Cerebrovascular disease, multiple sclerosis, or both? Case report and review of the challenging distinction between two potentially synergistic syndromes

Paola Suarez a, Lucas Restrepo b, ∗

a Cultural Neuropsychology Initiative, UCLA Semel Institute for Neuroscience & Human Behavior, Department of Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine at UCLA, United States

b David Geffen School of Medicine, Department of Neurology, University of California, Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095, United States.

Abstract

White matter changes (WMC) are frequently observed in clinical practice, but their clinical relevance is often obscured by radiology reports that do not clearly convey a likely diagnosis. In this regard, two attitudes contribute to diagnostic confusion: a tendency to dismiss findings as trivial (i.e., using vague characterizations such as “non-specific” or “normal for age”), and a gratuitous dilatation of the differential diagnosis (i.e., routinely adding rare diseases to the list, such as vasculitis). Very often, the finding of WMC presents physicians with a very practical problem, which is to determine whether the underlying etiology is an autoimmune demyelinating disease such as multiple sclerosis (MS), or a vasculopathy such as small vessel cerebrovascular disease (SVCVD). The implications of this distinction are great, because the treatment and prognosis of these two syndromes are very different. Here, we describe the challenging case of a relatively young woman with dementia due to a combination of MS and cerebrovascular disease.

Keywords:
Dementia
White matter changes
Multiple sclerosis
Small vessel cerebrovascular disease
Vascular dementia

Case description

A 52 year old Chinese female presented with a 9-year history of gradual cognitive difficulties, dysphoric mood and altered sleep-wake-sleep cycles, starting after an otherwise uneventful surgery to remove uterine fibroids. Symptoms were intense enough to delay her return to work for several months. The patient improved, but not to her baseline, and was well until symptoms spontaneously worsened 5 years later, with difficulties concentrating and thinking that culminated in being laid off from work. The patient described her symptoms as “having a constant cloud in the brain.” She had short-term recall difficulties and mental confusion, forgetting events, dates, and even the time of the day. She also had problems recognizing places, getting lost easily, while simple calculations became problematic, in spite of her background in economics. In parallel, she developed intermittent gait instability and left leg paresthesia. She was diagnosed with depression and anxiety, and started treatment with escitalopram, clonazepam, and quetiapine. While this treatment resulted in mood improvement, it exerted no effects on her cognitive symptoms, which continued to deteriorate.

Past medical history was relevant for hypertension and hyperlipidemia for 3 years, as well as asthma and allergic rhinitis. Interestingly, she reported an episode of “blindness” when she was a college student 20 years before, from which she recuperated completely within 48 hours. Unfortunately, she could not recall if this was monocular or binocular. She did not have symptoms of obstructive sleep apnea or obesity (BMI=21). Besides her psychiatric medications, she also took amiodipine and rosuvastatin. Her family history was significant for 2 maternal uncles with late-onset Alzheimer’s disease.

The neurological exam revealed a fully alert patient, oriented to person, time, place and circumstance. Her registration was 2/3 and delayed recall was 3/3. Speech was fluent, and she was able to name, repeat, follow commands, write, and read. She had significant acalculia. She had a right afferent pupillary defect and pupillary hipposy. Fundoscopy was normal. Motor exam and coordination were unremarkable. Deep tendon reflexes were 3+ symmetrically.

A comprehensive neurocognitive examination revealed a profile that was generally consistent with broad, non-dominant (right) hemisphere dysfunction, and deficits in visuospatial abilities, relative weakness in non-verbal memory, and lateralized motor testing (Table 1). In addition, several aspects of her testing and behavioral presentation (e.g., reduced inhibition, disorganization, impulsivity, stimulus-bound behavior, reduced comprehension, reduced confrontation naming, benefit from cueing) were suggestive of deficits with executive functions, comprehen-
Table 1  
Neuropsychological Data.

| Performance Validity Testing | Raw | Rating |
|------------------------------|-----|--------|
| VSVT Easy:                   | 24  | Valid  |
| VSVT Hard:                   | 24  | Valid  |
| VSVT Total:                  | 48  | Valid  |
| Reliable Digit Span:         | 9   | BR: >25 |
| CVLT-II Forced Choice:       | 16/16 | BR: 94.7 |
| E-Score                      | 384.8 | –      |

| Cognitive Screening          | Raw Score | Standard Score |
|------------------------------|-----------|----------------|
| MOCA (Chinese)               | 24/30     | –              |

| Functional abilities         | Raw Score Dem Corr | Standard Score % |
|------------------------------|-------------------|------------------|
| Texas Functional Living Scale|                   | T = 46           |
| Time                         | 8                 | –                |
| Money and calculation        | 6                 | –                |
| Communication                | 28                | –                |
| Memory                       | 4                 | –                |

| Intellectual Functioning     | Raw Score | Standard Score |
|------------------------------|-----------|----------------|
| Test of Premorbid Functioning| 26        | 84             |
| Predicted TOEFL              | –         | 121            |
| Wechsler Adult Intelligence Scale, 4th Ed. | – | 98 |
| Perceptual Reasoning Index   | –         | –              |

| Achievement Testing          | Raw Score | Standard Score |
|------------------------------|-----------|----------------|
| Wide Range Achievement Test, 4th Ed. |     |                |
| Math                         | 51        | Std = 116      |

| Attention / Working Memory   | Raw Score | Standard Score |
|------------------------------|-----------|----------------|
| Wechsler Adult Intelligence Scale, 4th Ed. |     |                |
| Digit Span Total             | 22        | SS = 7         |
| Forward                      | 8         | SS = 7         |
| Backward                     | 8         | SS = 9         |
| Sequencing                   | 6         | SS = 7         |

| Processing Speed             | Raw Score | Standard Score |
|------------------------------|-----------|----------------|
| Wechsler Adult Intelligence Scale, 4th Ed. |     |                |
| Coding                       | 56        | SS = 8         |
| D-KEFS Trial Making Test     | 17        | SS = 13        |
| Visual Scanning              | 26        | SS = 13        |
| Number Sequencing            | 33        | SS = 12        |
| Letter Sequencing            | 39        | SS = 9         |
| Motor Speed                  | –         | –              |
| D-KEFS Color-Word Interference|         |                |
| Color Naming                 | 31        | SS = 10        |
| Errors                       | Self Corrected: 0 |
| Word Reading                 | 20        | SS = 12        |
| Errors                       | Self Corrected: 0 |
| Color Trails Form A          | –         | –              |
| Part 1 (Chinese)             | Errors = 0 | 41 | Z = 0.48 |
| Symbol Digit Modalities Test | –         | –              |
| Word Score, Chinese version Errors = 0 | 49 | Z = 1.21 |

| Language                     | Raw Score | Standard Score |
|------------------------------|-----------|----------------|
| Wechsler Adult Intelligence Scale, 4th Ed. |     |                |
| WAIS-IV Verbal Comprehension Index | –         | –              |
| Similarities                 | 33        | SS = 15        |
| D-KEFS Verbal Fluency        | –         | –              |
| Letter Fluency               | 30        | SS = 8         |
| Category Fluency             | 26        | SS = 5         |
| Expressive One-Word Picture Vocabulary Test, 4th Ed. |     |                |
| EOWPVT-4 Total (+0 Gain w/ access to Mandarin) | 109 | Std = <.55 |
| Tokens Test                  | 35        | –              |
| Verbal Fluency, Chinese      | –         | Age Corr       |
| Character Fluency, Chinese   | 8         | Z = -1.50      |
| Semantic (Animal) Fluency, Chinese | 15 | Z = -0.80 |

*Normative sample is representative of Mandarin-speaking young adults (Mean age = 35.77, SD = 5.00) and should be interpreted cautiously.  
(continued on next page)
Table 1 (continued)

| Performance Validity Testing | Raw Score | Standard Score |
|------------------------------|-----------|----------------|

| Visuospatial Functioning | Raw Score | Standard Score |
|--------------------------|-----------|----------------|
| Wechsler Adult Intelligence Scale, 4th Ed. | | |
| Perceptual Reasoning Index | – | Std = 98 |
| Block Design | 33 | SS = 8 |
| Matrix Reasoning | 19 | SS = 11 |
| Delis-Kaplan Executive Functioning System | | |
| Condition 1: Filled Dots | 9 | SS = 10 |
| Errors | Set Loss: | 0 |
| Condition 2: Empty Dots | 9 | SS = 9 |
| Errors | Set Loss: | 0 |
| Condition 3: Switching | 8 | SS = 11 |
| Errors | Set Loss: | 0 |
| Total Correct Designs | 30 | SS = 10 |
| Rey Complex Figure Copy Test | | |
| Copy | 34 | – |
| **Hooper Visual Organization Test** | 20 | 62 |
| Judgment of Line Orientation | 28 | – |

**T-scores are inverted, with higher scores indicating greater likelihood of impairment**

| Verbal Memory | Raw Score | Standard Score |
|---------------|-----------|----------------|
| California Verbal Learning Test, 2nd Ed. | | |
| Trial 1 | 5 | \( z = -1 \) |
| Trial 5 | 12 | \( z = -0.5 \) |
| Total Trial 1 – 5 | 5/8/11/10/12 | 46 |
| Learning Slope 1 – 5 | 1.6 | \( z = 0 \) |
| List B | 3 | \( z = -1.5 \) |
| Short Delay Free Recall | 8 | \( z = -1 \) |
| Short Delay Cued Recall | 8 | \( z = -1.5 \) |
| Long Delay Free Recall | 8 | \( z = -1.5 \) |
| Long Delay Cued Recall | 10 | \( z = -1 \) |
| Semantic Clustering | -0.6 | \( z = -1 \) |
| Serial Clustering | 1.3 | \( z = 1 \) |
| % Recall from Primacy | 28 | \( z = 0 \) |
| % Recall from Recency | 35 | \( z = 1 \) |
| Across Trial Recall Consistency | 85 | \( z = 0.5 \) |
| Total Repetitions | 7 | \( z = -0.5 \) |
| Total Intrusions | 2 | \( z = 0.5 \) |
| Recognition Hits | 14 | \( z = 0.5 \) |
| Recognition False Positives | 2 | \( z = 0 \) |
| Total Recognition Discriminability | 2.7 | \( z = -0.5 \) |
| Wechsler Memory Scale, 4th Ed. | | |
| Logical Memory Immediate Recall | 21 | SS = 8 |
| Logical Memory Delayed Recall | 19 | SS = 9 |
| Logical Memory Recognition | 25 | – |

**Fluid Object Memory Test**

| (z) | |
| Trial 1 | 8 | -1.26 |
| Trial 2 | 11 | -0.73 |
| Trial 3 | 11 | -1.45 |
| Trial 4 | 9 | -3.25 |
| Trial 5 | 10 | -3.79 |
| Storage | 63 | 0.06 |
| Delayed Recall | 11 | -1.60 |

**Non-Verbal Memory**

| Rey Complex Figure Copy Test | Raw Score | Standard Score |
|-----------------------------|-----------|----------------|
| Immediate Recall | 6 | <20 |
| Delayed Recall | 6.5 | <20 |
| Recognition | 15 | <20 |

**Brief Visuospatial Memory Test, Revised**

| Trial 1 | 2 | 31 |
| Trial 2 | 3 | 23 |
| Trial 3 | 5 | 21 |
| Total Recall | 10 | 23 |
| Learning | 1 | 35 |
| Delayed Recall | 5 | 30 |

(continued on next page)
sion, and retrieval, which collectively implicated frontal-subcortical systems. It was concluded that some of her reported difficulties regulating mood were, at least, partly related to fronto-subcortical inefficiencies. The etiology of her neuropsychological profile at the time was considered to be vascular in nature, but the course, her significant mood symptoms, along with her considerable decline in overall cognition, raised concerns for a superimposed neurodegenerative process. Given the possible visuo-motor slowing contribution to visually mediated tasks, along with her fronto-subcortical involvement, MS was considered as part of the differential and a follow-up neurological evaluation was recommended.

Brain MRI revealed multiple, confluent and non-enhancing areas of prolonged T2 signal involving the subcortical white matter (Fig. 1). Contrast-enhanced MRA revealed multifocal luminal irregularity of intracranial arteries, mainly involving the right A2 and proximal upper and lower divisions of the right MCA. Neck MRA was normal.

The patient was diagnosed with vascular dementia and referred to the stroke clinic at UCLA, where detailed review of neuroimages and past medical history also raised concerns about MS. Importantly, MRI of the cervical spine revealed prolonged T2 cord signal extending from the C3 to C7 segments, indicative of a demyelinating process. The diagnostic work-up is summarized in Table 2. The patient was treated with ocrelizumab 150 mg IV every 6 months, resulting in stabilization of neurological symptoms. She expressed preference to not receive treatment with donepezil or memantine. Her blood pressure was kept < 140/80 mm Hg, while her LDL goal was < 70 mg/dL. She was counseled to take 81 mg of aspirin every day and a daily supplement of vitamin D, exercise daily, and adopt a Mediterranean-style diet.

### Discussion

We have described the case of a patient with early onset dementia associated with extensive WMC, who was initially considered to have vascular dementia but was subsequently diagnosed with MS after detailed review of past medical history, electrophysiology testing, and neuroimaging. The patient exhibited extensive abnormalities on brain MRI circumscribed to the white matter, with predilection for the corpus callosum, which had the typical appearance of “Dawson fingers” [1]. These WMC also involved the periventricular region and centrum semiovale, affecting juxta-cortical regions. This particular distribution is worrisome for a demyelinating disease rather than SVD, with MS being the most common culprit. The lack of gadolinium enhancement suggested an ostensibly quiescent process without active inflammation. At this stage, MS can still progress, indicating a neurodegenerative phase of the autoimmune disorder. Although the patient had cardiovascular risk factors, a right thalamic lesion consistent with a lacunar infarct, and evidence of intracranial atherosclerosis, the topography and features of white matter lesions was key to distinguish between cerebrovascular disease and demyelination. Cerebrovascular disease does not usually involve the corpus callosum, given redundant blood supply arising from both hemisphere [1]. Also, cerebrovascular disease does not typically involve the juxta-cortical region, where u-fibers predominate, also due to rich collateral supply. There are exceptions to this rule, with CADASIL being the most pertinent example. Young CADASIL patients, in particular, are sometimes misdiagnosed with MS [2,3]. However, our patient did not carry mutations of the NOTCH-3 gene spanning the Epidermal Growth Factor (EGF) motifs (Table 2). In addition, she lacked other clini-

### Table 1 (continued)

| Performance Validity Testing | Raw | Rating |
|-----------------------------|-----|--------|
| Percent Retained            | 100 | –      |
| Hits                        | 5   | –      |
| False Alarms                | 3   | –      |
| Discrimination Index        | 2   | –      |
| Response Bias               | .55 | –      |
| Executive Functioning       |     |        |

| Wechsler Adult Intelligence Scale, 4th Ed. | Raw Score | Standard Score |
|--------------------------------------------|-----------|----------------|
| Matrix Reasoning                           | 19        | SS = 11        |
| Similarities                               | 33        | SS = 15        |
| Delis-Kaplan Executive Functioning System  |           |                |
| Letter Fluency                             | 30        | SS = 8         |
| Category Switching                         | 17        | SS = 15        |
| Category Switching Accuracy                | 15        | SS = 13        |
| Color-Word Inhibition                      | 74        | SS = 7         |
| Errors (Self-Corrected/Uncorrected)       | 0/0       | SS = 12        |
| Color-Word Inhibition Switching            | 67        | SS = 11        |
| Errors (Self-Corrected/Uncorrected)       | 2/9       | SS = 7         |
| Trail Making Number-Letter Switching       | 97        | SS = 10        |
| Total Errors                               | 1         | SS = 10        |
| Condition 3: Design Switching              | 8         | SS = 11        |
| Errors                                     |           | Set Loss: 0    |
| WCST                                        | # Trials: 111 | (Age Corr Std) |
| Errors                                     | 30        | Std = 93       |
| Perseverative Responses                    | 16        | Std = 84       |
| Perseverative Errors                       | 12        | Std = 97       |
| Nonperseverative Errors                    | 18        | Std = 88       |
| Categories Completed                       | 6         | –              |
| Trials to Complete 1st Category            | 30        | –              |
| Failure to Maintain Set                    | 0         | –              |
| Color Trails Form A                        |           |                |
| Part 2 (Chinese)                           | Errors = 0 | 125            |

| Motor Functioning | Raw Score | Standard Score |
|-------------------|-----------|----------------|
| Grooved Pegboard  |           |                |
| Dominant          | Drops = 2 | 85             |
| Non-Dominant      | Drops = 5 | 100            |

| Grooved Pegboard | Raw Score | Standard Score |
|-------------------|-----------|----------------|
| Dominant          | Drops = 2 | 85             |
| Non-Dominant      | Drops = 5 | 100            |
Fig. 1. MRI of the Brain with and without contrast. Panels A-B show coronal views demonstrating confluent T2 hyperintense lesions involving the periventricular white matter, mainly on the right side, which extend to the juxta-cortical region (black arrow). These images also reveal substantial atrophy of the corpus callosum and neighboring cerebral cortex. The white arrow in panel B points to a small fluid-filled lesion involving the right thalamus; Panel C provides a T1 coronal view of this lesion, while Panel D demonstrates a hyperintense rim on FLAIR indicating perilesional gliosis (white arrow), which is consistent with a lacunar infarct. Panel E shows T2 hyperintense lesions in the corpus callosum on sagittal FLAIR. Panel F shows indentations of the corpus callosum on T1 sequences (arrow), while the FLAIR sequence on the right shows typical Dawson fingers. Panel G shows multifocal intracranial stenosis (white arrows), predominantly involving the right A2, right MCA branches, and right intradural vertebral artery. Lumen irregularity suggests that atherosclerosis is the underlying etiology. Panel H again shows juxta-cortical lesions (arrows) on sagittal FLAIR involving the left parietal lobe, while the asterisk marks another instance of Dawson fingers extending into the centrum semiovale on the right side.

Clinical features of CADASIL, including a history of headaches, family history of stroke, or involvement of the temporal poles and external capsule, which were spared in her case (Figure), the presence of brain microhemorrhages and absence of optic nerve and spinal cord abnormalities can help distinguish CADASIL from MS. We also considered an adult-onset leukodystrophy in the differential diagnosis, but a more symmetric and diffuse involvement of the white matter would be expected with this syndrome [4]. We did not test very long chain fatty acids or the HTRA1 gene.

Clinically, some important clues are also worth considering. The patient reported an episode of reversible blindness in her 20’s, and the neurological exam showed an afferent pupillary defect. While the evoked potentials were normal, the shape of the P100 peaks was doubled, which is suspicious for a post-chiasmatic conduction delay. Such episode could have represented optic neuritis, although the patient had difficulty remembering details. The symptoms of intermittent gait difficulties, together with the abnormal cervical spine imaging and somatosensory evoked potentials consistent with a demyelinating myelopathy, also point to a diagnosis of MS instead of cerebrovascular disease. An MS mimicking syndrome and a systemic vasculitis were entertained given the presence of faintly (+) ANA. However, the cardiolipin antibody panel was negative, as well as a comprehensive rheumatological work-up outlined in Table 2.

An important argument against the diagnosis of MS in this patient is that oligo-clonal bands (OCB) were not detected in the CSF. Although 1 out of 10 MS cases do not have OCB, the negative predictive value of this test is very high (~90%) [5]. We appropriately considered this a red flag, but could not ignore the other signs of demyelinating disease present in this patient. OCB-negative patients differ genetically from their OCB-positive counterparts, and also have less risk of clinical relapses and brain atrophy [6]. One may reasonably ponder whether OCB-negative MS represents a clinically distinct disease process. This said, no specific tests are currently available to diagnose MS, and physicians must rely on circumstantial evidence to make the diagnosis, using a combination of clinical findings, MRI, evoked potentials, and CSF analysis [7].

Cognitive impairment affects approximately 30–70% of MS patients, usually in association with older age of onset, progressive course, and larger burden of WMC on brain neuroimaging [8]. Jean-Martin Charcot himself noted memory enféeblement and slowness of thinking in MS -a disease that he was the first physician to describe- during a lecture held at the Salpêtrière Hospital in 1877 [9]. The usual cognitive profile of MS patients includes defects in attention, executive function, information processing speed, visuospatial ability, and episodic memory [9]. MS can lead to dementia, but its true prevalence is unclear because an apparent resistance in the literature to use this term, which is otherwise familiar to all neurologists and neuropsychologists. MS is also associated with affective disorders which can exert a negative impact on patient’s outcomes; a meta-analysis of 87,756 MS patients showed a pooled mean prevalence of 30.5% for depression, and 22.1% for anxiety [10]. Although depression can feature cognitive symptoms -sometimes referred to as pseudodementia- our patient’s cognition did not improve with psychopharmacotherapy, in spite of improvement of dysphoria.

Cardiovascular risk factors, particularly hypertension and hyperlipidemia, are very frequent in the general adult population. These, in turn,
may lead to WMC [11,12], which can be observed in up to two thirds of persons older than 75 years of age [13]. Gradual WMC accrual, typically due to SVCVD, is associated with cognitive decline and stroke [13–16].

Aggressive control of cardiovascular risk factors is advocated to prevent stroke and dementia. There is good evidence that intensive control of blood pressure slows the accumulation of WMC, in addition to well-known reductions in stroke and myocardial infarction [17]. Intensive control of blood pressure also reduces the risk of mild cognitive impairment [18], which may represent the prodrome of dementia in many but not all cases. An intensive control of cardiovascular risk factors, on the other hand, should be a key component of MS management, as a general strategy to curb all potential factors capable of undermining the integrity of white matter tracts. Hypertension and other cardiovascular risk factors are common in MS patients, increasing WMC burden and brain atrophy, both markers of poor outcomes [19]. Specifically, systolic hypertension has been linked with heavier posterior white matter tract loss and greater frontal cortical atrophy in MS patients [20]. Our case is also a reminder that the presence of cardiovascular risk factors can delay the diagnosis of MS, to the detriment of functional status [21].

Our patient had evidence of intracranial stenosis, likely caused by large vessel atherosclerosis, given the observed luminal irregularity on brain MRI and history of vascular risk factors. The principal neuroimaging finding in intracranial stenosis is cortical infarcts within the affected vascular territory, a feature absent in the case we have described. Moreover, the distribution of WMC in our patient was independent from the vascular territories of affected arteries. There is an unclear relationship between intracranial stenosis and ipsilateral WMC in current medical literature [22], compounded by the fact that hypertension and other vascular risk factors -more typically associated with SVCVD- are prevalent in these cases. However, some studies suggest a correlation between intra-cranial stenosis and ipsilateral WMC, although this association does not depend on the degree of stenosis but instead on novel indicators of hemodynamically relevant intracranial atherosclerosis, such as post- to pre-stenotic signal intensity ratios (SIR) generated from time-of-flight MRA [23] and high-resolution MRI (HRMRI) estimates of vessel wall thickness using axial 3D fast spin-echo T1 imaging at 3.0 Tesla [24].

In conclusion, WMC caused by MS can be confused with SVCVD, leading to a wrong diagnosis of vascular dementia. Moreover, many patients with MS have coexisting cardiovascular risk factors and even clear-cut evidence of cerebrovascular disease that can further undermine the integrity of white matter tracts. Therefore, serious consideration should be given to aggressive control of coexistent cardiovascular risk factors in MS, particularly hypertension, hyperlipidemia, and diabetes mellitus. Careful review of neuroimaging and past medical history is needed in young individuals with a presumptive diagnosis of vascular dementia, and if doubts linger, the diagnostic work up should be supplemented with a spinal tap, spine imaging, and evoked potentials to rule out MS.

### Declaration of Competing Interest

None.
Funding

None.

References

[1] N Sarbu, RV Shih, RV Jones, et al., White matter diseases with radiologic-pathologic correlation, Radiographics 36 (2016) 1426–1447.
[2] S Joshi, W Yau, A. Kermod, CADASIL mimicking multiple sclerosis: the importance of clinical and MRI red flags. J. Clin. Neurosci. 35 (2017) 75–77.
[3] A Goulard, S Blank, K Bushby, RN Kalra, DJ Burn, Distribution of cranial MRI abnormalities in patients with symptomatic and subclinical CADASIL. Br. J. Radiol. 73 (2000) 256–265.
[4] MS Van der Knaap, M Bugiani, Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms, Acta Neuropathol. 134 (2017) 351–382.
[5] A Bouraghjoo, J De Seze, R Guttierrez, et al., CSF isoelectrofocusing in a large cohort of MS and other neurological diseases, Eur. J. Neurol. 11 (2004) 525–529.
[6] D Ferreira, O Voevodskaya, K Imrell, et al., Multiple sclerosis patients lacking oligoclonal bands in the cerebrospinal fluid have less global and regional brain atrophy, J. Neuroimmunol. 274 (2014) 149–154.
[7] F Deisenhammer, H Zetterberg, B Fitzner, UK. Zettl, The cerebrospinal fluid in multiple sclerosis, Front. Immunol. 10 (2019) 726.
[8] MP Amato, F Prestipino, A Belliniva, C Nicolai, L Razzolini, L Past, R Fratangelo, L Tudisco, M Fonderico, PL Mattiolo, B Goretti, GB Zimatore, NA Losignore, E Portaccio, F. Lolli, Cognitive impairment in Multiple Sclerosis: an exploratory analysis of environmental and lifestyle risk factors, PLoS One 14 (10) (2019) e0222929.
[9] JS Sumowski, R Benedikt, C Ernzerf, M Filippi, JJ Gurts, P Hamalainen, H Hult, M Inglese, VM Leavitt, MA Rocca, EM Rosti-Otajarvi, S. Rao, Cognition in multiple sclerosis: state of the field and priorities for the future, Neurology 90 (2018) 278–288.
[10] RE Boeschoten, AMJ Braamse, AT Beekman, P Cuippers, P van Oppen, J Dekker, BMJ. Uitdehaag, Prevalence of depression and anxiety in Multiple Sclerosis: a systematic review and meta-analysis, J. Neurol. Sci. 572 (2017) 331–341.
[11] WT Longstreth Jr, TA Manolas, A Arnold, GL Burke, N Bryan, CA Jungreis, PL Enright, D O’Leary, I Fried, Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the Cardiovascular Health Study, Stroke 27 (1996) 1274–1282.
[12] C Paglieri, D Bistocci, M Caserta, F Rabbia, C Bertello, A Canadé, F. Veglio, Hypertension and cognitive function, Clin. Exp. Hypertens. 30 (2008) 701–710.
[13] WB White, L Wolfson, DB Wakefield, CB Hall, P Campbell, N Moscufo, J Schmidt, RF Kaplan, G Pearlson, CR. Guttman, Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people, Circulation 124 (2011) 2312–2319.
[14] S Debette, S Bombais, A Bruandet, X Delbeuck, S Lepoittevin, C Deloer, D Leys, F. Pasquier, Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment, Stroke 38 (2007) 2924–2930.
[15] GC Román, T Erkinjuntti, A Wallin, L Pantoni, HC. Choi, Subcortical ischaemic vascular dementia, Lancet Neurol. 1 (2002) 426–436.
[16] A Wallin, GC Román, M Ésiri, P Kettunen, J Svensson, GP Paraskevas, E Kapaki, Update on vascular cognitive impairment associated with subcortical small-vessel disease, J. Alzheimers Dis. 62 (2018) 1417–1441.
[17] WB White, DB Wakefield, N Moscufo, CR Guttman, RF Kaplan, RW Bohannon, D Fellows, CB Hall, L. Wolfson, Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY), Circulation 140 (2019) 1626–1635.
[18] The SPRINT MIND Investigators for the SPRINT Research Group, Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial, JAMA 321 (2019) 553–561.
[19] N Kuppus, B Weinstock-Guttman, J Hagemeier, C Kennedy, R Melia, E Carl, et al., Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in Multiple Sclerosis, J. Neurol. Neurosurg. Psychiatry 87 (2016) 181–187.
[20] DE Dossi, H Chaves, ES Heck, et al., Effects of systolic blood pressure on brain integrity in Multiple Sclerosis, PLoS. Neurol. 9 (2018) 487, doi:10.3389/fneur.2018.00487.
[21] RA Marrie, R Horwitz, G Cutter, T Tyrre, D Campagnolo, T. Vollmer, Comorbidity delays diagnosis and increases disability at diagnosis in MS, Neurology 72 (2009) 117–124.
[22] Y Pu, L Liu, X Zou, P Chen, Y Wang, Y Zhou, K Dong, X Zhao, C Wang, Y. Wang, Relationship between leukoaraiosis and cerebral large artery stenosis, Neurol. Res. 31 (4) (2009) 376–380.
[23] H Fang, X Leng, Y. Pu, X Zou, Y Pan, B Song, Y. YO. Soo, TWH Leung, C Wang, X Zhao, Y Wang, Y Wang, KS Wong, L Liu, Y Xu, GCAS Study Group, Hemodynamic significance of middle cerebral artery stenosis associated with the severity of ipsilateral white matter changes, Front. Neurol. 11 (2020) 214.
[24] TH Kim, JW Choi, HG Roh, WJ Moon, SG Moon, Y1 Chun, HY. Kim, Atherosclerotic arterial wall change of non-stenotic intracranial arteries on high-resolution MRI at 3.0T: correlation with cerebrovascular risk factors and white matter hyperintensity, Clin. Neurol. Neurosurg. 126 (2014) 1–6.