99mTc-HMPAO brain SPECT in the monitoring of cerebral vasculitis therapy

Viviana Frantellizzi[1,3] ,MD; Manuela Morreale[2], MD, PhD; Mariano Pontico[1], MD; Ada Francia[2], MD; Francesco Maria Drudi[1], MD; Alessio Farcomeni[4], PhD; Mauro Liberatore[1] MD.

[1]Department of Radiological, Oncological and Anatomo-Pathological Sciences, "Sapienza" University of Rome , Rome; [2]Department of Neurology and Psychiatry, "Sapienza" University of Rome , Rome; [3]PhD Program: Angio-Cardio-Thoracic Pathophisiology and Imaging, "Sapienza" University of Rome, Rome; [4]Department of Public Health and Infectious Diseases, "Sapienza" University of Rome , Rome.

Corresponding Author: Viviana Frantellizzi, Policlinico Umberto I°, Viale Regina Elena 324, 00161 Roma. Tel. +39 06 49978590. Fax: +39 06 49978592.

E-mail: viviana.frantellizzi@uniroma1.it

All authors have no conflicts of interest.

99mTc-HMPAO brain SPECT in the monitoring of cerebral vasculitis therapy

Abstract

Objective.

The central nervous system (CNS) may be involved in a variety of inflammatory diseases of blood vessels, generally known as vasculitis. The clinical diagnosis of such involvement in early stages is difficult, since a mild cognitive impairment can be the only symptom. It was hypothesized that brain-perfusion SPECT would be able to reveal CNS involvement and to monitor the course of the disease. The purpose of this study was assess if and when an improvement of cerebral perfusion can be registered by SPECT during the follow-up of these diseases.

Material and methods.

Eighteen patients affected by Systemic Lupus Erythematosus (SLE), 22 by Undifferentiated Vasculitis (UV), 5 by Behcet's Disease (BD) and 5 by Primary Sjogren's Syndrome (pSS) were enrolled in this prospective study. A 99mTc-HMPAO brain perfusion SPECT was performed before the treatment and was repeated during the follow-up at different time interval. Image analysis was performed on 10 cerebral areas using a specific software.

Results.

In the SLE patients, no significant improvement of brain perfusion was found. On the contrary, in the UV the cerebral uptake of the tracer has begun to significantly improve since the twenty-fourth month (18/22 patients). Patients with BD showed an improvement of scintigraphic findings (5/5 patients) , while a similar result was obtained only in 2 of the patients with pSS.

Conclusions

In conclusion, brain SPECT seems to be able to monitoring disease in UV, showing when an improvement of cerebral perfusion is achieved. In SLE patients this scintigraphic technique has not find significant improvement in CNS perfusion.

Key words: Vasculitis; Brain perfusion; SPECT; Monitoring of therapy

99mTc-HMPAO SPECT cerebral en la monitorización de la terapia de vasculitis cerebral

Abstract

Objetivo.

El sistema nervioso central (SNC) puede estar afectado en una variedad de enfermedades inflamatorias de los vasos sanguíneos, generalmente conocidas como vasculitis. El diagnóstico clínico de dicha afectación en etapas tempranas es difícil, ya que un leve deterioro cognitivo puede ser el único síntoma. Se planteó la hipótesis de que la SPECT de perfusion cerebral podria mostrar la afectación del SNC y podria servir para controlar el curso de la enfermedad. El propósito de este estudio fue evaluar si y cuando una mejora de la perfusión cerebral puede ser registrada por SPECT durante el seguimiento de estas enfermedades.

Material y métodos.

Dieciocho pacientes afectados por Lupus eritematoso sistémico (LES), 22 por vasculitis indiferenciada (UV), 5 por la enfermedad de Behcet (BD) y 5 por el síndrome de Sjogren Primario (pSS) se incluyeron en este estudio prospectivo. Se realizó una SPECT de perfusión cerebral 99mTc-HMPAO antes del tratamiento y se repitió durante el seguimiento a diferentes intervalos de tiempo. El análisis de imagen se realizó en 10 áreas cerebrales utilizando un software específico.

Resultados.

En los pacientes con LES, no se encontró una mejora significativa de la perfusión cerebral. Por el contrario, en la UV la captación cerebral del trazador ha comenzado a mejorar significativamente desde el vigésimo cuarto mes (18/22 pacientes). Los pacientes con BD mostraron una mejora de los hallazgos gammagráficos (5/5 pacientes), mientras que un resultado similar se obtuvo sólo en 2 de los pacientes con pSS.

Conclusiones

En conclusión, el SPECT cerebral parece ser capaz de monitorear la enfermedad en UV, evaluando cuando se puede registrar una mejoría de la perfusión cerebral. En los pacientes

con LES, esta técnica escintigráfica no ha encontrado una mejoría significativa en la perfusión del SNC.

Key words: Vasculitis; Perfusión cerebral; SPECT; Seguimiento de la terapia.

Introduction

The central nervous system (CNS) may be involved in a variety of inflammatory diseases of blood vessels, generally known as vasculitis.

Vasculitis is defined as an inflammation of blood vessels with or without necrosis of the vessel wall. It could be classified into primary and secondary subtypes: the primary vasculitis of the central nervous system is a rare disorder of unknown aetiology specifically targeting the CNS small vessels, whereas in the secondary subtype the systemic vasculitis involves the CNS among other organs and systems. The majority of CNS vasculitis are secondary forms. A further classification is based on the etiopathogenesis and it consists into immuno-allergic, infectious and neoplastic forms. In each of these forms, to confirm the diagnosis of vessel inflammation histological examination is usually required [1].

Due to the low incidence of these pathologies, a lack exist of epidemiological studies and valid data about the frequency of CNS involvement in each type of autoimmune vasculitis. Approximately, in Systemic Lupus Erythematosus (SLE) cerebral involvement affects nearly 40% of patients, but it seems to be directly related to vasculitis in less than 10% of these cases only. It has been reported around 5% of cases in Primary Sjogren's Syndrome (pSS) and in 10-30% of patients diagnosed with mixed connective tissue diseases. The frequency of neuro-Behçet is around 5-10% [2].

In general, the clinical diagnosis of CNS vasculitis is difficult, particularly in early stages, in which a mild cognitive impairment can be the only symptom [3]. Furthermore CNS involvement can precede clinical diagnosis by many years and determine an underestimation of other neurological and/or systemic diseases [4]. Nevertheless, a prompt diagnosis and treatment of these pathologies can improve the clinical manifestations and the prognosis of the patients.

To date, there is no single diagnostic test that is sensitive and specific for neuropsychiatric manifestations related to vasculitis. The assessment of individual

patients is based on clinical neurologic and rheumatologic evaluation, immune-serologic testing, brain imaging, and psychiatric and neuropsychological assessment. These examinations are used to support or refute the clinical diagnostic impression and to exclude alternative better explanations [5].

The most used imaging techniques, such as magnetic resonance imaging (MRI), have shown to be not enough sensitive and specific in revealing the cerebral damage related to vasculitis, while the Brain Perfusion - Single Photon Emission Computed Tomography (BP-SPECT) seems to provide better results [6-7]. Furthermore, it has been hypothesized that BP-SPECT could be able to monitoring the course of the disease and the relative treatment, allowing to distinguish between patients with high likelihood to obtain benefit from specific treatment, and non-responders, to which could be avoided unnecessary side effects [8]. Such a distinction would be of paramount importance if you know how long after the beginning of treatment you are entitled to regard a patient as responders.

The aims of this study was monitoring the treatment of cerebral vasculitis in order to assess if and especially when, during the course of the disease, an improvement of cerebral perfusion can be registered and if there is a correlation between cerebral perfusion and non-focal CNS involvement in autoimmune diseases both in the diagnostic and in the follow up stage.

Material and Methods

Patients

Fifty patients (47 females and 3 males, mean age 39,8 **years ± 4,2)** affected by autoimmune systemic vasculitis previously diagnosed according to American College of Rheumatology (ACR) criteria, underwent to our observation from 2010 to 2015 and were consecutively enrolled in this prospective study. All patients complained non-specific clinical symptoms of CNS involvement.

Based on diagnosis, this group of patients can be subdivided in 18 patients suffering by SLE, 22 by Undifferentiated Vasculitis (UV), 5 by Behcet's Disease (BD) and 5 by pSS.

Inclusion criteria were: 1) age less than 45 years; 2) negative basal brain MRI; 3) presence of non-focal neurological signs and neuropsychiatric symptoms; 4) no corticosteroids treatments for at least 3 months prior to basal BP-SPECT, 5) time from diagnosis to basal BP-SPET less than 2 years.

Cardiovascular risk factors including hypertension, diabetes, dyslipidemia, cardiological illnesses, arhythmias and cigarette smoking were considered as exclusion criteria, as well as acute and chronic infectious diseases, the presence of familiar and personal history of other neurological and psychiatric disorders or of neoplasms.

Written informed consent was obtained from all patients and the study protocol was approved by our Institutional Ethics Committee and conducted in accordance with the Ethical Guidelines of the 1975 Helsinki Declaration.

Clinical evaluation

All patients underwent a wide neurologic anamnestic investigation, objective examination and a panel of serological tests. Specific subjective symptoms were evaluated with appropriate tools.

The Second Edition of the International Classification of Headache Disorders (ICHD-II) was applied to establish a headache diagnosis and score. The psychiatric assessment was based on history and clinical interview focused on: 1) current or past psychopathological disorders; 2) structure of the personality; 3) signs and symptoms of reactive disorders to chronic illness, steroids, or disease-modifying (biological) therapies.

All patients underwent a global screening test with Clinical Global Impression Severity Scale (CGIs) and the following specific tests to detect possible behavioural correlates of executive functions: Beck Depression Scale II – BDII, State-Trait Anxiety Inventory Y1 and Y2 – STAY.

Basal cognitive evaluation was based on Mini-Mental State Examination (MMSE) for cognitive efficiency and Brief Intelligence Test (TIB) for IQ. Regardless of screening tests, all patients underwent a complete neuropsychological assessment in order to explore the main cognitive domains by means of: Verbal Span; Trail Making Test (parts A & B); Rey Auditory Verbal Learning Test; The Rey-Osterrieth Complex Figure Test (ROCF) (with immediate and delayed recall); Test of Weights and Measures Estimation (STEP); Test of Phonological Verbal Fluency / Semantics; Corsi

Block Tapping Test; Tower of London - Italian version; Token Test; AachenerAphasie Test. Raw scores were adjusted for age, sex, education parameters and where applicable, test-specific correction factors.

Scintigraphic studies

A 99mTc-HMPAO BP- SPECT was carried out after the onset of symptoms of vasculitic cerebral involvement and before setting an appropriate treatment and was subsequently repeated during the follow-up at different time interval (12, 24 and 36 months). All patients were prescribed to suspend the intake of coffee, alcohol, and tobacco at least 48 h before scintigraphic examination.

Technetium-99m-HMPAO is a lipophilic radiopharmaceutical, also known as 99mTc-exametazime, used for the assessment of the cerebral perfusion. Before the administration of this radiopharmaceutical a cannula (21G) was introduced into a venous vessel in the arm of the patient. Then the patient was placed on the bed of the gamma-camera and his head was fixed in the orbitomeatal line position by a hemi-cylindrical plastic head-holder to maintain immobilization during acquisition and kept away from light and sound stimulation for 15 min. The radio-labelled compound was prepared adding to a commercial kit (Ceretec™, GE Healthcare, Norway) 740-1100 MBq of sodium pertechnetate diluted in 2 ml of saline solution (0.9% Sodium Chloride) and it was administered to patients intravenously within 15 min. after its preparation. Twenty minutes later, BP-SPECT was performed by a dual-head, large field of view gamma camera (Infinia®, GE Healthcare, Milwaukee, USA) equipped with a couple of high-resolution low-energy parallel holes collimators (LEHR).

Acquisition was performed on a circular orbit of 360°, applying the smallest possible radius, with sampling angle of about 3° and a time of 25s per projection, with acquisition matrix 128×128. The energy window was positioned on the peak of 99mTc (140keV ±10%). Image reconstruction was performed using filtered back projection (FBP), attenuation correction was based on Chang method (attenuation coefficient 0.12).

Transaxial, coronal and sagittal sections, oriented along the orbitomeatal line, were than generated. Image analysis was performed using a specific software (Neurogam®, GE Healthcare) capable of providing for each cerebral area the mean and the standard

deviation (SD) of the counts recorded expressed as the percentage of maximum count rate registered on the encephalon.

NeuroGam® is a comprehensive processing protocol providing cerebral SPECT data analysis, providing co-registration of SPECT data with the Talairach reference template, quantitative and qualitative comparison of sequential brain images on the same patient, in both Talairach and image space, or according to either arterial basins or Brodmann functional areas.

Ten regions of interest (ROI) were selected for each patient, corresponding to the entire right and left hemisphere cortex, parietal, temporal, frontal and occipital regions.

Pharmacological treatment

Once the clinical evaluation and the first BP-SPECT was carried out, all patients started a specific pharmacological treatment on the basis of rheumatologist prescription. All patients received corticosteroids, at doses ranging from 5 to 25 mg/day, and immunomodulatory drugs.

Statistical Analysis

Data are expressed as mean +/- standard deviation, median +/- inter-quartile range or percentages as appropriate. Longitudinal data have been analyzed by means of mixed effects linear regression models. Dependence arising from repeated measurements at different time points for the same subject are taken into account through a subject-specific intercept, which is assumed to be distributed according to a zero-centered Gaussian. Wald tests have been used to assess statistical significance of variations. Given that we also performed subgroup analyses and have separately assessed ROIs, several p-values have been computed. To take into account the multiplicity issues arising from assessment of several significance levels simultaneously, we used Bonferroni correction. We report adjusted p-values, so that $p<0.05$ can be interpreted as *global* statistical significance. Statistical analysis was carried-out for the entire series and for the subgroup of SLE and UV. BD and pSS were excluded due to low number of cases.

Results

Clinical evaluation

All patients did not complain of any significant focal neurological symptoms. Neurological examination did not reveal any sign or symptom of both focal central and peripheral nervous system involvement. Percentage of central nervous system manifestations occurred in patients were as follows: headache 76% (38 patients); cognitive impairment 44% (22 patients); sensitive disorders and pain 24% (12 patients); fatigue 34% (17 patients), mood disorders 42% (21 patients), primary generalized seizures 0,04% (2 patients). None of the patients showed focal neurological deficits. From the cognitive point of view, 52% (n = 26) of the patients enrolled presented an impairment of at least one neuropsychological tests used. The most compromised of the explored domains were executive functions and verbal memory, altered in 66.7% (n = 8) patients. The Trail Making Test and Tower of London, which respectively explore shifting executive capacities and planning abilities, were the most frequently abnormal tests. On the basis of psychiatric evaluation, 42% (n = 21) of patients were in depressive disorder.

The neurological and neuropsychiatric follow-up was performed up to 36 months after the beginning of the treatment. At this time, 2 of the patients with UV showed worsening in clinical and neuropsychiatric evaluations in spite of treatment, whereas the other an amelioration. In the SLE patients the clinical course was stable (n=13) or worsened (n=5). All patients with BD showed an improvement of the clinical picture, while only in 2 of the patients with pSS such a results was obtained.

Scintigraphic studies

Data of BP- SPECT were evaluated as a whole and for each subgroup of disease (SLE, UV, SS, BD). The analysis of the entire series showed that, during the imaging follow-up, the first overall improvement in brain perfusion is achievable after 12 months in 3 of 10 ROIs studied (cortex sx, frontal sx and occipital sx). After 24 months, the improvement appear to be strongly evident in all of the studied ROIs, even with higher significance in each single ROI considered. This pattern is then confirmed clearly at 36 months' time interval SPECT scans, which showed an overall

improvement of brain perfusion in each of the 10 cerebral areas taken in consideration (Table 1).

In the SLE subgroup, the differences between the overall means calculated on the areas of interest before and after the treatment, resulted as follow. No significant differences resulted at 12, 24 and 36 months in most of the ROIs and in the ROI of whole brain (Table 2). In the other hand, in the UV group no significant differences were found at 12 months, while such differences became significant at 24 ($p = 0.027$) and 36 months ($p = 0.001$) (Table 3). These results are consistent with the clinical course observed in patients.

All patients with BD showed an improvement of scintigraphic findings already evident at 12 month, while a similar result was obtained only in 2 of the patients with pSS.

Discussion

There is a considerable amount of work carried out to compare the results of MRI and BP-SPECT in the study of CNS involvement in patients affected by autoimmune vasculitis. A comparative study indicate that SPECT is more sensitive than MRI in diagnosis of CNS involvement in SLE patients [9]. A comparison of BP-SPECT with a particular MRI technique such as perfusion-weighted imaging (*PWI*) showed a greater sensitivity of the radionuclide technique (85% versus 50%) [10]. Nobili et al feel that BP-SPECT, in Behcet's disease, can be clinically meaningful in patients with neuropsychiatric disorders but inconclusive brain morphological investigations, since it could disclose sub-clinical brain impairment in patients without neuropsychiatric complaints [11].

Diffuse symptoms such as headache and cognitive and psychiatric manifestations in pSS seem to be more frequent than focal involvement and potentially related to a vasculitic damage [12-13]. Similarities with neuropsychiatric systemic lupus erythematosus (CNS-SLE) suggested such a role of impairment of both regional and general cerebral blood flow (CBF), as observed in CNS-SLE by means of several imaging methods including positron emission tomography (PET), SPECT and MRI [14-15].

Although the role of focal ischemic damage in determining clinical involvement of the CNS related to pSS is still controversial, regional CBF fluctuations with BP-SPECT have been observed in these patients when no structural brain lesions are visible and has been related to

neuropsychological symptoms, but some limitations such as high costs and availability of the equipment strongly impact the clinical use of this tool [16-18]. BP-SPECT may better identify diffuse CNS involvement and provide information about cerebral metabolism and perfusion defects in autoimmune diseases, especially SLE and pSS [19].

Morreale et al. recently observed an association with immunological biomarkers, metabolic cerebral dysfunction and microvascular damage in a heterogeneous sample of pSS patients with and without neuropsychiatric manifestations, suggesting a possible endothelial dysfunction of the cerebral microcirculation or a potential inflammation mediated shift of the neurovascular coupling [20].

As reported by Castellino et al. MRI results correlate with CNS manifestations, particularly in those with focal presentation. BP-SPECT is more frequently abnormal than MRI in diffuse CNS-vasculitis, were MRI does not give significant information about metabolism or perfusion defects detected by BP-SPECT. Coupling the two techniques may be more helpful in excluding CNS involvement than in confirming it [21]. A recent review has carefully analysed the diagnostic tools for diagnosis of SLE coming to the conclusion that no single imaging procedure covers all aspects of the disease. Modern MRI techniques provide useful information to assess brain tissue damage, however a multimodal approach that couples a morphological imaging technique and a functional one is recommended [22-23]. By considering the above mentioned BP-SPECT and MRI discrepancies and to the difficult interpretation of the BP-SPECT abnormalities in patients with autoimmune vasculitis without CNS involvement, the study we present was designed on patients with non-focal neurological and neuropsychiatric symptoms and negative MRI. Furthermore, a similar study design was suggested by some reports, in the literature, regarding the use of BP-SPECT in the follow-up of cerebral vasculitis. The findings of these researches indicated that BP-SPECT is more useful than MRI as diagnostic tool for monitoring disease activity and treatment. Sun et. al [24] reported the resolution of BP-SPECT abnormalities following treatment with corticosteroids in patients affected by SLE with normal MRI. These results were confirmed by a similar study where, once again, after treatment, 10 out 12 patients showed complete recovery and two showed partial recovery of abnormalities in BP-SPECT images [25]. In another study, repeated BP-SPECT after treatment (two months later) showed that perfusion defect had improved significantly or even disappeared in 11 of 13 patients with CNS-SLE with abnormal findings

before treatment. In the opinion of these authors, BP-SPECT seems useful in follow-up of vasculitis, especially for monitoring disease severity and guiding treatment [11]. Similar results are reported in patients affected by SLE [26-27] and other vasculitis [8, 28-29].

The first data emerging from the analysis of our results is the significant global improvement of cerebral perfusion determined by the treatment in UV (Figure 1). These results are in agreement with those reported by other Authors in various autoimmune vasculitis [27-29]. However, it is worth pointing out that these results can be achieved within 24 and 36 months from the beginning of therapy. This means that an early evaluation of treatment effect by BP-SPECT could not be useful. From similar results, the importance of the BP-SPECT in the clinical management of these patients could come out resized, but it should always be kept in mind that vasculitis are chronic diseases that, in general, require a very long treatment, not always effective. On the contrary, in the group of SLE patients, no statistically significant improvement was found in most of the ROIs and in the ROI of whole brain, independently of the execution time of the control BP-SPECT (Figure 2). These findings are in agreement with time course of clinical picture in this group of patients. Similar results were reported by Castellino et al. [30], who noted that BP-SPECT findings, after a 4-year follow-up, were globally unchanged, rarely improved, in some cases worsened, but without correlation with clinical picture. However, we must emphasize that this latter was performed also in patients with focal presentation of CNS involvement, with visual interpretation of scintigraphic images. On the contrary, our experience was carried out in patients with non-focal and subclinical CNS involvement using quantitative interpretation of BP-SPECT.

Other Authors, conversely, demonstrated an improvement in perfusion defect after therapy in SLE patients, but this improvement was obtained in patients with severe focal neuropsychiatric involvement [31]. These results were not confirmed by several other authors [7, 9-10, 14].

Taking into account previous longitudinal studies conducted in SLE patients, the scintigraphic results are not surprising. In fact, generally, in patients with SLE disease activity tends to decline over time, while organ damage steadily accumulates throughout life [32]. On this basis, it would be very strange to find a significant improvement of BP-SPECT in these patients.

Table 1 regards the whole group of studied vasculitis and shows an overall improvement, statistically significant, of BP-SPECT results, confirming the findings visually appreciable in our experience. It would seem to conflict with data reported in Tables 2 and 3, were a relevant difference between SLE and UV, in terms of results, can be found. This apparent inconsistency can not simply be explained by the small simple size of the two subgroups, but, more likely, by a completely different pathological mechanism subtended to different diseases, that only apparently results in similar macroscopic findings.

Due to the low number of cases, caution should be exercised in the evaluation of the results obtained in patients with BD and pSS, although it must remember that these are quite rare diseases, also studied in sub-clinical stage. Anyway, BP-SPECT was found to reveal CNS involvement in BD patients without neurological complaints 10] and, at least from this point of view, can be considered clinically useful.

In conclusion, BP-SPECT is useful in revealing the involvement of the CNS in patients with negative MRI findings. Furthermore it seems to be able to monitoring disease in UV assessing when an improvement of cerebral perfusion can be registered. In SLE patients, BP-SPECT in the follow-up of cerebral vasculitis, does not show significant improvement in CNS perfusion. This is probably due to the organ damage, which is reported to accumulate in time in these patients. A possible limitation of this study is represented by the fact that a causal relationship between the administered treatment and perfusion variations, which might also be due, almost partially, to the natural history of the disease.

However, it must not underestimate the usefulness of BP-SPECT in detecting non-focal CNS involvement. Such assessment may suggest the use of a more aggressive therapy with the aim to obtain, at least, a stability of the disease, which, as clinical experience demonstrate, can already be considered a partial success.

References

1) Salvarani C, Brown jr RD, Hunder GG. Adult primary central nervous system vasculitis. The Lancet. 2012 Aug; 380(9843): 767-777.

2) Harboe E, Tjensvoll AB, Maroni S, Gøransson LG, Greve OJ, Beyer MK, et al. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and primary Sjögren syndrome: A comparative population-based study. Ann Rheum Dis. 2009 Oct;68(10):1541-6.

3) Kozora E, Filley CM, Zhang L, Brown MS, Miller DE, Arciniegas DB, et al. Immune function and brain abnormalities in patients with systemic lupus erythematosus without overt neuropsychiatric manifestations. Lupus 2012 Apr;21(4):402-11.

4) Massara A, Bonazza S, Castellino G, Caniatti L, Trotta F, Borrelli M, et al. Central nervous system involvement in Sjögren' sindrome: Unusual, but non unremarkable--clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology (Oxford) 2010 Aug;49(8):1540-9.

5) Becker J, Horn PA, Keyvani K, Metz I, Wegner C, Brück W, Heinemann FM, Schwitalla JC, Berlit P, Kraemer M. Primary central nervous system vasculitis and its mimicking diseases - clinical features, outcome, comorbidities and diagnostic results - A case control study. Clin Neurol Neurosurg. 2017 May;156:48-54. doi: 10.1016/j.clineuro.2017.03.006. Epub 2017 Mar 8.

6) Axford JS, Howe FA, Heron C, Griffiths JR. Sensitivity of quantitative (1) H magnetic resonance spectroscopy of the brain in detecting early neuronal damage in systemic lupus erythematosus. Ann Rheum Dis 2001 Feb;60(2):106-11.

7) Zhang X, Zhu Z, Zhang F, Shu H, Li F, Dong Y. Diagnostic value of single-photon-emission computed tomography in severe central nervous system involvement of systemic lupus erythematosus: A case-control study. Arthritis Rheum 2005 Dec 15;53(6):845-9.

8) Liberatore M, Morreale M, Megna V, Collorone S, Sotirios C, Drudi F, et al. Role of Brain Perfusion SPECT with 99mTc HMPAO in the Assessment of Response to Drug Therapy in Patients with Autoimmune Vasculitis: A Prospective Study. N Am J Med Sci. 2015 Apr;7(4):135-42.

9) Oku K, Atsumi T, Furukawa S, Horita T, Sakai Y, Jodo S, et al. Cerebral imaging by magnetic resonance imaging and single photon emission computed tomography in systemic lupus erythematosus with central nervous system involvement. Rheumatology (Oxford). 2003 Jun;42(6):773-7

10) Borrelli M, Tamarozzi R, Colamussi P, Govoni M, Trotta F, Lappi S. Evaluation with MR, perfusion MR and cerebral flow SPECT in NPSLE patients. Radiol Med. 2003 May-Jun;105(5-6):482-9.

11) Nobili F, Cutolo M, Sulli A, Vitali P, Vignola S, Rodriguez G. Brain functional involvement by perfusion SPECT in systemic Sclerosis and Behcet's disease. Ann NY Acad Sci 2002, Jun; 966: 409-414.

12) Skopouli FN, Moutsopoulos HM. Autoimmune epitheliitis: Sjögren's syndrome. Clin Exp Rheumatol 1994; 12: S9–S11

13) Tzioufas AG, Kapsogeorgou EK, Moutsopoulos HM. Pathogenesis of Sjogren's syndrome: what we now and what we should learn. J Autoimmun 2012; 39: 4–8

14) Lass P, Koseda M, Romanowicz G, Mechlińska J, Banecka Z, Góra M, et al. Cerebral blood flow assessed by brain SPECT with 99mTcHMPAO utilising the acetazolamide test in systemic lupus erythematosus. Nucl Med Rev Cent East Eur 1998; 1: 20–24

15) Lee SW, Park MC, Lee SK, Park YB. The efficacy of brain (18)Ffluorodeoxyglucose positron emission tomography in neuropsychiatric lupus patients with normal brain magnetic resonance imaging findings. Lupus 2012; 21:1531–1537

16) Mataró M, Escudero D, Ariza M, Sánchez-Ojanguren J, Latorre P, Junqué C, et al. Magnetic resonance abnormalities associated with cognitive dysfunction in primary Sjögren syndrome. J Neurol 2003; 250:1070–1076

17) Yoshida A, Shishido F, Kato K, Watanabe H, Seino O.. Evaluation of cerebral perfusion in patients with neuropsychiatric systemic lupus erythematosus using 123IIMP SPECT. Ann Nucl Med 2007; 11: 151–158

18) Belin C, Moroni C, CaillatVigneron N, Debray M, Baudin M, Dumas JL, et al. Central nervous system involvement in Sjögren's syndrome: evidence from neuropsychological testing and HMPAO-SPECT. Ann Med Interne (Paris) 1999; 150:598–604

19) Chang CP, Shiau YC, Wang JJ, Ho ST, Kao A. Abnormal regional cerebral blood flow on 99mTcECD brain SPECT in patients with primary Sjögren's syndrome and normal findings on brain magnetic resonance imaging. Ann Rheum Dis 2002; 61:774–778

20) Morreale M, Marchione P, Giacomini P, Pontecorvo S, Marianetti M, Vento C, et al. Neurological involvement in primary Sjögren' syndrome: a focus on central nervous system. PLoS One 2014; 9: e84605

21) Castellino G, Padovan M, Bortoluzzi A, Borrelli M, Feggi L, Caniatti ML, et al. Single photon emission computed tomography and magnetic resonance imaging evaluation in SLE patients with and without neuropsychiatric involvement. Rheumatology (Oxford). 2008 Mar;47(3):319-23.

22) Zardi EM, Taccone A, Marigliano B, Margiotta DP, Afeltra A. Neuropsychiatric systemic lupus erythematosus: tools for the diagnosis. Autoimmun Rev. 2014 Aug;13(8):831-9.

23) Govoni M, Castellino G, Padovan M, Borrelli M, Trotta F. Recent advances and future perspective in neuroimaging in neuropsychiatric systemic lupus erythematosus. Lupus. 2004;13(3):149-58.

24) Sun SS, Huang WS, Chen JJ, Chang CP, Kao CH, Wang JJ. Evaluation of the effects of methylprednisolone pulse therapy in patients with systemic lupus erythematosus with brain involvement by Tc-99m HMPAO brain SPECT. Eur Radiol. 2004 Jul;14(7):1311-5.

25) Liu FY, Huang WS, Kao CH, Yen RF, Wang JJ, Ho ST. Usefulness of Tc-99m ECD brain SPECT to evaluate the effects of methylprednisolone pulse therapy in lupus erythematosus with brain involvement: a preliminary report. Rheumatol Int. 2003 Jul;23(4):182-5.

26) Kikukawa K, Toyama H, Katayama M, Nishimura T, Ejiri K, Minami K, et al. Early and delayed Tc-99m ECD brain SPECT in SLE patients with CNS involvement. Ann Nucl Med. 2000 Feb;14(1):25-32.

27) Mathieu A, Sanna G, Mameli A, Pinna C, Vacca A, Cauli A, et al. Sustained normalization of cerebral blood-flow after iloprost therapy in a patient with neuropsychiatric systemic lupus erythematosus. Lupus. 2002;11(1):52-6.

28) Suh JS, Hahn WH, Cho BS, Kim SD, Hong IK. A rare case of cerebral vasculitis in Henoch-Schönlein purpura with emphasis on the diagnostic value of

magnetic resonance angiography (MRA) and single-photon emission computed tomography (SPECT) given normal magnetic resonance imaging (MRI). Int J Dermatol. 2010 Jul;49(7):803-5.

29) Okamoto M, Ashida KI, Imaizumi M. Hypoperfusion following encephalitis: SPECT with acetazolamide. Eur J Neurol. 2001 Sep;8(5):471-4.

30) Castellino G, Bortoluzzi A, Padovan M, Borrelli M, Feggi L, Govoni M. Repeated brain conventional MRI and SPECT evaluation in systemic lupus erythematosus patients with and without neuropsychiatric involvement: a follow up study. Lupus. 2011 Nov;20(13):1387-95.)

31) Qiu J, Hu SY, Zuo XX. Single photon emission computed tomography evaluation for severe neuropsychiatric systemic lupus erythematosus. Clin Exp Rheumatol. 2013 Jan-Feb;31(1):159).

32) Maddison P, Farewell V, Isenberg D, Aranow C, Bae SC, Barr S, et al. The rate and pattern of organ damage in late onset systemic lupus erythematosus. J Rheumatol. 2002 May; 29(5):913-7.

Figures legend

Fig. 1 ^{99}mTc-HMPAO perfusion brain SPECT scans of a patient with SLE at 0, 12, 24 and 36 months from the beginning of treatment (respectively in A, B, C and D) in transaxial and sagittal reconstructions. No significant changes in SPECT findings were found

Fig. 2 ^{99}mTc-HMPAO perfusion brain SPECT scans of a patient with UV at 0, 12, 24 and 36 months from the beginning of treatment (respectively in A, B, C and D) in transaxial and sagittal reconstructions. As can be seen, SPECT results show an improvement of brain perfusion

Table 1. Estimated changes of percentage of maximum count rate registered on the encephalon at each time point, by SPECT and within the whole group of studied vasculitis (n=50)

	12 Months				24 Months				36 Months			
Area	**Variation**	**95% CI**		**p-value**	**Variation**	**95% CI**		**p-value**	**Variation**	**95% CI**		**p-value**
Cort. dx	-1.031	-3.113	1.051	0.332	-3.248	-5.016	-1.481	**0.000**	-5.466	-7.544	-3.388	**0.000**
Cort. sx	-2.320	-4.392	-0.249	**0.028**	-3.871	-5.683	-2.059	**0.000**	-5.421	-7.511	-3.331	**0.000**
Front dx	-1.579	-3.491	0.332	0.105	-3.951	-5.612	-2.290	**0.000**	-6.323	-8.247	-4.398	**0.000**
Front sx	-2.172	-4.180	-0.163	**0.034**	-4.352	-6.083	-2.622	**0.000**	-6.533	-8.549	-4.516	**0.000**
Occ. dx	-1.324	-3.606	0.959	0.256	-2.191	-4.021	-0.360	**0.019**	-3.058	-5.259	-0.856	**0.006**
Occ sx	-2.116	-4.070	-0.162	**0.034**	-2.541	-4.149	-0.933	**0.002**	-2.966	-4.884	-1.047	**0.002**
Par dx	-1.292	-3.647	1.064	0.282	-3.177	-5.049	-1.305	**0.001**	-5.062	-7.318	-2.807	**0.000**
Par sx	-1.521	-4.100	1.058	0.248	-3.059	-5.295	-0.824	**0.007**	-4.597	-7.192	-2.003	**0.001**
Temp dx	-0.859	-3.358	1.640	0.500	-4.210	-6.283	-2.138	**0.000**	-7.562	-10.026	-5.097	**0.000**
Temp sx	-1.821	-4.288	0.647	0.148	-3.994	-6.178	-1.811	**0.000**	-6.168	-8.664	-3.672	**0.000**
Whole	-1.940	-3.596	-0.284	**0.022**	-3.164	-4.770	-1.558	**0.001**	-4.3876	-6.0599	-2.7153	**0.0001**

Cort, cortex; Front, frontal; Occ, occipital; Par, parietal; Temp, temporal; Whole, Brain in toto; CI, Confidence Interval.
Significant p-values are reported in bold

Table 2. Estimated changes of percentage of maximum count rate registered on the encephalon at each time point, by SPECT in the SLE patients (n=18)

	12 Months				24 Months				36 Months			
Area	**Variation**	**95% CI**		**p-value**	**Variation**	**95% CI**		**p-value**	**Variation**	**95% CI**		**p-value**
Cort. dx	-2.605	-7.255	2.046	0.272	-3.801	-8.107	0.505	0.084	-4.998	-9.461	-0.535	**0.028**
Cort. sx	-1.917	-5.417	1.583	0.283	-2.177	-5.565	1.21	0.208	-2.437	-5.877	1.002	0.165
Front dx	-2.631	-6.918	1.655	0.229	-3.895	-7.92	0.131	0.058	-5.158	-9.303	-1.013	**0.015**
Front sx	-2.38	-5.864	1.104	0.181	-3.414	-6.61	-0.218	**0.036**	-4.448	-7.775	-1.121	**0.009**
Occ. dx	-2.436	-6.874	2.001	0.282	-2.599	-6.465	1.266	0.188	-2.762	-6.877	1.352	0.188
Occ sx	-1.368	-4.617	1.882	0.409	-1.412	-4.057	1.233	0.295	-1.456	-4.339	1.428	0.322
Par dx	-1.855	-6.206	2.496	0.403	-2.949	-6.867	0.968	0.14	-4.044	-8.155	0.068	0.054
Par sx	-1.015	-5.248	3.218	0.638	-1.073	-5.074	2.929	0.599	-1.13	-5.238	2.978	0.59
Temp dx	-1.458	-6.587	3.671	0.577	-4.463	-9.01	0.085	0.054	-7.467	-12.272	-2.662	**0.002**
Temp sx	-0.868	-5.822	4.087	0.731	-2.807	-7.459	1.845	0.237	-4.746	-9.537	0.044	0.052
Whole	-2.352	-6.223	1.519	0.234	-2.76	-6.573	1.053	0.156	-3.168	-7.008	0.671	0.106

Cort, cortex; Front, frontal; Occ, occipital; Par, parietal; Temp, temporal; Whole, Brain in toto; CI, Confidence Interval
Significant p-values are reported in bold

Table 3. Estimated changes of percentage of maximum count rate registered on the encephalon at each time point, by SPECT in the UV patients (n=22)

	12 Months				24 Months				36 Months			
Area	**Variation**	**95% CI**		**p-value**	**Variation**	**95% CI**		**p-value**	**Variation**	**95% CI**		**p-value**
Cort. dx	-0.37	-3.903	3.163	0.837	-2.875	-6.002	0.251	0.071	-5.381	-9.038	-1.723	**0.004**
Cort. sx	-2.942	-6.977	1.093	0.153	-5.271	-8.962	-1.58	**0.005**	-7.599	-11.841	-3.357	**0.001**
Front dx	-0.882	-3.862	2.098	0.562	-3.79	-6.456	-1.125	**0.005**	-6.699	-9.803	-3.596	**0.001**
Front sx	-2.497	-6.252	1.258	0.192	-5.477	-8.896	-2.059	**0.002**	-8.457	-12.398	-4.516	**0.001**
Occ. dx	-0.383	-4.3	3.535	0.848	-1.141	-4.422	2.139	0.495	-1.9	-5.784	1.985	0.338
Occ sx	-2.158	-5.781	1.465	0.243	-3.156	-6.483	0.17	0.063	-4.155	-7.968	-0.341	**0.033**
Par dx	-1.348	-5.682	2.985	0.542	-3.027	-6.569	0.516	0.094	-4.705	-8.901	-0.509	**0.028**
Par sx	-2.059	-7.078	2.96	0.421	-4.421	-9.023	0.18	0.06	-6.784	-12.064	-1.504	**0.012**
Temp dx	-0.714	-4.96	3.532	0.742	-4.094	-7.785	-0.403	**0.03**	-7.475	-11.818	-3.131	**0.001**
Temp sx	-2.849	-7.019	1.321	0.181	-5.182	-8.981	-1.383	**0.008**	-7.515	-11.894	-3.137	**0.001**
Whole	-1.587	-4.712	1.539	0.32	-3.47	-6.55	-0.39	**0.027**	-5.353	-8.56	-2.147	**0.001**

Cort, cortex; Front, frontal; Occ, occipital; Par, parietal; Temp, temporal; Whole, Brain in toto; CI, Confidence Interval
Significant p-values are reported in bold