Correlations between Peripheral Trans Fatty Acids, Lipid Peroxidation Markers and Cognition in Dementia

Amira Zarrouk1*, Imed Cheraif2, Samia Hadj-Ahmed1, Wafa Chaabane1, Sonia Hammami, Meryam Debbabi1, Mahbouba Frih3, Olivier Rouaud4, Thibault Moreau5, Gérard Lizard6* and Mohamed Hammami7

1LR12ES05, Lab-NAFS ‘Nutrition - Functional Food and Vascular Health’, University of Monastir, Monastir, Tunisia
2Team ‘Biochemistry of the peroxisome, inflammation and lipid metabolism’ EA7270/INSERM, Dijon, France
3Neurology department, University Hospital F. Bourgogne, Monastir, Tunisia
4Memory Center, Resources and Research of Burgundy, University Hospital, Dijon, France
5Department of Neurology, University Hospital/University of Bourgogne Franche Comté, Dijon, France

Abstract

Relationships between alterations in lipid metabolism, oxidative stress and dementia are widely suspected. In order to determine the impact of trans fatty acids (TFA) on oxidative stress and lipid peroxidation in demented patients, plasma and red blood cells (RBCs) were collected from patients diagnosed with Alzheimer’s diseases (AD) or vascular dementia, and from an age-matched healthy control group of elderly individuals. Fatty acid profiles were established by gas chromatography on matched plasma and RBCs. Lipid peroxidation biomarkers (malondialdehyde (MDA) and conjugated dienes (CD)) were analyzed using spectrophotometric methods. The severity of dementia was evaluated with the Mini-Mental State Examination (MMSE). An accumulation of MDA and CD and of several TFA including elaidic and vaccenic acids was observed in the plasma and RBCs of demented patients. In the plasma and RBCs, positive correlations were found between CD and TFA: C18:1 trans 11 (vaccenic acid) in AD patients; sum of TFA and C18:2 cis 9 trans 12 in patients with vascular dementia (P<0.05). In RBCs, a negative correlation was observed between C18:1 trans 11 and MMSE scores in vascular dementia. Altogether, our data suggest the existence of relationships between TFA, oxidative stress, lipid peroxidation and the risk of cognitive disorders.

Keywords: Trans fatty acids; Dementia; Oxidative stress; Lipid peroxidation; Red blood cells; Plasma

Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that leads to dementia and affects approximately 10% of the population older than 65 years of age. Memory loss is the first sign of cognitive impairment, followed by aphasia, agnosia, apraxia, and behavioral disturbances [1]. The two main types of brain lesions observed in AD are amyloid deposits and neurofibrillary tangles (NFTs). Amyloid deposits, which constitute senile plaques can be influenced by the lipid status, and result from the extracellular accumulation of a peptide referred to as Aβ [1,2], Hyperphosphorylated tau protein aggregates and altered tubulin microfilaments are major components of NFTs identified in dying neurons [1].

Trans fatty acids (TFA) are unsaturated fatty acids (UFA) containing at least one non-conjugated carbon–carbon double bond in the trans configuration [3]. UFA are synthesized only in the cis configuration in humans whereas TFA are mainly provided from the diet. Indeed, TFA can be found in some plants or produced by bacteria in the rumen of ruminants, and they account for 2–5% of the total fatty acid content of their meat and milk [3]. However, the major dietary source of these fats is industrial [4]. So far, TFA have been linked to coronary diseases and arteriosclerosis [5]. In fact, the consumption of industrial TFA is believed to have adverse effects on cardiovascular health by altering blood lipid profiles, by modifying apolipoprotein levels (raising the LDL-cholesterol/HDL-cholesterol ratio and levels of Lp(a)) and by promoting systemic inflammation as well as endothelial dysfunctions [5-7].

So far, the evidence of a direct relationship between the uptake of TFA and neurodegenerative diseases is limited. Only two epidemiological studies have examined the link between TFA intake and the relative risk of developing AD, and the results were contradictory [8,9] in that one showed a non-significant negative finding [8] and the other a positive association at the beginning of the epidemiological study [10].

On the other hand, a high consumption of both industrial and natural TFA has been shown to cause oxidative stress, but it has been reported that the reverse phenomenon can also happen. Indeed, an oxidative stress-mediated increase in TFA in vivo was first demonstrated in the liver, heart, kidney, adipose tissue, and erythrocyte membrane phospholipids of young adult rats fed with a diet free of trans isomers exposed to γ-irradiation [11].

At the moment, whereas there is some evidence that TFA are associated with the occurrence of cardiovascular diseases, little is known about the impact of TFA on the development of dementia. We therefore set out to investigate the relationship between the TFA profile and the occurrence of AD and vascular dementia. To this end, TFA profiles in plasma and RBCs from patients with AD and vascular dementia and healthy age-matched controls were determined by gas chromatography (GC) and the results were compared. In our study, we: 1) assessed lipid peroxidation markers (malondialdehyde (MDA) and conjugated diene (CD)) and 2) assessed the plasma levels of TFA, and iii) explored the relationships between TFA levels, oxidative stress, and the Mini-Mental State Examination test (MMSE).

*Corresponding authors: Amira Zarrouk, PhD, Faculty of Medicine, University of Monastir, Monastir, Tunisia, E-mail: zarroukamira@gmail.com

Gérard Lizard, PhD, EA 7270, INSERM, Faculty of Sciences, University of Bourgogne Franche Comté, France, Tel: +33 380 39 62 56; Fax: +33 380 39 62 50; E-mail: gerard.lizard@u-bourgogne.fr

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Materials and Methods

Patients

All assessments were carried out after written and/or verbal informed consent had been obtained from the family of patients and from healthy controls. A total of 43 demented patients (15 women, 28 men) with either AD or vascular dementia were included (Table 1). All of them were from central Tunisia and consulted at Fattouma Bourguiba University Hospital (Monastir, Tunisia) between January and July 2011. The control group contained 54 age-matched subjects (24 women, 30 men; Age: mean ± SD: 71 ± 8 years; Median/range: 70/56–92 years) with no memory complaints or other cognitive impairment. These control subjects were recruited from nursing homes for the elderly in central Tunisia (Sousse, Madhia, and Monastir). All participants underwent a complete clinical investigation, including medical history, neurological and neuropsychological examinations; MMSE (Mini Mental State Examination), screening laboratory tests and magnetic resonance neuroimaging. The following groups of patients were investigated. The group of AD patients (n=26) consisted of patients diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). These patients were further classified according to their MMSE scores as follows: mild AD (MMSE 19-26), moderate AD (MMSE 10-19) and severe AD (MMSE<10). The patients with vascular dementia (n=17) were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).

Preparation of blood samples

Venous blood samples were collected into EDTA tubes after overnight fasting. Then, the plasma and red blood cells (RBCs) were separated by centrifugation at 1,400 g for 10 min at 4°C. The plasma was then removed, and the RBCs were washed three times in saline solution (0.9% NaCl), centrifuged and stored at -80°C until biochemical analysis. Conventional biochemical characteristics of patients including total cholesterol and triglycerides were determined as described previously [12].

Extraction of fatty acids and total fatty acids for profile analysis

Fatty acids were analyzed as fatty acid methyl esters (FAMEs) by gas chromatography (GC). Total lipids were extracted from the plasma and RBCs as described by Folch et al. by using a chloroform-methanol (2:1, v/v) solvent system containing 0.01% butylated hydroxytoluene as the antioxidant and C17:0 as the internal standard [13]. Aliquots of total lipids were converted into methyl esters using 14% methanol-boron trifluoride (BF3) at 50°C for 30 min. FAMEs were analyzed in duplicate by comparing their retention times with those of individual standards. The fatty acid composition was reported as a relative percentage of the total peak area using an HP Chemstation integrator. The percentage of each fatty acid was determined by dividing the peak area of each fatty acid by the total peak area.

Determination of lipid peroxidation products

Lipid peroxidation was determined indirectly by measuring the production of malondialdehyde (MDA) in the plasma and RBCs lysate following the method of Yoshioka et al. [14]. Briefly, 250 μL of plasma or RBCs lysate was mixed with 1.25 mL of trichloracetic acid (20%) to precipitate the proteins. Thiobarbituric acid (0.67%) was then added, and the mixture was incubated for 30 min at 95°C. After cooling to room temperature, 4 mL of n-butanol were added and absorbance was measured at 530 nm.

Conjugated dienes (CD) are another indicator of lipid peroxidation and these were measured as described by Esterbauer et al. [15]. The results were expressed as μmoles hydroperoxide / mg protein.

Statistical analyses

The lipid profile data were analyzed using the Statistical Package for Social Sciences (SPSS 18.0 for Windows). Means of all measurements are presented with standard deviations (mean ± SD). A non-parametric Mann-Whitney test was used. The Spearman correlation test was also used to evaluate the relationships between various parameters. Differences with P ≤ 0.05 were considered significant.

Results

Clinical, cognitive and biochemical characteristics of patients

The clinical features of controls and patients with AD and vascular dementia are summarized in Table 1. Most of the demented patients were suffering from moderate dementia as evaluated with the Mini Mental State Examination (MMSE) test. No significant differences in cholesterol, triglyceride, and lipoprotein levels were observed between controls and demented patients.

Evaluation of trans fatty acid profiles in red blood cells and plasma

The fatty acid profile of RBC membranes is given in Table 2. Analysis of the fatty acid composition of RBCs in demented patients showed a significantly lower sum of saturated fatty acids (ΣSFA) in the patients with AD than in controls. The sum of monounsaturated fatty acids (ΣMUFA) was significantly lower in the group of patients with vascular dementia than in controls. At the opposite, the sum of polyunsaturated fatty acids (ΣPUFA) was significantly higher in AD patients as compared with vascular dementia patients.

Table 1: Demographic and biochemical characteristics of controls and demented patients.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Controls n=54</th>
<th>Alzheimer’s disease n=26</th>
<th>Vascular dementia n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>71 ± 8</td>
<td>74 ± 7</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>Median (range)</td>
<td>70 (56-92)</td>
<td>73 (60-83)</td>
<td>74 (59-91)</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>24/30</td>
<td>Dec-14</td>
<td>Mar-14</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>16 (30 %)</td>
<td>10 (38.5 %)</td>
<td>9 (53 %)</td>
</tr>
<tr>
<td>MMSE Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;26</td>
<td>54 (100 %)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mild [19-26]</td>
<td>-</td>
<td>4 (15.4 %)</td>
<td>3 (17.6 %)</td>
</tr>
<tr>
<td>Moderate [10-19]</td>
<td>-</td>
<td>14 (53.9 %)</td>
<td>13 (76.5 %)</td>
</tr>
<tr>
<td>Severe &lt;10</td>
<td>8 (30.8 %)</td>
<td>1 (5.9 %)</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.08 ± 0.54</td>
<td>2.42 ± 0.75</td>
<td>2.06 ± 0.91</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.66 ± 0.47</td>
<td>1.71 ± 0.61</td>
<td>1.70 ± 0.40</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.27 ± 0.32</td>
<td>1.13 ± 0.53</td>
<td>1.24 ± 0.34</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.37 ± 0.82</td>
<td>4.71 ± 3.19</td>
<td>4.33 ± 1.23</td>
</tr>
<tr>
<td>Apo-A1 (g/L)</td>
<td>1.41 ± 0.30</td>
<td>1.38 ± 0.43</td>
<td>1.38 ± 0.26</td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>0.72 ± 0.22</td>
<td>0.71 ± 0.14</td>
<td>0.60 ± 0.29</td>
</tr>
<tr>
<td>Cholesterol/HDL-C</td>
<td>2.67 ± 0.87</td>
<td>2.79 ± 0.51</td>
<td>2.55 ± 0.48</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>1.42 ± 0.59</td>
<td>1.45 ± 0.42</td>
<td>1.21 ± 0.44</td>
</tr>
</tbody>
</table>

Table 2: Fatty acid composition of red blood cells.
Evaluation of lipid peroxidation biomarkers in red blood cells and plasma

We focused on the quantification of various lipid peroxidation products of cellular constituents of RBCs and plasma of demented patients and healthy age-matched controls. The results of this analysis are presented in Table 4. Significantly higher levels of malondialdehyde (MDA) were observed in RBCs from demented patients (AD and vascular dementia) than in RBCs from controls. Higher levels of CD were also observed in RBCs from patients with AD and vascular dementia than in control RBCs. MDA and CD levels were also significantly higher in plasma from demented patients (AD and vascular dementia) than in plasma from controls.

Evaluation of the relationships between trans fatty acid levels in red blood cells or plasma and MMSE

To determine the relationships between TFA levels and cognition, a statistical analysis of the different TFAs and MMSE scores was performed with the Spearman correlation test. In the vascular dementia group, a significant negative correlation was found between MMSE scores and levels of C18:1 trans 11 (vaccenic acid) in RBCs (r=-0.69; p<0.05) (Figure 1). In the AD group, negative correlations were also found between ΣTFA and ΣUFA in plasma (r=-0.50, p<0.05) (Figure 2).

Evaluation of the relationships between trans fatty acid levels in red blood cells or plasma and lipid peroxidation biomarkers

In AD patients, a significant positive correlation was found between C18:1 trans 11 (vaccenic acid) and CD in RBCs (Figure 3A). In patients with vascular dementia, a positive correlation was observed between CD in RBCs and ΣTFA in plasma, as well as between CD in RBCs and

### Table 2: Fatty acid profiles in Red blood cells (RBCs) of controls and demented patients determined by gas chromatography.

<table>
<thead>
<tr>
<th>Trans Fatty acids</th>
<th>Controls n=54</th>
<th>Alzheimer’s disease n=26</th>
<th>Vascular dementia n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>C16:1 cis 11</td>
<td>1.10 ± 0.59</td>
<td>0.49 ± 0.23*</td>
<td>0.39 ± 0.17*</td>
</tr>
<tr>
<td>C18:1 trans 9</td>
<td>0.65 ± 0.14</td>
<td>0.56 ± 0.13</td>
<td>1.20 ± 0.37*</td>
</tr>
<tr>
<td>C18:1 cis 11</td>
<td>1.02 ± 0.22</td>
<td>1.43 ± 0.58</td>
<td>2.33 ± 0.21*</td>
</tr>
<tr>
<td>C18:2 trans 9 cis 12</td>
<td>0.50 ± 0.26</td>
<td>0.43 ± 0.12</td>
<td>0.21 ± 0.14</td>
</tr>
<tr>
<td>C18:2 cis 9 cis 12</td>
<td>0.42 ± 0.15</td>
<td>0.38 ± 0.14</td>
<td>0.48 ± 0.16</td>
</tr>
<tr>
<td>C18:2 cis 9 trans 12</td>
<td>0.30 ± 0.12</td>
<td>0.95 ± 0.22*</td>
<td>0.59 ± 0.13</td>
</tr>
<tr>
<td>C20:1 cis 11</td>
<td>0.38 ± 0.12</td>
<td>0.47 ± 0.23</td>
<td>0.76 ± 0.23*</td>
</tr>
<tr>
<td>C18:2 cis 9 trans 11</td>
<td>0.23 ± 0.02</td>
<td>0.33 ± 0.09</td>
<td>0.25 ± 0.10</td>
</tr>
<tr>
<td>C18:2 trans 10 cis 12</td>
<td>0.29 ± 0.10</td>
<td>0.32 ± 0.08</td>
<td>0.38 ± 0.04</td>
</tr>
</tbody>
</table>

Data are expressed as relative values (%): mean % of total FA ± SD. Σ MUFA: sum of monounsaturated fatty acids. A significant difference between controls and demented patients is indicated by *(P<0.05). The Mann-Whitney test was used.

### Table 4: Malondialdehyde (MDA) and conjugated diene (CD) levels in the plasma and red blood cells (RBCs) of controls and demented patients with Alzheimer’s disease or vascular dementia.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Alzheimer’s disease</th>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Σ MUFA</td>
<td>34.07 ± 4.96</td>
<td>36.63 ± 6.68*</td>
<td>37.08 ± 5.32*</td>
</tr>
<tr>
<td>Σ UFA</td>
<td>29.00 ± 11.02</td>
<td>34.39 ± 5.19*</td>
<td>36.88 ± 4.62</td>
</tr>
<tr>
<td>Σ TFA</td>
<td>4.78 ± 0.92</td>
<td>4.97 ± 1.15*</td>
<td>3.16 ± 1.01</td>
</tr>
<tr>
<td>Σ SFA</td>
<td>9.01 ± 5.75</td>
<td>9.32 ± 11.11*</td>
<td>12.34 ± 11.18</td>
</tr>
<tr>
<td>Σ PUFA</td>
<td>0.18 ± 0.05</td>
<td>0.28 ± 0.08*</td>
<td>0.25 ± 0.08*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Conjugated dienes (CD) malondialdehyde (MDA) levels are shown in the plasma and RBCs of controls, and patients with Alzheimer’s disease (AD) or vascular dementia. Statistical analyses were performed with the Mann-Whitney test. Significant differences between controls and demented patients were observed as follows: *: P<0.05; **: P<0.001.

plasma levels of C18:1 trans 9 (elaidic acid) and C18:2 trans 9 cis 12 (r=0.73, r=0.57 and r=0.70, respectively; p<0.05) (Figure 3B).

**Discussion**

Alzheimer disease (AD) is the most prevalent type of dementia in the world. Several lipid alterations, which could contribute to RedOx imbalance, have been associated with dementia. Among these lipids, the role played by trans fatty acids (TFA), which are UFA containing non-conjugated carbon–carbon double bonds in the trans configuration, is still not well known. These fatty acids are metabolized normally and deposited in tissues. TFA and cis fatty acids are transported in a similar fashion and are incorporated into cell membranes at the same level. Correlations between TFA uptake and the development of cardiovascular diseases have been reported by several studies. It has also been reported that TFAs tended to increase plasma concentrations of total and low-density lipoprotein cholesterol (LDL–C), which, in turn, may be associated with the risk of AD [16]. However, the evidence of relationships between TFA and neurodegenerative disease is still limited. The present study conducted in patients with AD and vascular dementia versus age-matched healthy subjects brings new evidence that TFA might contribute to the development of AD and vascular dementia. Our data showed that levels of oxidative stress and TFA in the plasma...
and RBCs were greater in patients with AD and vascular dementia than in controls. Positive correlations were also found between TFA and CD, and negative correlations were observed between TFA and the MMSE.

As oxidative stress is believed to contribute to cognitive impairment associated with AD [17], we attempted to establish in first the existence of relationships between TFA levels and oxidative stress. At the moment, high intra-cerebral levels of MDA, 4-hydroxynonenal (4-HNE), and F2-isoprostane, which are indicators of lipid peroxidation, have been found in the cerebrospinal fluid of AD patients [16,18]. A high consumption of industrial and/or natural TFA has been shown to cause oxidative stress. One study showed a 20% increase in the level of an isoprostane (8-iso-PGF2α) in the urine of healthy subjects after three weeks of a diet rich in industrial TFA in comparison with the control diet [19]. Besides, the impact of oxidative events on TFA generation remains to be determined. It has been suggested that free radicals formed during stressful conditions are able to induce the formation of TFA in vivo via cis-trans isomerization of their cis precursor [11]. Indeed, it has been demonstrated that free-radical stress coupled with weakened defense systems can change the molecular shape of UFA residues in vivo. The role of reactive oxygen species (ROS) and NO radicals as important mediators in lipid isomerization has been highlighted [20]. In fact, PUFA and phospholipids in cellular membranes may be chemically modified under oxidative conditions. Thus, Zghibeh et al. demonstrated that some isomers of trans-arachidonic acid may originate from NO-mediated arachidonic acid isomerization in humans [20]. This process is of potential importance in ageing and neurodegenerative diseases since oxidative stress has largely been described as an essential inducer of several disorders observed in these diseases. In the present study, a clear correlation was shown between oxidative stress and TFA, and the role played by environmental oxidative conditions and increases in TFA levels in the RBCs and plasma of patients with AD and vascular dementia must be taken in consideration. In this regard, several significant and positive correlations were found. The C18:2 cis 9 trans 12 isomer showed a strong correlation with CD in RBCs, thus suggesting potential competition between lipid peroxidation and fatty acid isomerization. As it is known that PUFA are more easily isomerized than MUFA [21], a stronger link between C18:2 isomers and CD, a biomarker of lipid peroxidation, was expected and revealed. This was in agreement with an in vitro study which investigated the competition between lipid peroxidation and isomerization. Indeed, the major trans isomer of C18:2 cis 9 cis 12 formed in liposomes was C18:2 trans 9 cis 12 [22]. On the other hand, the peripheral fatty acid profile is known to be influenced by dietary habits [23,24]. The dietary intake of industrial TFA or TFA produced by ruminants could be evaluated by determining C18:1 trans 9 and C18:1 trans 11 levels in plasma and RBCs. An accumulation of TFA (C18:1 trans 9 (elaidic acid), C18:1 trans 11 (vaccenic acid), C20:1 cis 11, C18:2 cis 9 trans 12, C18:2 trans 9 trans 12, C18:2 trans 9 cis 12, and C18:2 trans 10 cis 12) was indeed observed in the plasma and/or RBCs of our patients with AD and vascular dementia. The higher levels of C18:1 trans 11 and C18:1 trans 9 might also reflect an increased intake of dairy fat and/or the regular consumption of margarine, as previously reported [25].

In a future study, it could be consequently of interest to evaluate the nutritional habits of demented patients in order to clarify the origin of the increase in TFA in plasma and RBCs cells. Indeed, it cannot be excluded that the levels of TFA could also depend on the initial amounts of their cis precursor in the blood. Indeed, in RBCs and plasma, C18:1 cis 9 accounts for about 20% of total fatty acid content while C18:1 cis 11 accounts for less than 3%. Thus, the C18:1 cis 9 fatty acid is more likely to be isomerized by free radicals than is C18:1 cis 11 fatty acid. Similar observations can be made concerning C18:2 cis 9 trans 12, whose precursor, linoleic acid (C18:2 cis 9 cis 12), is the most abundant of all UFA. Of note, the trans-18:2 isomers have generally been associated with a higher relative risk of cardiovascular diseases than trans-18:1 isomers [26].

From a biological point of view, the occurrence of cis-trans isomerization by free radicals may have important side effects on several biological functions since the predominant geometry displayed by UFA in eukaryotes is cis. The formation of trans isomers can have important meaning and consequences connected to radical stress. Indeed, TFA can influence the physical characteristics of bilayer microdomains, thus affecting membrane properties and functions [27,28]. Trans arachidonic acids were also shown to induce the selective apoptosis of microvascular endothelial cells in vitro and to favor retinal microvascular degeneration ex vivo and in vivo, and they may contribute to vascular dementia. These effects seemed to be independent of classical major arachidonic acid metabolic pathways [29]. In addition, trans arachidonic acid isomers may serve as precursors for unusual eicosanoids, via lipoygenase and cyclooxygenase pathways. According to Grimm et al. TFA could also favor the cleavage of β-Amyloid precursor protein (APP) via the amyloidogenic pathway. The non-amyloidogenic pathway was shown to be repressed in the presence of TFA. In fact, a decrease in ADAM 10 gene expression as well as the expression of α-secretase is associated with an increase in BACE1 expression and in proteins forming the β-secretase complex. Furthermore, it was demonstrated that TFA favor the oligomerization and the accumulation of Aβ [30]. Therefore, these different arguments support the presence of a link between TFA and amyloidogenesis. It was therefore of interest to determine whether there was a relationship between TFA and the severity of dementia evaluated with the MMSE. As a negative correlation was observed between C18:1 trans 11 and the MMSE score in vascular dementia group, our data bring additional evidence supporting the hypothesis that some TFA might have a negative impact on cognition, and are potential risk factors for the development of AD. These data also suggest that some TFA might constitute potential biomarkers of AD.

In conclusion, our data demonstrate an accumulation of several TFA in the plasma and RBCs of demented patients with AD or vascular dementia, and they suggest a link between TFA and oxidative stress in the plasma and RBCs of these patients, thus reinforcing the hypothesis that TFA, especially those present in high amounts in numerous processed foods, could contribute to neurodegeneration. However, it cannot be excluded that TFA could also be formed in vivo by oxidative stress [31]. These two pathways might coexist in patients with AD and vascular dementia, and could explain, at least in part, the correlation between TFA, oxidative stress and lipid peroxidation, and the decline in cognitive performances in the patients included in the present study. Altogether, our data provide new evidence of altered fatty acid profiles in demented patients [32,33], and they underline the potential risks of TFA in the development of dementia.

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Applications des Sciences de l'Information en Médecine (ABASIM, Dijon, France) for their financial supports.

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