline in AD and propose the clinical potential of assessing CSF lactate levels in patients with AD to better define the neuronal brain metabolism damage.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder clinically characterised by progressive cognitive decline, for which the 'in vivo' diagnosis depends on clinical, imaging and neuropsychological testing. Neuropathologically, AD is marked by extracellular amyloid plaques, composed of β-amyloid$_{1–42}$ (Aβ$_{1–42}$) peptides, intracellular neurofibrillary tangles (NFTs), containing τ proteins and both synaptic and neuronal loss.[1] In the past decades, the amyloid hypothesis has been the primary focus of AD research, since changing in intracellular and extracellular proteins content has been considered as the core of pathological processes causing AD. Hence, Aβ$_{1–42}$, total τ (t-τ) and phosphorylated-τ (p-τ) proteins become the established cerebrospinal fluid (CSF) biomarkers to support AD diagnosis, follow the disease progression rate and, possibly, predict treatment response.[2 3] However, recent studies have suggested that alterations of Aβ$_{1–42}$ and t-τ proteins, although primary, do not cover all the pathological processes present in AD.[4] Unfortunately, trials failed to find new markers to better help understand the AD pathology, to predict outcome and contain the neurodegenerative processes. In past years, a lot of clinical studies and experimental researches were carried out in order to expand our knowledge about additional cellular and molecular mechanisms possibly involved in AD, including oxidative stress, inflammatory processes, insulin signalling and proteomic analyses, among others.[5] In this context, neuronal energy metabolism has been largely investigated, demonstrating the impairment of mitochondrial function and turnover in AD.[4 6–9] Furthermore, CSF studies showed an increase of pyruvate and lactate levels in patients with AD, considering these findings as the result of mitochondrial dysfunction.[10–12]

The aim of the present analysis was to investigate if in patients with AD the impairment of neuronal energy metabolism, as measured by means of CSF lactate levels, may be linked to cognitive impairment and CSF AD biomarkers (t-τ, p-τ and Aβ$_{1–42}$).

METHODS

Participants and study design

We consecutively recruited inpatients admitted to the Neurology Clinic of the University of Rome "Tor Vergata". All patients underwent a standard dementia screening counting physical and neurological examination, laboratory tests, neuropsychological testing, EEG, brain MRI and lumbar puncture (LP) for CSF analysis. All of them received the diagnosis of AD according to the recently proposed version of the diagnostic guidelines for AD.[13] The biomarkers were considered as positive for the AD process when one or more following abnormalities were observed: medial temporal lobe atrophy on MRI, cortical temporoparietal hypometabolism on 18FDG-PET, decreased CSF levels of Aβ$_{1–42}$ and increased CSF levels of t-τ or p-τ.[13]

In this study, we also enrolled a population of patients with vascular dementia (VaD), similar to patients with AD for age, sex and cognitive

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impairment. Diagnosis of VaD was performed according to standard criteria.[14]

AD and VaD eligible patients were also required to meet the following entry criteria: no concomitant neurological or psychiatric diseases except cognitive impairment and no use of acetylcholinesterase inhibitors or other drugs active on the central nervous system (CNS). Exclusion criteria were the following: systemic and/or neurologic infectious, inflammatory or autoimmune diseases; diabetes; radiculopathies; and abnormal cell count (>4 cells/μL) at the CSF sample analysis. At the time of enrolment, a cognitive evaluation including the Mini-Mental State Examination (MMSE) score, corrected for age and education, quantified the cognitive profile of patients. Based on MMSE, patients with AD have been divided in two subgroups: mild AD (mAD, MMSE ≥21) and moderate–severe AD (msAD, MMSE<21).[15 16]

We also enrolled a control group similar for age and sex with AD and VaD groups. All of them were inpatients at the same neurology clinic, who underwent clinical neurologic investigation, brain MRI and LP for diagnostic purposes. In particular, control subjects were inpatients admitted for suspected subarachnoid haemorrhage or polyneuropathies, ruled out after diagnostic investigations. Inclusion criteria for controls were: clinical and instrumental data excluding central and peripheral nervous system diseases; no cognitive decline measured at MMSE; no systemic disorders or diabetes; no abnormalities in cell count and in the assessment of AD biomarkers at the CSF analysis. Exclusion criterion was intake of CNS active drugs.

The study protocol with prospective design and single-blind analysis was considered as observational by the internal review board of the Local Ethical Committee because of the lack of randomisation. The database was declared to the ad hoc commission protecting personal data. 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 decubit-position between 8:00 and 9:00 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. The first 4 mL CSF sample was used for biochemistry routine analysis including total cell count and lactate levels. A second 4 mL CSF sample was centrifuged to eliminate cells and cellular debris and immediately frozen at −80°C until the analysis to assess t-τ, p-τ and $A\beta_{1–42}$ amount. Chemistry assays were carried out using commercially available kits following the manufacturer's specifications (Flex reagent cartridge, Dimension Vista System, Siemens Healthcare Diagnostics GmbH, Munich, Germany). The $A\beta_{1–42}$, t-τ and p-τ CSF levels were determined according to previously published standard procedures, using commercially available sandwich ELISA (Innotest β-Amyloid1_42, Innotest h-T-τ, Innotest Phospho-T-τ 181; Innogenetics, Ghent, Belgium).[17]

Data and statistical analysis

A non-parametric Kruskal-Wallis analysis of variance (ANOVA), coupled with the Mann-Whitney U test was used to compare CSF lactate levels among AD versus VaD versus controls and mAD versus msAD versus controls.

Within the AD, VaD and control groups, correlations between CSF levels of $A\beta_{1–42}$, t-τ, p-τ and lactate were separately performed by utilising the non-parametric Spearman rank order test. The same analysis was used to correlate the different CSF parameters with MMSE and disease duration of patients with AD and VaD. p Value <0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical data

Two hundred and five consecutive patients with AD were enrolled from April 2011 to December 2013. Among these patients, 60 presented some exclusion criteria for this study and thus they were excluded. In particular 25 presented inflammatory/infectious conditions, 15 reported intense low-back pain with radiculopathy and 20 had abnormal cell count at CSF analysis.

Therefore, 145 patients with AD completely met the eligible criteria and were included in the study. Sixty-seven patients with AD were included in the mAD group, whereas 78 constituted the msAD group. The control group consisted of 80 age matched healthy individuals, whereas 44 patients constituted the VaD population.

Demographic and clinical features of patients and controls are summarised in table 1.

Between group analysis

By comparing CSF lactate levels in AD, VaD and control groups, we found a more significant increase of CSF lactate levels in patients with AD than in controls and patients with VaD (figure 1). Moreover, controls and VaD did not differ in CSF lactate amount.

Both mAD and msAD groups showed higher CSF lactate levels in respect to controls and VaD. In addition, patients with mAD had higher CSF lactate levels than msAD (figure 1).

CSF correlations in patients with AD

In the whole AD group, Spearman's rank order correlations proved a significant negative correlation between CSF lactate content and CSF t-τ levels ($R=-0.56$, $p<0.0001$; figure 2A). A significant negative correlation was also found between CSF lactate concentration and CSF p-τ levels ($R=-0.55$, $p<0.0001$; figure 2B). These correlations remained considering the two AD subgroups (t-τ: mAD, $R=-0.74$, $p<0.0001$; msAD, $R=-0.38$, $p<0.001$; p-τ: mAD, $R=-0.65$, $p<0.0001$; msAD, $R=-0.41$, $p=0001$).

At contrast, no significant correlation was found between CSF lactate and $A\beta_{1–42}$ concentrations in all AD groups. Finally, considering the whole group of patients with AD, we found a weak positive correlation between MMSE score and lactate ($R=0.31$, $p=0.0001$), but no correlations between MMSE and both AD biomarkers and disease duration.

We found no correlation between CSF lactate, t-τ, p-τ and $A\beta_{1–42}$ levels in VaD and control groups.

DISCUSSION

This study shows the reciprocal relationship between the alteration of neuronal energy metabolism, as expressed by means of CSF lactate concentration, the severity of AD neurodegenerative processes, evaluated by assessing CSF t-τ and p-τ proteins, and the impairment of cognitive abilities, measured by rating MMSE.

In past years, increasing evidence supported the view that different cellular mechanisms may be involved in AD, strongly suggesting that mitochondrial dysfunction may contribute to AD pathogenesis and progression because mitochondria are directly vulnerable to the effects of oxidative stress.[6 7 18–22]

Nowadays, measurement of CSF lactate concentration is used as a reliable tool for the diagnosis of mitochondrial deficit, since

Table 1 Demographic and CSF data of AD, VaD and controls (mean value±SD)

Demographic data	AD (n=145)	mAD (n=67)	msAD (n=78)	VaD (n=44)	Controls (n=80)
Age (years)	71.78±6.75	72.37±5.83	71.30±7.44	70.0±7.06	68.07±7.64
Gender	75F 70M	35F 32M	40F 38M	23F 21M	42F 38M
MMSE score	19.72±5.81	25.14±2.22	15.06±3.38	20.6±3.61	27.79±0.91
Estimated disease duration (years)	2.63±1.84	2.09±1.32	3.09±2.10	2.96±1.97	NA
CSF data (pg/mL)					
t-τ	689.87±432.75	570.92±380.43	792.05±449.45	236.42±103.26	204.93±94
p-τ	83.55±46.11	72.95±42.88	92.65±47.29	43.06±13.84	41.48±14.45
$A\beta_{1-42}$	320.71±127.05	330.66±110.791	312.18±140.70	746.12±169.31	836.52±232.71

AD, Alzheimer's disease; $A\beta_{1-42}$, β-amyloid$_{1-42}$; CSF, cerebrospinal fluid; F, female; M, male; mAD, mild AD; MMSE, Mini-Mental State Examination; msAD, moderate–severe AD; NA, not applicable; p-τ, phosphorylated-τ proteins; t-τ, total τ proteins; VaD, vascular dementia.

elevated CSF lactate levels may represent the result of accumulating energetic metabolites due to mitochondrial dysfunction.[23] In past years, high lactate concentrations were reported in CSF of patients with AD, thus supporting the hypothesis that mitochondria alteration may be involved in AD processes.[10 11] According to these CSF data, in the present study, carried out in a cohort of more than 100 untreated patients with AD, we confirmed the significant increase of CSF lactate levels in AD, probably due to the deranged use of energetic substrates caused by the impairment of the oxidative phosphorylation cycle in damaged mitochondria.

Increasing evidence suggests that τ toxicity, mediated by NFTs and abnormal phosphorylation of τ proteins, may cause cellular damage by acting via multiple mechanisms, including aberrant interaction with kinesin regulating intracellular organelle transport.[24–27] In this line, τ-mediated deficit in axonal transport has been reported to interfere with function, cellular localisation and turn-over of mitochondria.[27–31] Transgenic animal models have also suggested that τ proteins may act 'directly' on mitochondria by affecting the complexes of the respiratory chain.[32–36] All considered, these data support the hypothesis that τ proteins may be involved in mitochondrial dysfunction in AD, and allow inferring that the increment of CSF lactate levels, as presently reported, may be interpreted as an index of the altered activity of mitochondria in AD neurons.

However, if we take into account the assessment of CSF AD biomarkers, we observe that patients with AD, albeit showing CSF lactate mean values significantly higher than controls, are featured by a negative correlation between lactate and both CSF t-τ and p-τ levels, thus exhibiting a CSF profile in which higher levels of t-τ and p-τ proteins correspond to lower concentrations of lactate.

If we hypothesise that τ protein levels and expression of τ toxicity may exert a detrimental effect on the entire cellular energy metabolism, it is conceivable to speculate that beyond the damage of mitochondria, the efficiency and function of the glycolytic component of the neuronal energetic system may also

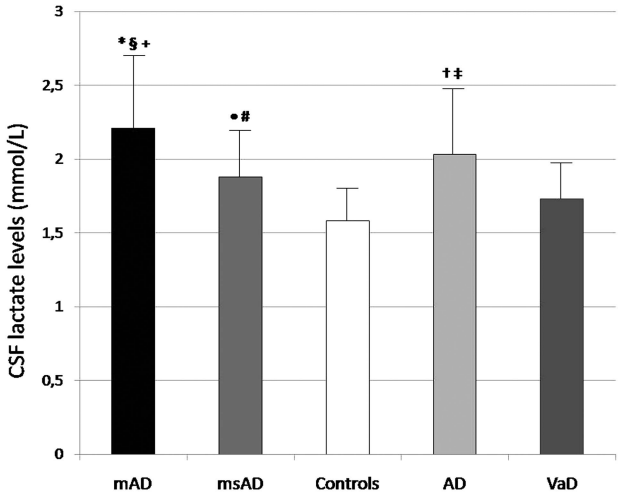

Figure 1 Cerebrospinal fluid (CSF) lactate levels of Alzheimer's disease (AD), vascular dementia (VaD) and control groups. Bars with whiskers show means and SDs. †AD versus controls, p<0.0001; ‡AD vs VaD, p<0.0001; *mild AD (mAD) versus moderate–severe (msAD), p<0.0001; §mAD versus controls, p<0.0001; +mAD versus VaD, p<0.001; •msAD versus controls, p<0.0001; #msAD versus VaD, p<0.05.

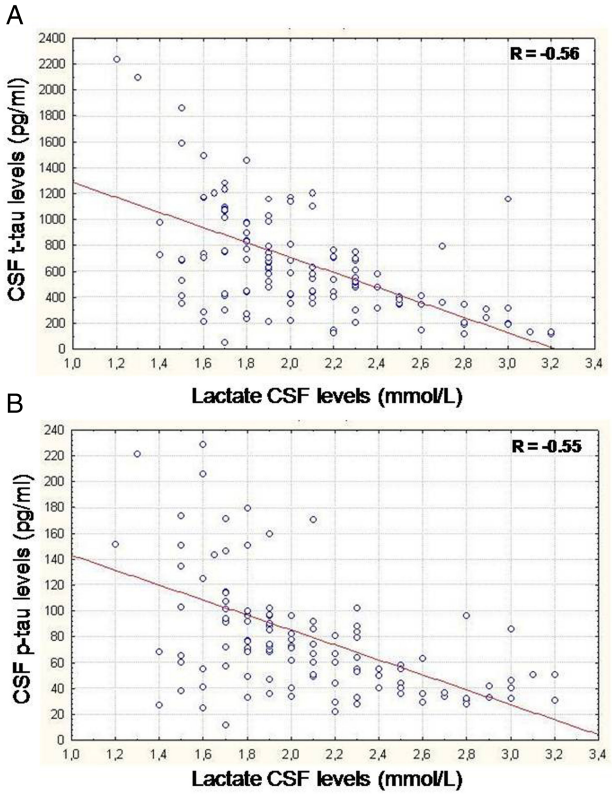

Figure 2 Scatter plots show the negative correlation between cerebrospinal fluid (CSF) lactate levels and total τ (t-τ) proteins (A, p<0.0001) and phosphorylated-τ (p-τ) proteins (B, p<0.0001).

be affected in severe forms of AD. In fact, postmortem brains from patients with AD proved evidence for the impairment of several enzymes related to glycolysis, including enolase, pyruvate kinase and lactate dehydrogenase, due to oxidative damage.[37–39] In other words, it is likely that the oxidative inactivation of glycolytic enzymes may lead to a reduced synthesis of pyruvate, which may in turn determine a reduced production of lactate and thus hamper the increase of lactate due to mitochondria damage. Our results seem to suggest a dynamic relationship between efficiency of energy machine and contents of t-τ and p-τ proteins in AD. However, the pleiomorphism of the pathological process underlying AD cannot exclude the fact that the CSF levels of lactate and τ proteins, although correlated in a mutual interplay, may be the effect of independent pathologies concurrently affecting different functional systems involved in AD.

We next found that patients with AD with mild cognitive decline (mAD group) showed higher CSF lactate levels than the more compromised ones (msAD group), thus documenting that CSF lactate concentrations seem to decrease in parallel with the cognitive dysfunction (figure 1). In addition, we documented a weak positive correlation between MMSE score and lactate levels in the whole AD group. These CSF data suggest that mitochondrial and glycolytic metabolic pathways in AD might be impaired differently along with the disease progression, since glycolytic metabolism seems to be involved in severe phases of the AD neurodegenerative process.

Moreover, we found that patients with AD showed higher CSF lactate levels with respect to patients with VaD, who did not differ from controls. These data underline that change in lactate levels may be taking into account the hypothesis of the cognitive neurodegenerative process.

Hence, we propose the clinical potential of assessing CSF lactate levels as a helpful and simple tool for assisting clinicians to better define the damage of neuronal brain metabolism in patients with AD.

Treatment in AD still represents a great challenge and a vast amount of effort has been spent in order to find alternative therapeutic approaches to counterbalance disease progression. In this aim, numerous experimental studies in AD models have been designed to test the potential effect of molecules and biological products in preserving mitochondrial energetic metabolism.[40 41] Our present clinical data propose that the damage of energetic cellular metabolism in AD may involve not only mitochondria but also glycolysis. Therefore, we would point out the opportunity to extend our frontiers in identifying novel anti-AD drugs targeted at restoring the entire cellular energetic enzymes function, also improving the glycolytic metabolism.

Contributors CL was involved in acquisition of data, study concept, data analysis and interpretation, statistical analysis and drafting the manuscript. AS and GS carried out study supervision and critical revision of the manuscript for important intellectual content. GMS was involved in data analysis. MGM carried out study supervision. MP participated in study concept and supervision, data analysis and interpretation, statistical analysis and drafting the manuscript.

Competing interests None.

Ethics approval Rome Tor Vergata Ethical Committee.

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Notes