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Decreased arylesterase activity of paraoxonase-1 (PON-1) might be a common denominator of neuroinflammatory and neurodegenerative diseases

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ABSTRACT

High-density lipoprotein (HDL)-bound paraoxonase-1 (PON-1) is mechanistically related to oxidative stress, inflammation and atherosclerosis and this multirole nature positions the enzyme as potential pathogenic player and candidate biomarker for many diseases. Our previous work suggests that decline in serum PON-1 activities, *i.e.* arylesterase and paraoxonase, might be associated with the occurrence of mild cognitive impairment (MCI) to late onset Alzheimer's disease (LOAD) or vascular dementia (VAD). The present study aimed to: (1) expand our previous findings in a larger and different population, including patients with LOAD-VAD mixed dementia (MD); (2) explore a possible association between PON-1 and multiple sclerosis (MS); (3) evaluate if cerebrospinal fluid (CSF) levels of PON-1 activities might be useful biomarkers for MS. We found that serum arylesterase, but not paraoxonase, levels of PON-1 were significantly lower in patients affected by MCI (n = 232), VAD (n = 65), LOAD (n = 175), MD (n = 88) as well as those with MS (n = 104) as compared to healthy controls. Notably, the most pronounced decline in this activity was shown by MD (−18%, $p < 0.01$) and MS (−23%, $p < 0.001$), while the lowest changes were detected in the MCI group (11%, $p < 0.05$). Only arylesterase was detectable in the CSF of MS patients and the levels were not significantly different from those detected in the other two neurological control groups. Overall our data suggest that a depressed arylesterase activity could be a common denominator of different neurological diseases which, independently of their peculiar ethiopathogenesis and pathophysiology, appear to be all characterized by an altered systemic redox balance.

Abbreviations: ARE, arylesterase; B, unstandardized regression coefficient; CSF, Cerebrospinal Fluid; CT, Computer tomography; CVD, cardiovascular disease; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; LOAD, late onset Alzheimer's disease; MCI, mild cognitive impairment; MD, mixed dementia; MMSE, mini mental state examination; MS, multiple sclerosis; NSAID-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; OR, Odds Ratio; OxS, Oxidative Stress; PON-1, Paraoxonase-1; ROS, reactive oxygen species; VAD, vascular dementia.

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1. Introduction

Paraoxonase-1 (PON-1) is an enzyme residing on high density lipoprotein (HDL) that catalyzes the hydrolysis of various aromatic carboxylic acid esters, organophosphates and lactones (James, 2006). Three distinct catalytic activities have been attributed to PON-1 machinery: (1) paraoxonase, hydrolyzing organophosphates and pesticides; (2) arylesterase (ARE), catalyzing the hydrolysis of non-phosphorous arylesters; 3) lactonase, hydrolyzing lactones (Khersonsky and Tawfik, 2006). These multiple activities strongly contribute to the well-recognized anti-inflammatory and antioxidant functions of HDLs. In particular, lactonase and ARE activities might be important for the hydrolysis of lipid hydroperoxides either free or present in minimally oxidized low density lipoproteins (LDL) (Aviram et al., 1998; Rosenblat et al., 2006b). Besides, PON-1 appears to protect HDL itself by lipoperoxidation, thereby preserving oxidative-sensitive anti-inflammatory function of the lipoproteins (Aviram et al., 1998). Notably, growing experimental evidence showed that the antioxidant shield afforded by PON-1 is essential for HDL role in preventing endothelial damage as well as in mediating cholesterol efflux from macrophage foam cells in atherosclerotic lesions (Rosenblat et al., 2006a,b; Aviram et al., 1998).

The pronounced multifactorial essence of PON-1 might account for the well-documented association between serum paraoxonase, but mostly, ARE and vascular diseases such as coronary arterial disease and vascular dementia (VAD) (Cervellati et al., 2015a; Bhattacharyya et al., 2008; Wehr et al., 2009), as well as neurodegenerative diseases, such as Parkinson's and late onset Alzheimer's diseases (LOAD) (Cervellati et al., 2015a,b; Lee et al., 2013; Dantoine et al., 2002; Zengi et al., 2012). Noteworthy, we have recently found that patients experiencing the prodromal phase of LOAD, mild cognitive impairment (MCI), already presented a significant decline in ARE accompanied by a precocious derangement of systemic redox homeostasis (Cervellati et al., 2013, 2014b, 2015a)

Oxidative injury primarily caused by respiratory burst of invading and resident macrophages and astrocytes are widely suggested to play a central role in the pathogenesis of another neurological disease, multiple sclerosis (MS) (Lassmann and van Horssen, 2016). MS is a chronic inflammatory disease of the central nervous system (CNS), of supposed autoimmune origin, in which both demyelination and neurodegenaration are observed (Goverman, 2009). Activation of CNS immune cells in this pathological scenario leads to the generation of reactive oxygen species (ROS) by nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases (Fischer et al., 2012) and myeloperoxidase (Gray et al., 2008). Excess reactive oxygen species (ROS) impairs the function of the mitochondrial respiratory chain, leading to electron leakage and amplification of Oxidative Stress (OxS) which contribute to the onset and progression of the common pathophysiological hallmarks: inflammation, demyelination, axonal damage, and repair processes (Miller et al., 2014; Fischer et al., 2012; Haider, 2015).

The intimate implication of oxidative processes in MS development are supported by recent findings showing that oxidized lipids (malondialdehyde) and DNA (8-hydroxy-D-guanosine) were highly enriched in neurons and oligodendrocytes of active multiple sclerosis plaques (Haider et al., 2011). Oxidative damage also appears to reflect in blood, saliva and urine (Karlík et al., 2015; Guan et al., 2015) and cerebrospinal fluid (CSF) of MS patients when compared with healthy controls (Mattsson et al., 2007).

The aforementioned thriving body of epidemiological and experimental evidence suggests that antioxidant and anti-inflammatory properties of PON-1 put this enzyme as a potential player in the pathogenesis and progression of MS. To address this hypothesis, we evaluated paraoxonase/ARE activities in serum of patients with relapsing-remitting MS (RRMS) and compared the levels to those of: (1) healthy individuals; (2) patients affected by MCI, LOAD and VAD, where PON-1 has been already found to be associated with; (3) patients affected by LOAD/VAD mixed dementia (MD). CSF is regarded as a reliable source of molecular biomarkers of neurological function since it is in direct contact with the extracellular space of the brain. Since HDLs are also present in this biological fluid, we investigated whether CSF paraoxonase/ARE activities could be potential biomarkers for MS.

Table 1
Main demographic and clinical characteristics of *MS cohort* including patients with multiple sclerosis (MS), other inflammatory neurological diseases (OIND) and non-inflammatory neurological diseases (NIND).

	MS (n = 104)	OIND (n = 76)	NIND (n = 72)
Age, years	38 ± 10	52 ± 12[a]	59 ± 11[a]
Gender, females (%)	58	40[a]	44[a]
Disease duration, months	2 (1, 24)	–	–
EDSS	2.0 ± 1.4	–	–
Disease activity			
Gd^+ n (%)	29 (40)		
GD^- n, (%)	44 (60)		

Data are presented as mean ± standard deviation for age and EDSS, median (interquartile range) for disease duration, percentage for gender and number of subjects (%) for disease activity.
Pairwise comparison: [a] $p < 0.05$ *vs* MS.
EDSS, expanded disability status scale; Gd^+: magnetic resonance imaging (MRI) appearance of gadolium-enhancing lesions; Gd^-: no MRI evidence of gadolium-enhancing lesion.

2. Materials and methods

2.1. Patients selection

The study was conducted on two cohorts that will be referred as "MS" and "Dementia" for matter of clarity (main demographic characteristics are shown in Tables 1 and 2, respectively).

2.1.1. MS cohort

This cohort included 104 consecutive untreated patients with definite relapsing–remitting (RR) MS according to the current criteria (Polman et al., 2011) attending to the MS Center of Ferrara (Italy). All patients were imaged with a 1.5-T magnetic resonance imaging (MRI) unit within 48 h after blood sampling. At the time of sample collection (a) the disease severity was scored using Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) (mean score = 2.0 ± 1.4); (b) the presence of relapse was classified as clinical activity; (c) the lesions showing Gd-enhancement on

Table 2
Main demographic characteristics of *Dementia cohort* including patients with late onset Alzheimer disease (LOAD), vascular dementia (VAD), mixed Alzheimer's/vascular dementia (MD) mild cognitive impairment (MCI), and healthy individuals (CONTROLS).

	CONTROLS (n = 165)	MCI (n = 232)	VAD (n = 65)	LOAD (n = 174)	MD (n = 88)
Age, years	67 ± 10	76 ± 6[a]	78 ± 7[a]	78 ± 6[a]	80 ± 4[a]
Gender, females (%)	74[b,c]	59[a]	54[a]	72[b,c]	65[a,b]

Data are presented as mean ± standard deviation for age and percentage for gender.
Pairwise comparison: [a] $p < 0.05$ vs. CONTROLS; [b] $p < 0.05$ vs. VAD; [c] $p < 0.05$ vs. MCI.

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T1-weighted scans were defined as MRI activity. The inclusion criteria were: no fever or other symptoms or signs of acute infection; no potential disease-modifying therapies during the six months before the study. Seventy-six patients with other inflammatory neurological disorders (OIND) and 72 with non-inflammatory neurological disorders (NIND) were selected as neurological controls. OIND group included patients with chronic inflammatory demyelinating polyneuropathy (n = 23), acute inflammatory demyelinating polyneuropathy (n = 16), viral encephalomyelitis (n = 11), bacterial meningitis (n = 8) and other diseases with minor prevalence (n = 18). NIND group included patients with headache (n = 12), epilepsy (n = 8), brain tumor (n = 7), ischemic stroke (n = 6), amyotrophic lateral sclerosis (n = 4), compression neuropathy (n = 4,) and other diseases with minor prevalence (n = 31).

The study on MS cohort was performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the guidelines for Good Clinical Practice (European Medicines Agency). The approvals of the Committee for Medical Ethics in Research of the University of Ferrara has been obtained for experiments involving human subjects. Written informed consent was obtained from each patient before inclusion in the study.

2.1.2. Dementia cohort

Seven hundred and two consecutive subjects referring to the Day Hospital Services for Cognitive Decline (University of Ferrara, Italy) were enrolled into this cohort as described in details in previous published studies (Cervellati et al., 2014b; Cervellati et al., 2015b).

The cohort included the following subsets: (1) 175 patients with LOAD as diagnosed by the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Only patients with "probable" Alzheimer's disease were included; patients with "possible" LOAD or with LOAD and significant cerebrovascular disease on computed tomography (CT) scans were excluded; mini mental status examination (MMSE) score ranged (interquartile) between 18 and 24; (2) 232 individuals with MCI, defined as the presence of short/long-term memory impairment, with/without impairment in other single or multiple cognitive domains, in an individual who didn't meet the standardized criteria for dementia (other details regarding diagnostic criteria used have been previously reported here Cervellati et al., 2013); MMSE range: 22–27; (3) 65 patients with VAD as diagnosed according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Román et al., 1993); MMSE range: 19–23; (4) 88 patients were categorized as MD according to the NINDS-AIREN criteria for this type of dementia; both the VAD and MD groups presented significant vascular disease as observed on brain CT, either in the form of multiple infarcts, or multiple and/or confluent lacunar infarct, along with multiple risk factors including an history of cardiovascular accidents, type II diabetes and hypertension; MMSE range: 17–23; (5) 165 apparently healthy individuals (CONTROLS) without evidence of dementia and without any functional disability attributable to cognitive impairment or neurological disease. MMSE range: 25–28. Moreover, to obtain a control group with a mean age closer to the one of MS patients, an additional subset of healthy women (n = 37, mean age = 51 ± 9) randomly selected from the sample recruited (Cervellati et al., 2011) by Menopausal and Osteoporosis Centre (University of Ferrara) was added.

The study on this cohort was carried out according to the Declaration of Helsinki (World Medical Association, http://www.wma.net), the guidelines for Good Clinical Practice (European Medicines Agency, http://www.ema.europa.eu) and it was approved by the local Ethic Committee. Signed informed consent, which was written in compliance with local and national ethical guidelines, was obtained from each patient prior to the inclusion into the study. Personal data and medical history were collected by a structured interview from participants and/or their caregiver (if demented) during the first visit.

All patients underwent a general and neurological examination. For neuropsychological assessment, all patients were given a battery of tests as previously reported (Cervellati et al., 2013). Routine analyses including liver function, serum folate and B12 vitamin, thyroid function, blood cell count, and arterial oxygen saturation were performed to exclude causes of secondary cognitive impairment. Subjects affected by severe congestive heart failure, severe liver or kidney disease, cancer, and chronic obstructive pulmonary disease were not included in the study. There were no evidences of acute illnesses at the time of clinical observation and blood sampling; no subject was taking Nonsteroidal anti-inflammatory drugs (NSAIDS), antibiotics or steroids at the time of recruitment.

Lastly, no identifying information were available to the Authors of the study in order to protect the anonymity of the patients.

2.2. CSF and serum sampling

Venous blood was withdrawn from all subjects (both cohorts) upon an overnight fast, between 8.30 and 9.30 A.M. Paired CSF and serum samples were exclusively collected from MS, OIND and NIND patients for diagnostic purposes. CSF samples were obtained by atraumatic lumbar puncture performed in the absence of contraindications. Both cell-free CSF and serum samples were obtained after centrifugation at 3000 rpm at 20 °C for 15 min. Supernatants were collected, under sterile conditions, aliquoted and stored at −80 °C until assay.

2.3. Biochemical assays in serum and CSF samples

Serum paraoxonase and ARE activities were measured by UV–vis spectrophotometric assays in a 96-well plate format by using a Tecan Infinite M200 microplate reader (Tecan group Ltd., Switzerland).

Briefly, paraoxonase activity was determined by measuring the 412 nm absorbance increase due to 4-nitrophenol formed upon addition of 5 μL of serum in 195 μL of reaction solution consisting in 1.5 mM paraoxon (Cat. No. 855790, Sigma-Aldrich, Milan, Italy), 0.9 M NaCl, and 2 mM $CaCl_2$ dissolved in 10 mM Tris–HCl, pH 8 (Charlton-Menys et al., 2006). A molar extinction coefficient of 17000 M^{-1} cm^{-1} was used for the calculation of enzyme activity, expressed in units per liter. One unit of paraoxonase activity is defined as 1 μmol of 4-nitrophenol formed per minute under the given conditions. Paraoxonase activity was undetectable in the CSF of study subjects.

ARE activity was assessed by adding 10 μL of serum (1:25 diluted) or 10 μL of CSF to 190 or 90 μL, respectively, of reaction mixture including 1 mM phenylacetate and 0.9 mM $CaCl_2$ dissolved in 9 mM Tris-HCl, pH 8 (Gan et al., 1991). A molar extinction coefficient of 1310 M^{-1} cm^{-1} was used for the calculation of enzyme activity, expressed in kilo unit per liter. One unit of ARE activity accounts for 1 μmol of phenol produced in a minute under the conditions of the assay.

2.4. Statistical analysis

Data analysis was performed using SPSS Statistics for Windows, version 18.0 (SPSS, Inc., Chicago, IL, USA). Chi-square tests were used to compare differences in categorical variables. Continuous variables were first checked for normal distribution using Kolmogorov-Smirnov test. Group comparisons were performed using one-way analysis of variance (ANOVA) with Bonferroni *post-*

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hoc test and Kruskall-Wallis followed by Mann-Whitney *U* tests (Bonferroni correction for multiple comparisons) for normally and non-normally (after base-10 logarithm transformation) distributed variables, respectively. Simple correlation analyses were performed using Pearson's and Spearman's tests for normally and non-normally distributed variables, respectively. Age and gender adjusted logistic regression analysis was used to assess the independent effects of low levels of ARE or paraoxonase activity on the likelihood of being affected by one disease compared to CONTROLS. Two-tailed probability values <0.05 were considered statistically significant.

3. Results

As first step of our analyses, we checked if the levels of serum ARE and paraoxonase activities detected in MS were different from those found in CONTROLS and in the other 4 groups of patients affected by other types of neurological diseases, *i.e.* MCI, LOAD, VAD and MD. The analysis by ANOVA, implemented by *post-hoc test* for pairwise comparison, revealed a significant ($p < 0.001$) decrease (−23%) in the normally-distributed ARE levels of MS patients compared to CONTROLS (median values = 76200 and 98850 U/L, respectively) (Fig. 1). The same statistical approach showed a slighter but still significant decrease of this activity in patients with MCI (−11%, $p < 0.05$), LOAD (−13%, $p < 0.01$), VAD (-15%, $p < 0.01$) and MD (−18%, $p < 0.01$) compared to CONTROLS. Of note, the group including individuals experiencing the so-called preclinical stage of dementia had significantly higher ($p < 0.05$) ARE levels as compared to MS.

Since serum paraoxonase activity showed a non-gaussian distribution, we analyzed its behavior across the groups by Kruskall-Wallis test, which was implemented by Mann-Whitney test for pairwise comparisons (Fig. 2). As the other PON-1 activity, serum paraoxonase exhibited a trend towards lower levels in MS and in the other patient groups compared to CONTROLS, but the differences did not reach significance levels (overall Kruskall-Wallis, $p = 0.340$). In particular, MS patients showed a very moderate decreased serum paraoxonase activity (median levels: 81.9 *vs* 86.5, 5% decrease).

Then, we focused on MS and we explored whether the two PON-1 activities were associated with MRI disease activity, duration of the disease and disease severity. Considering the restricted group of MS patients (n = 63) with available MRI data, we found no significant difference in these activities between subjects with and without MRI evidence of disease activity (Fig. 3A and B). Additionally, neither ARE nor paraoxonase correlated with EDSS score and disease duration as expressed in months (data not shown).

The results described so far, were interpreted as a clue that a decline in the ARE levels might be a feature shared by different forms of single disease affecting the CNS. To check this hypothesis, we employed a more robust statistical analysis, logistic regression, that allowed to evaluate the potential confounding effects of age and gender (both variables significantly varied across the groups as shown in Tables 1 and 2) on the observed univariate relationships. Since the reference intervals for ARE levels have not been established yet, we used the median values of these activities among CONTROLS (98820 U/L) as cut-off to define low and high levels of this marker. As shown in Fig. 4, low levels of serum ARE were significantly associated with an increased likelihood of a having MS (Odds Ratio (O.R.): 3.68, 95% Confidence Interval (CI): 1.50–9.20), MCI (O.R.: 1.91, 95% C.I.: 1.19–3.07), LOAD (O.R.: 2.40, 95% C.I.: 1.19–4.86), VAD (O.R.: 2.24, 95% C.I.: 1.32–3.81), MD (O.R.: 4.09, 95% C.I.: 1.99–8.45) compared to CONTROLS.

To further check on the possible interference of age on the outcomes regarding ARE, we tested if they were associated to each other by Spearman's test. The absence of significant correlation (within the whole sample: $r = 0.033$, $p = 0.0357$) represents an additional evidence in support of the independence of the above described relationships involving ARE.

The second part of our study was focused on the assessment of PON-1 activities in the CSF of MS, OIND and NIND (this specimen was unavailable in CONTROLS as described in Materials and Methods section) (serum and CSF ARE, and serum paraoxonase levels are summarized in supplementary material (1). Indeed, despite the lack of direct evidence, we expected to find detectable traces of this enzyme since HDLs, that carry PON-1 in plasma, are the only lipoprotein present in CNS (Wang and Eckel, 2014). We were able to detect only ARE activity (three orders of magnitude lower than

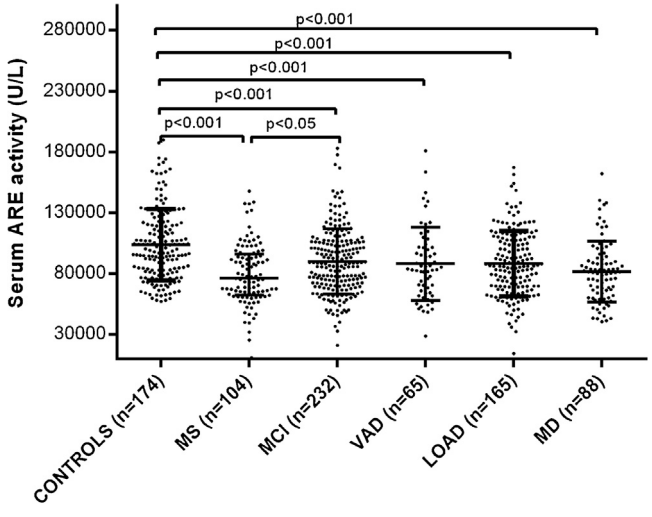

Fig. 1. Serum arylesterase (ARE) levels in CONTROLS were significantly, and similarly, lower than those measured in multiple sclerosis (MS), mild cognitive impairment (MCI), mixed dementia (MD), vascular dementia (VAD) or late Alzheimer disease (LOAD).
Medians of serum ARE: CONTROLS, 98820 U/L; MS, 76215 U/L; MCI, 88321 U/L; MD, 80911 U/L; VAD, 86210 U/L; LOAD, 86210 U/L. Horizontal bars indicate medians and error bars correspond to interquartile range. Probability (p) for pairwise comparison were calculated by Bonferroni *post-hoc* test

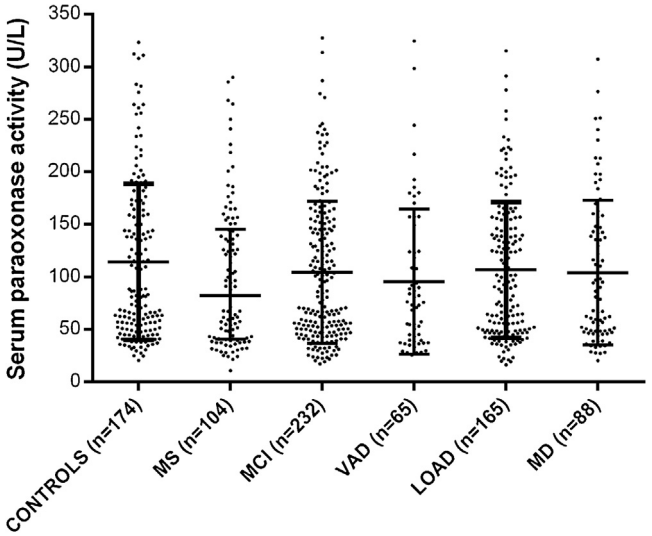

Fig. 2. Serum paraoxonase levels did not differ between CONTROLS multiple sclerosis (MS), mild cognitive impairment (MCI), mixed dementia (MD), vascular dementia (VAD) or late Alzheimer disease (LOAD).
Medians of serum paraoxonase: CONTROLS, 86.5 U/L; MS, 81.9 U/L, MCI, 82.7 U/L; MD, 80.9 U/L; VAD, 75.7 U/L, LOAD, 95.2 U/L. Horizontal bars indicate medians and error bars correspond to interquartile range.

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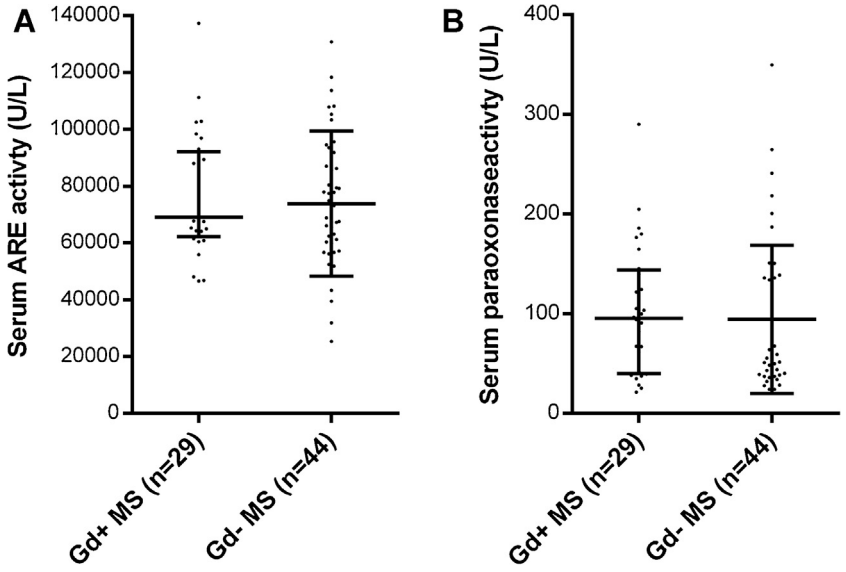

Fig. 3. Levels of serum arylesterase (ARE) (A) or paraoxonase (B) did not discriminate multiple sclerosis (MS) patients with (Gd $^{+}$ MS) from those without (Gd $^{-}$ MS) evidence of disease activity as assessed by the detection of gadolium-enhancing lesions by magnetic resonance.
Horizontal bars indicate medians and error bars correspond to interquartile range.

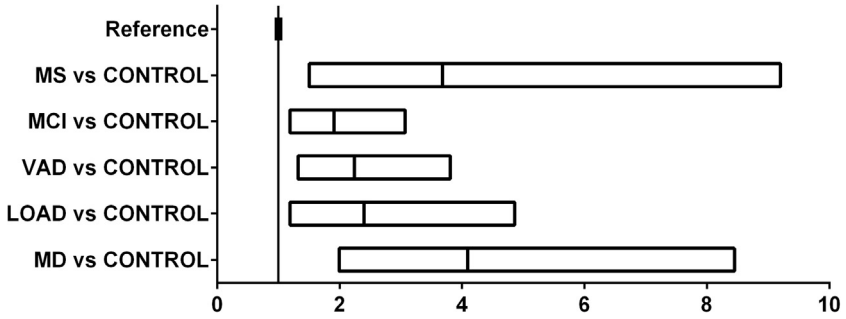

Fig. 4. Low levels of serum arylesterase (ARE) were associated with an increased risk of having multiple sclerosis (MS), mild cognitive impairment (MCI), mixed dementia (MD), vascular dementia (VAD) or late Alzheimer disease (LOAD) compared to CONTROLS, regardless of age and gender. Horizontal bars indicate medians and error bars correspond to interquartile range.
Multi adjusted odds ratio (95% confidence interval): MS, 3.7 (1.5–9.9); MCI, 1.9 (1.2–3.1); MD, 4.1 (2.0–8.4); VAD, 2.2 (1.36–3.8); LOAD, 2.4 (1.2–4.9). Serum ARE cut-off = 96.8 KU/L. Covariates: age and gender.

serum) in 100% of MS cohort, most likely because the proportion between paraoxonase/ARE of the serum isoform (around 1:1000) found in this and other studies was approximately maintained in CSF. Kruskall-Wallis analysis showed that OIND and MS had similar median levels of CSF ARE (56.5 and 55.8 U/L, respectively) but only the former was significantly ($p < 0.05$) different from NIND (median value = 32.8 U/L) and MS (Fig. 5). Of note, CSF ARE did not correlate with the serum levels in any of the three groups (data not shown).

4. Discussion

The multifunctional nature of PON-1 makes this HDL-bound enzyme a potential reliable marker and pathogenic player for several diseases. This consideration brought us to compare the levels of ARE and paraoxonase activities of a large group of healthy individuals with those of the three major forms of dementia, VAD, LOAD and MD; the so-called pre-dementia condition, MCI; and the leading cause of neurological disability in young and middle aged individuals in developed countries, MS. The main finding of our study was that a decreased serum level of ARE, but not paraoxonase, was the common denominator of all the neuropathological conditions considered in this study. The association between low serum ARE activity and the risk of MCI, VAD or LOAD has been already described in previous reports (Cervellati et al., 2015b; Cervellati et al., 2015a). The present work confirms and extends the existing results in a larger sample (725 subjects *vs.* previous 593) that includes also individuals with mixed VAD/LOAD form (MD). Decreased levels of ARE were also found to be significantly, and independently of confounders such as age and gender, associated with an increased likelihood of having MS. Unfortunately, the attempt to translate this evidence into clinical practice failed, because: (1) serum ARE did not correlate with disease activity detected by MRI, duration and disability; (2) CSF ARE did not discriminate patients with MS from those with other inflammatory neurological diseases.

Presently, though the existence of overlaps is becoming increasingly evident, LOAD and VAD are still mostly considered as two distinct disorders (De La Torre 2004; Kalaria et al., 2008). Ischemic or hemorrhagic brain injury primarily caused by atherosclerosis are the main pathogenic mechanisms in VAD (Iemolo et al., 2009). The observed connection between this form of dementia and PON-1 is consistent with the recent evidence of an inverse correlation of both ARE/paraoxonase serum activities with carotid atherosclerosis and cerebral arteriosclerosis in stroke patients (Shenhar-Tsarfaty et al., 2013). The important contribution of PON-1 to HDL anti-atherosclerotic function appeared to relate

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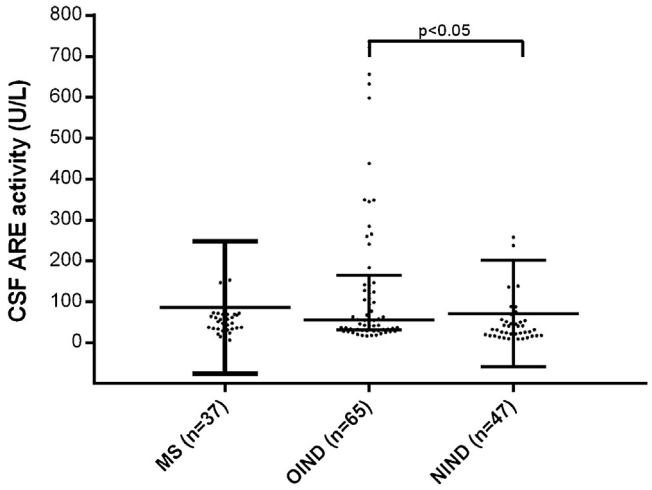

Fig. 5. Levels of arylesterase activity (ARE) in CSF were NOT able to discriminate multiple sclerosis (MS) from other inflammatory neurological disorders (OIND) or non-inflammatory neurological disorders (NIND).
Medians of serum paraoxonase: MS, 56.5 U/L; OIND, 55.8 U/L, NIND, 32.9. Horizontal bars indicate medians and error bars correspond to interquartile range.
Probability (p) for pairwise comparison were calculated by Mann-Whitney *U* tests (Bonferroni correction for multiple comparisons).

with its ability to stimulate endothelial nitric oxide sinthetase (eNOS)-dependent production of artery-relaxing NO (Besler et al., 2011) and cholesterol efflux from cholesterol-laden macrophages (Rosenblat et al., 2006b), and to protect cells and lipoprotein from oxidative damage (Aviram et al., 1998; Bhattacharyya et al., 2008). ARE, rather than paraoxonase (that is regarded as a promiscuous activity of PON-1 against active metabolites of organophosphorus pesticides), seems to contribute to the systemic antioxidant function of circulatory HDL. Indeed, in vitro evidence suggests that ARE might act in combination with lactonase function (and most likely Apo-A1), in the catalytic process leading to the hydrolysis of truncated oxidized fatty acids from phospholipid, cholesterylester, and triglyceride hydroperoxides (Rosenblat et al., 2006a; Mackness and Mackness, 2015). In the case of phospholipids, the proposed catalytic mechanism considers as initial step the lactonization of the oxidized lipid to yield lysophospholipids and the respective lactone, which is then hydrolyzed by PON-1 (Rosenblat et al., 2006a).

The systemic impact of ARE activity on OxS might also account for the decrease that we observed in patients with MD (a dementia type where peripheral and brain vascular damage still play a relevant pathogenic role) but also with those affected by MCI and LOAD. Indeed, early and late involvement of OxS both in periphery and brain of patients with Alzheimer's disease have been shown by a wealth of experimental and epidemiological evidence (Butterfield et al., 2013; Praticò et al., 2000; Cervellati et al., 2014a, 2016). It is tempting to suggest that the decrease in the antioxidant protection afforded by PON-1 can be one of the culprits of derangement in systemic redox balance. At the same time, it cannot be ruled out that depression of ARE activity might be a downstream event of OxS rise, since, as nicely shown by Huang et al. and others (Huang et al., 2013; Aviram et al., 1999), PON-1 structure and function are impaired in a ROS-rich environment.

The contextualization of our findings regarding MS into the current state of literature is much more complicated because the available epidemiological studies on the topic are scarce and mostly affected by small sample size. However, it is fair to underscore that a trend toward lower levels of serum PON-1 activity in MS patients compared to healthy was also reported in other two studies (Ferretti et al., 2005; Kirbas et al., 2013). In contrast, Moghtaderi et al. did not find any significant difference between MS and healthy individuals in a recent work (Moghtaderi et al., 2011). Interestingly, this study along with two others (Martínez et al., 2010; Feeney and Handley, 2006), dealt with the main two single nucleotide polymorphisms (SNPs) (Q192R and L55M) of PON-1. The lack of association between PON-1 polymorphisms and MS highlighted in these studies (as well as in other studies on dementia (Pi et al., 2012)) might be explained by the fact that they do not substantially influence ARE while do affect paraoxonase function (Cervellati et al., 2016). Interestingly, the strong effect of SNPs on paraoxonase might account for the high variability of this activity within the single subsamples (see Fig. 2).

The well-documented implication of inflammation and OxS in MS could be the key for interpreting our results. The ethiopathogenesis of MS is still obscure, although involvement of intensive autoaggressive immune response leading to uncontrolled inflammatory response has been clearly demonstrated (Loma and Heyman, 2011). Both innate and adaptive immune responses involving, at various extent, T and B cells, macrophages, dendritic cells and astrocytes are implicated in the disease initiation (Loma and Heyman, 2011). The body of evidence regarding the "specific weight" of inflammation in the progression of the disease is more contrasting, since some studies suggest the occurrence of an inflammation-independent axonal loss in primary progressive (PPMS) and secondary progressive (SPMS) forms of the disease (Romme Christensen et al., 2013). On the other hand, the presence of inflamed white matter in the CNS of patients with the more frequent RRMS form (that affects our patients), characterized by acute attacks followed by partial or full recovery, has been widely proven (Loma and Heyman, 2011). Therefore, neuroinflammation is a hallmark of MS, as amyloid-beta neurodegeneration and cerebrovascular damage are for LOAD and VAD, respectively.

It is now well recognized that inflammation and OxS act as cooperative and synergistic partners in the pathogenesis of many diseases (Crowley, 2014). As proposed by Ortiz and colleagues (Ortiz et al., 2013), neuroinflammation can spark reactive species generation by activated glia but also by arachidonic acid signaling through the activation of cyclooxygenase and lipoxygenase pathways. Converging lines of evidence have shown massive lipoperoxidation in the brain and also in the periphery of MS patients (Haider et al., 2011; Mattsson et al., 2007; Karlík et al., 2015; Ferretti and Bacchetti, 2011). The chain reaction that characterizes this process is particularly deleterious in areas enriched in polyunsaturated fatty acid (PUFAs) such as neuronal membranes and myelin sheaths (Moore, 2001). Peroxidation by-products can react with reduced iron (or other reduced metals), which has been shown to be at high levels in MS brain, to give rise to highly reactive aldehyde such as malondialdehyde (MDA) and 4-hydroxy-2-hexenal (4-HNE), and isoprostanes (Dalle-Donne et al., 2006). These substances are less reactive than ROS and thus can diffuse to sites far away from the initial oxidation event and actively participate to the pathogenic mechanisms of MS (Ortiz et al., 2013). In particular, 4-HNE can damage biological membranes of neurons, thereby affecting permeability and ionic potentials, alter tight-junctions and impair the blood brain barrier (BBB). The damaged BBB, a frequent pathophysiological feature of MS but not of dementia-related diseases, allows cross-talk between periphery and CNS involving inflammatory cytokines and cells but, most likely, also chemically stable oxidants or by-products of oxidative processes (Ortiz et al., 2013). This diffusion might contribute to the increase in peripheral OxS markers observed by some of the epidemiological studies on the topic.

In this hypothetical scenario, the lower levels of serum ARE observed in MS patients compared to controls found in our study might represent an effect rather than a cause of systemic OxS. Indeed as anticipated earlier, increase in oxidized lipids in HDL could affect the physical interaction of PON-1 with the lipopro-

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tein, thereby leading to the impairment of its enzymatic machinery (Huang et al., 2013; Aviram et al., 1999). Notably, experimental evidence demonstrated that loss in PON-1 function also occurs upon selective oxidative modification of apoliprotein A1 (Apo-A1), suggesting the essential role of this apoliprotein in binding PON-1 and modulating its biological functions (Rosenblat et al., 2006a; Huang et al., 2013). Apo A-1 is also present (along with APOE, APOj, *etc.*) in the so-called HDL-like particles that are secreted by glial cells and represent the large majority of lipoprotein present in CSF (Wang and Eckel, 2014; Ferretti and Bacchetti, 2011). This consideration, in combination with a recent finding of altered concentration of PON-1 in CSF of the most commonly studied animal model of MS, the experimental autoimmune encephalomyelitis (EAE) (Wang and Eckel, 2014), prompted us to search for ARE activity in this fluid in MS patients.

As the CSF contains metabolites and other molecules that can reflect altered brain function, studies of this fluid composition may offer new insights into CNS diseases and, at the same time, novel reliable biomarkers to employ for diagnostic purposes (Schwarz et al., 2012). To test the potential of ARE activity as candidate biomarker for MS, we measured its levels in CSF of patients affected by the demyelinating disease and two different neurological control groups. The results obtained were, at least partially, disappointing, because ARE was not able to differentiate MS from OIND or NIND. However, we firmly believe that our novel discovery of detectable levels of ARE in CSF of patients affected by different pathological conditions opens still unexplored avenues in the field of biomarkers for neurological diseases. Indeed, the method employed for assessing this biological index is simple, fast and cheap, as well as presents good analytical performances both in serum and CSF (low inter- and intra assay CV).

4.1. Conclusion

Taken together our findings suggest that neurological diseases as LOAD, VAD and MS, though presenting altogether different etiopathogenic mechanisms and pathophysiology, are all characterized by low levels of serum ARE activity of PON-1. This enzyme, has been implicated in several protective processes, such as anti-inflammatory, antioxidant and anti-atherosclerotic. This multi-function nature might explain the association found in our study, even though it remains unclear if the alteration of its activity can be ascribed as downstream or upstream event of these disorders. Finally, we believe that the novel finding of a detectable amount of ARE in CSF of patients with MS, OIND and NIND might have important spillovers in the research of novel biomarkers for neurological diseases.

Conflict of interest disclosure

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biocel.2016.06.008.

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