Review Article

# Heterogeneity of Antiphospholipid Syndrome (APS) as Characterized by Brain Perfusion Techniques. Towards New Ways of Syndrome Characterization

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## 1. Abstract

Antiphospholipid Syndrome (APS) syndrome is an autoimmune condition that affects the way that blood cells in humans bind together. Though the cause of APS is unclear, researchers believe that many factors have an impact on developing this pathological condition. Phospholipids (PLs) play numerous central roles in biological systems, and processes of biological systems regulation act through the liberation of a vast amount of different signalling molecules, which are also involved in the modulation of cell proliferation, inflammation, oxidative stress, neurotransmission and many other processes.A global landmark, holistic, is required to evaluate different phenotypes in APS. All thecriteria validated for the APS diagnosislead to an extremely heterogeneous landmark of the pathology and related to several manifestations in different systems. Heterogeneity also characterizes the SPECT acquisition of the patients and it is connected to several neurological and underestimates symptoms of the pathology.

We present some examples to highlight the connection between heterogeneity in SPECT and APS markers of pathology indicating the needs to approach to the Syndrome in a holistic way. At the end of the paper we suggested the multidisciplinary approach that we are tuning for our analysis, approach based on Imaging, Metabolomic and Clinical evaluation, including mental health test for a neuropsychiatric characterization of the pathology.

## 2. Introduction

Antiphospholipid Syndrome (APS) syndrome, also known as "sticky blood syndrome", is an autoimmune condition that affects the way that blood cells in humans bind together, or clot [1]. AP syndrome is considered a rare syndrome. Recurrent thromboembolism and miscarriages characterize APS among young adults, as well as other pregnancy-related complications such as stillbirth, preterm delivery, and severe preeclampsia [2]. For example, people who have a stroke before age 50 sometimes can discover that AP syndrome was an underlying cause. AP syndrome affects three to five times as many women as men. Though the cause of APS is unclear, researchers believe that diet, lifestyle, and genetics can all have an impact on developing this pathological condition [3]. Phospholipids (PLs) play numerous central roles in biological systems, including the formation of the lipid bilayer in cellular membranes and the regulation of multiple biological pathways and process. Processes of biological systems regulation act through the liberation of a vast amount of different signalling molecules, which are also involved in the modulation of cell proliferation, inflammation, oxidative stress, neurotransmission and many other processes. Blood phospholipids composition, the so-called Metabolome, can influence reactions and process in humans related to the life of organs and tissues; composition of the phospholipids, named Phospholipidome, generated by AP syndrome regulates the human Metabolome. Complexity in the Phospholipidome results in a complex Metabolome, related to the responsivity of

organs and tissue to APS. It is important to note that, as for other medical fields, this is the paradigm for the application of Metabolomics as a complementary technique for APS syndrome characterization. Metabolome, and the study of the Metabolome, Metabolomics, can be related to the different and heterogeneous effects generated in carriers of APS [3].

As for other pathologies, like Multiple Sclerosis, for example, the autoimmune reaction is regulated by external and internal perturbation of the homeostasis in humans. A global landmark, holistic, is required to evaluate different phenotypes in APS. The Syndrome, that has an autoimmune origin, provokes blood clots, defined thrombosis, in both arteries and veins. The Syndrome is the most common cause of acquired thrombophilia, and it can result in many organs and functions pathologies or complications in humans [4]. APS is associated with the presence of different antibodies in the blood: antiphospholipids aCL IgG / IgM and anti-β2GPI IgG / IgM with medium-high levels. The Syndrome is defined as primary if it is not associated with another autoimmune disease; otherwise, it is called secondary and, in this case, it is mainly associated with Systemic Lupus Erythematosus (LES) [5-10]. The term Antiphospholipid Antibody Syndrome dates back to the 1980s, but only in 1999 were officially established criteria accepted for the classification of the Syndrome, following the International Workshop of Sapporo. These criteria were reviewed during the XI International Congress on Antiphospholipid antibodies, held in Sydney in 2004 and published in 2006. There are some clinical manifestations of the Syndrome that do not fall within the so-called "clinical criteria" for diagnosis of APS and are defined "non-criteria" symptoms. These are the heart valve disease (occurring in the absence of other causes), coronary ischemia, ventricular dysfunctions, mainly microangiopathic nephropathy or ischemic and finally some neurological manifestations such as cognitive deficits, complex movements disorders, migraine, multiple sclerosis, transverse myelitis, epilepsy and others [11]. Based on the currently accepted criteria, it is possible to diagnose APS if we have both at least one of the clinical and laboratory criteria, acquired no less than twelve weeks and no more than five years.

"Clinical Criteria" and "Non-Clinical Criteria" are extremely heterogeneous and related to several manifestations of pathology. This extensive heterogeneity of Antiphospholipid syndrome (APS), especially related to neurological manifestations such as cognitive deficits, complex movements disorders, migraine, multiple sclerosis, transverse myelitis, epilepsy, is frequently reported in the literature and characterized by several brain imaging techniques; this is another suggestion for the need of a multidisciplinary approach towards AP syndrome characterization [11-13].

There is another important aspect related to the proper classification of APS; it requires evidence of several clinical events and the quantification of the continuous and abundant presence of antiphospholipid antibodies. Clinical tests used to detect APS include lupus anticoagulant (LAC), anti-cardiolipin (ACL) antibodies, and anti-β2-glycoprotein I antibodies. All patients who have an Antiphospholipid Antibody Syndrome have the laboratory dosage of anti-cardiolipin, anti-B2Glycoprotein I and LAC antibodies [14-16]. APS has different effects classified by pieces of evidence of neurological and neuropsychiatric symptoms. The neurological and neuropsychiatric manifestations of APS can include headache, dizziness, vertigo, seizure, depression and psychosis, and they can affect individuals could exhibit these symptoms before they develop thromboembolism. We have to consider that presentations of APS such as nephropathy, valvulopathy and neuropsychiatric symptoms, defined as non-criteria symptoms, can adversely affect patients' quality of life and work capacity. Biochemical information and measurements can be connected with the measurement of the cognitive status. The different neuropsychiatric manifestations of APS can be related to alteration of brain activity signals measured by different techniques [16, 8]. Imaging is one of the most important techniques for monitoring and diagnosis in APS, but it is not the only one. Several techniques can produce information about APS, and the unification of these data can result in a strengthening of the information content useful for the APS characterization [23].

Brain perfusion SPECT is a clinical practice used to evaluate physiologic and physiopathological events; it is a functional neuroimaging technique based on the revelation of radiopharmaceutical injected in the patient and revealed with scintigraphy technique. With the appropriate technology and careful interpretation of the data acquired, brain perfusion SPECT has proven to be useful for APS patient management. SPECT has excellent clinical value in the diagnosis, and also in the therapeutic management and the follow-up of APS patients [19].

Generally speaking, brain perfusion SPECT has a great success in the application to the metabolic alteration of the brain diseases, due to the ability of the technique to be sensitive to functional modification of the central nervous system. Brain perfusion SPECT is a powerful research tool in neurosciences.

Apart of the SPECT, in the recent past, magnetic resonance imaging (MRI) was applied to the brain analysis related to the APS, but it seemed to have a lower sensibility in the identification of the cerebrovascular lesions associated with APS in the case of non-criteria APS patients [20]. The non-criteria symptoms, or effects, are the manifestations of the APS syndrome that are

not included in the diagnosis criteria due to low specificity of these symptoms. Further, there is to consider that MRI applied to the functionality analysis in the brain is based on the BOLD mechanism, Blood oxygenation level demand, which presupposes a correct coupling between neural activity and brain circulation.

Further, Computer Tomography can give information about APS damages; computer tomography scan uses a combination of many X-ray expositions taken from different angles to produce tomographic images of specific areas and reconstructed by dedicated computer (reconstructors computer).

The Antiphospholipid Antibodies in Stroke Study Group reports several neuroradiological findings in APS with different Imaging techniques, to compare for sensibility and specificity of diagnosis; in 128 APS cases, CT detected single infarctions in 53 patients (46 %) and multiple infarctions in 28 patients (24 %). The MR images were able to detect brain abnormalities in APS more sensitively than CT [4]; the MR findings of APS include infarctions, cortical atrophy, and white matter abnormalities. However, according to Levine and Bray, these MR features are observed in many other diseases and are not specific for APS. At the moment, SPECT seems to give much more insight than other Imaging techniques. It is the best functional technique to correlate metabolic alteration in ASP and functional reorganizations of brain activity after circulation damages. It is important to emphasis the brain function dynamics are hugely varying due to the self-organization property of the brain neurons; this is important also for the need to monitoring the evolution of brain perfusion after therapy. Also, in the case of APS, previous studies reported that single-photon emission computed tomography (SPECT) could detect the decreased brain blood flow in APS patients with a history of thrombotic events. Nonetheless, the usefulness of brain SPECT for assessing non-criteria APS is still unclear because SPECT elaborations report a very different picture of brain perfusion. Altered areas of perfusion in the brain can regard several functions, and they are in different regions of the brains.

It is also essential to consider that different populations of antiphospholipid antibodies can result in a different metabolic composition of blood, and it can result in different behaviours of neurons of the brain; this could be the basic idea of nature of the heterogeneity of the SPECT findings in APS.

Findings in the Imaging applied to the APS suggest some crucial questions: can we map the most common effects in the brain related to the altered coagulation of the brain blood? Further, can we obtain a metabolic guide to classify the regions of the brain most frequently attached by this altered brain blood coagulation?

From the metabolic point of view, we can consider that different phenotypes of blood composition can affect in different ways the brain functions; this could lead to the heterogeneity of SPECT analysis.

However, what is the factors influencing this heterogeneity? First of all, the composition of the antibodies activated in APS could be a leading force to define the phenotypes in APS. Antiphospholipid antibodies are a heterogeneous population of antibodies directed against a combination of negatively charged phospholipids and phospholipid-binding protein and include the anti-cardiolipin antibody and the lupus anticoagulant antibody. The anti-cardiolipin antibody binds to cardiolipin through beta 2-glycoprotein I and may inhibit the formation of beta 2-glycoprotein I or block its physiological function. Beta 2-glycoprotein I is a phospholipid-binding plasma protein that inhibits the generation of the coagulant factor Xa by activated platelets. Thus, the thromboembolic complications of APS may be due to the presence of anti-cardiolipin antibodies. The lupus anticoagulant antibody, another antiphospholipid antibody, recognizes the lipid-bound human prothrombin complex.

Details of the mechanism underlying all these interactions are still unclear have not been clarified. This picture leads to the possibility of diffuse alterations in organs and tissue due to APS. Probably only a merging of different techniques can give the researchers the ability to differentiate all the phenotypes; this is the reason because, in our opinion, ASP investigation should be operated with a large number of tools contemporary to SPECT examination, and we present some data supporting our deductions and suggestion for a proper protocol of syndrome analysis.

**3. Materials and Methods**

To support our suggestion about a most appropriate procedurefor APS characterization, we present some notations about some Tc-99m ethyl cysteinate dimer (ECD) SPECT operated on patients with the APS diagnosis with the idea to assess circulation insufficiency in the brains of patients with antiphospholipid antibodies and evaluate neurological and neuropsychiatric signs and classify the single subject effects.We evaluated the data from 22 patients APS. Each participant received the injection of about 800 MBq 99mTc-ECD [20, 22-24]. After 20 minutes, the patient underwent the SPECT examinations on a Varicam GEMS Genie 1; data were analyzed by XELERIS-MNNLATM work station and then processed by SPM12 [17]. Fanbeam collimators were used.

Control group was patients underwent SPECT examination resulted in no brain perfusion alteration and without ASP diagnosis. We used a BioImage Suite Web 1.0.0 and Xjview to represent images of contrasts. Some results are exciting because they can explain the significant heterogeneity of SPECT signal

alteration and clinical note recorded at the examination time [12, 23].

**4. Results**

We report data for a subset of samples that are still under observation in our hospital (9 up to 22 subjects). All SPECTs are used to evaluate single subject findings (I level analysis) and group effects (II level analysis). We report data for the first level analysis of single-subject with cluster p-value<0,05 corrected for multiple connections with FWE. 4 patients up to 9, in our database, have this kind of information. The first patient presents extended of altered brain perfusion areas in several critical regions. First of all, there is an essential area of altered signal in the cerebellar region that is not frequently revelled in the APS patient. Further, brain perfusion is statistically altered in the frontal cortex related to different brain circuits for the "control function". It is involved primary the Brodmann Area BA11. BA11, located at the base of the frontal pole, relates to a function that could be termed as "personality integrity." Traumatic brain injury individuals present personality changes are supposed to result from damage of this orbital frontal area and could be related to patients with ASP and locally altered brain perfusion signal. of course, "personality" (i.e., style of behaviour) is a challenging concept to approach with SPECT Imaging, and it is also difficult to define in fMRI experiments without tests as Mini-Mental Status Examination (MMSE) test and test as the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), which is the most widely used structured interview in the world, in the scientific field, for the qualitative and quantitative assessment of obsessive-compulsive symptoms, and YGTSS Yale Global Tic Severity Scale, Y-BOCS Yale-Brown Obsessive-Compulsive Scale, OCD obsessive-compulsive disorder (**Figure 1**).

Alteration of the performances of the neurons in this area and neighbouring areas are related to alteration in different functional performances and personal behaviour. Nonetheless, we can conjecture that BA11 participates in some individual's style of reacting. In the available fMRI reports, which could drive the experiments for the behaviour evaluation in the APS patients, there is some paucity in the analysis of the emotional components of behaviour because it is challenging to study the correlation with the clinical and measurable variables. So, extended testing should be performed.

For the 2nd patient presented in this study, we find a small area of brain lower perfusion over the statistical limit of the p-value<0,05 (corrected).This area is close to other ones interesting for the personal behaviour evaluation, the BA 23, the posterior cingulate gyrus, connected, from the functional point of view to areas as 24, 32 and 33 located in the anterior cingulate gyrus. Nevertheless, for this patient, we have not an alteration of perfusion in these areas, we have a small and located cluster in the BA23 area of the posterior cingulate gyrus.From the information that comes mainly from functional studies, the posterior cingulate gyrus is active when the learning and the execution of a complex motor task are operated by the patient. The posterior cingulate gyrus is also activated during the operation of language tasks, but its role in emotion is evident as well as its participation in different types of memory (e.g., topographic memory, episodic memory, et cetera). For these reasons the brain areas involved in emotion, most of all the limbic system, including the cingulate gyrus, are the same areas involved in the execution of memory tasks; this means there is a close correlation between emotion, motivation and memory functions. Lower perfusion in these areas is in accord with difficult in memories of routine events, without the emotional involvement of the patient (**Figure 2**).

The cingulate gyrus is part of the limbic system, and its involvement in emotional processes is well described in the literature. Damage to anterior cingulate gyrus can be associated with muteness and akinesia. Recent studies of magnetic resonance imaging reveal its involvement in emotional experiments such as the processing of emotional signals, such as sexual excitation following visual stimuli and also in the organization and planning of movements, conscious inhibition of involuntary motor and linguistic activities. Also, from functional neuroimaging studies, some particular functions of the BA24 BA32 and BA33 areas are highlighted, such as the response to vestibular and ocular motor stimulation, executive functions such as deductive reasoning and inductive reasoning, and the activation of different types of memory, such as episodic memory, et cetera). Those areas have partially lower perfusion in the patient number 3 with partial projection in the inferior frontal gyrus the area named BA47 (**Figure 3**).

The amount of language-related functions associable with BA47, such as semantic processing, phonological processing, semantic encoding, and others, is surprising. In these cases, BA47 is simply one of the multiple steps in the brain language processing network. It could be further speculated that in these verbal related functions, the inferior frontal gyrus may play a more emotional/motivational function. Moreover, anatomically BA47 is adjacent to BA45, a clear language brain area. BA47 participates in some emotional related activities (e.g., adverse emotional inhibition) and also in executive functions (e.g., deductive reasoning)., as in the working memory and episodic long-term memory. Other functions involved are: behavioural and motor inhibition, adverse emotional inhibition, non-spatial auditory processing, processing of fine-structured stimuli (i.e. music), temporal coherence (language and music), lexico-semantic access to melodic representations, smelling familiar odors, attribution of intention to others, decision making (involving conflict and reward) and

Deductive Reasoning.

Finally, Patient4 presented a signal alteration in extend areas of the brain. Before admission, the neuropsychiatric complaints rapidly worsened, resulting in frequent confusion states with impairment of verbal fluency. Nevertheless, it is essential to underline the reduced perfusion in the area of the motor cortex, primary and secondary, is extended. At that time, patient also developed involuntary movements of the limbs, more severe in the left side of the body. Her past medical history was not registered; particularly, there were no reports of previous thrombotic events. There was neither family history of neurological and psychiatric diseases nor personal history of infections or drugs intake before symptoms occurred. Studying with SPM the altered perfusion brain areas we found several clusters of lower perfusions in strategic areas of the brain related to the BA 4 of the primary motor cortex (Figure 4). This is a typical and common picture of altered motor circuit in case of comorbid Parkinsonism and AP syndrome [25].

The primary motor cortex, Brodmann area 4, is a brain region located in the dorsal part of the frontal lobe. As reported by functional neuroimaging techniques, BA4 participates in three different groups of superior functions: motor, somatosensory, and other functionality such as "verbal encoding during a non-semantic process", "attention to action", and "motor memory for visual landmarks". As a region of the motor system, it works in association with many other motor areas such as premotor cortex, the supplementary motor area, posterior parietal cortex, and several subcortical brain regions, to plan and execute movements. Motor function is an essential and primary function, and it has been reported that the primary motor cortex reacts to sensory stimulation. Nonetheless, in these cases the primary motor lower perfusion is found in addition to a more extensive pattern of hypoperfusion, obviously including sensory areas; that is, the BA4 may sometimes be included in a brain circuitry supporting sensory perception; BA4 activation may be activated in those cases that imply mental representation of a potential movement (motor strategy). This implicit representation of movements can also account for "attention to action" and "motor memory". The clusters of voxels with hypoperfusion are extended in this patient, and it generates a complex interaction of the brain areas to re-organize functions. Some of these clusters have coordinates in the Insula Cortex. The insula receives information from the ventral medial nucleus of the thalamus, the ventral posterior inferior nucleus of the thalamus, and the central nucleus of the amygdala. Reciprocal connections exist between the primary somatosensory cortex and the insula. The wide diversity of functions connected to these brain areas emphasizes its tremendous heterogeneity. Further research is required to pinpoint the participation of different insula areas into diverse brain networks. fMRI studies have significantly contributed and continue contributing to our understanding of the insula functions (Table 1).

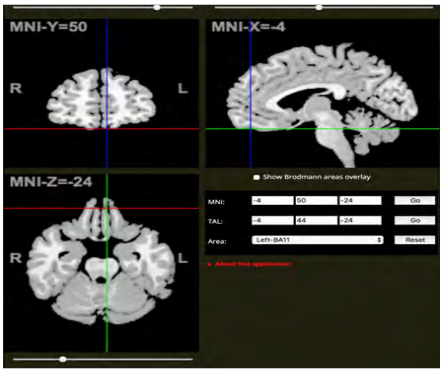


**Figure 1**: Patient 1 altered brain perfusion area.

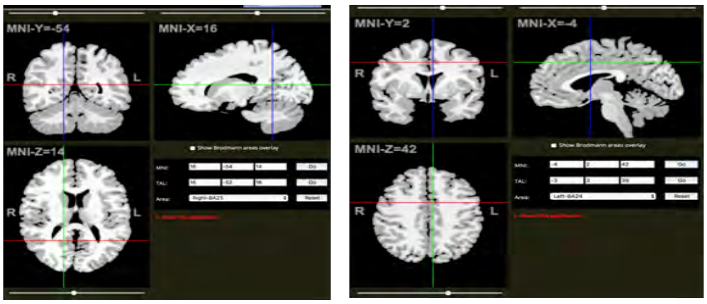


**Figure 2:** Patient 2altered brain perfusion area.

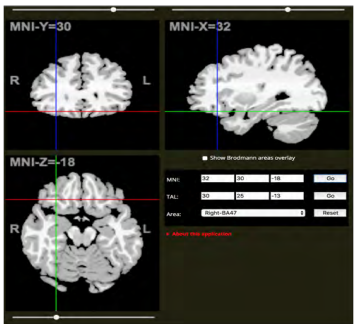


**Figure 3:** Patient 3 altered brain perfusion area.

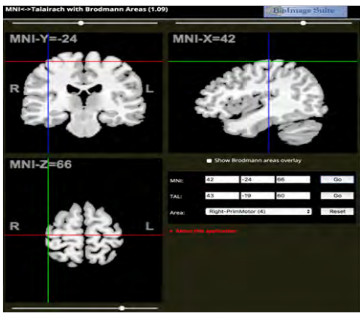


**Figure 4:** Patient 4 altered brain perfusion area.

**Table 1:** Principal reference for altered brain areas in patients.

| ID patient | Maincluster | X | Y | Z | Brodmann area |
|---|---|---|---|---|---|
| 1 | cluster 1 | -4 | 50 | -30 | BA11 |
| 2 | cluster 6 | -4 | 2 | 42 | BA24 |
| 3 | cluster 6 | 32 | 30 | -18 | BA47 |
| 4 | sparse | - | - | - | BA4 |

## 5. Conclusion

Our study, still in progress for the acquisition of all patient's data, confirms that Tc-99m ECD SPECT can detect, with fast and specific profiles of disease, the alteration of perfusion in brain areas and the effects of the increased heterogeneity of brain circulation in antiphospholipid antibody carriers; APS characterization is related to important factors for the quality of life of patients. We find confirmations of the connection between the great variety of brain perfusion alteration and central nervous system involvement in antiphospholipid antibody syndrome. There is the need to characterize APS patient also with an innovative multi-techniques approach to investigate at best the inner mechanism of pathology evolvement. Patients with APS should perform tests about cognitive impairments and motor deficits in order to classify the neurological and neuropsychiatric damages induced by altered circulation in the brain.In summary, our findings suggest that Tc-99m ECD SPECT can be useful to describe the increased heterogeneity of brain perfusion and related brain function alteration in antiphospholipid antibody carriers with neuropsychiatric manifestations; but, there is the need to acquire a blood fingerprint to correlate with the Tc-99m ECD SPECT findings and with all other clinical parameters. Due to the different profiles of diseases, it is crucial to evaluate all the aspects related to motor and cognitive deficits to connect with the functions associated with the areas of lower perfusion. Phenotypes of APS carriers can be characterized by the usual criteria of classification associated with the new approach to the systems biology in humans and the powerful Imaging techniques of Tc-99m ECD SPECT.

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