ANTIPHOSPHOLIPID ANTIBODIES IN NEUROLOGY IN 2008: DIFFICULTIES FOR GUIDELINES

Radu TANASESCU[1,2,3,4]

[1]*"Carol Davila" Medicine and Pharmacy University, Bucharest, Romania*
[2]*Neurology Department, Colentina Clinical Hospital, Bucharest, Romania*
[3]*Unit of Clinical Epidemiology – "Carol Davila" U.M.Ph.*
[4]*Réseau d'Epidémiologie Clinique International Francophone (RECIF)*

ABSTRACT

Antiphospholipid antibodies (APL) and neurological diseases are a subject of great interest in the last 20 years, but also a field of controversy. Several consensus meetings have raised expert points of view, and some studies provided evidence-based data, however, a guideline for the management of neurological manifestations associated to APL is difficult to be generated. Some of the controversy points and difficulty in ordering rules for practice are debated.

Key words: antiphospholipid antibodies, antiphospholipid syndrome, stroke, neurological non-ischemic manifestations, guideline

Antiphospholipid antibodies (APL) and neurological diseases are a subject of great interest in the last 20 years, but also a field of controversy. In the general practice of neurology, the need for clear management principles in front of neurological manifestations associated to APL rise the need for a consensus in diagnosis and treatment decisions. However, the evidence-based approach is difficult in a field with few studies that can touch, at desired level, the controversy points. Since the study of APL was an issue perpetuated by several groups derived from Hughes' initial team, and since the complexity of the subject often resulted in contradictory results, the general neurologist had two kinds of reactions: to overestimate the presence and use of APL testing in a variety of neurological diseases, or to avoid to deal with decision-making in the situation of the lack of evidence. However, the need for guidelines generated several expert consensus, and debate is taking place concerning how many (or how few) "good practice points" must have a guideline in order to weight more medical evidence instead subjective, even highly competent, opinions. Some of the controversy points are listed below and debate is raised to neurological community in order to discuss if existing consensus provide some efficient tools for practice and of the moment of new guidelines.

BACKGROUND

APS diagnosis and neurological associated manifestations

APL are an heterogeneous group of circulating immunoglobulins arising in a wide range of infectious and autoimmune diseases. APL can impair phospholipid-dependent clotting assays, activate endothelial cells, platelets and biochemical cascades (1). Low titer and often non-pathogenic APL are found in 5–10% of healthy individuals and may be transiently elevated after viral infections and drug exposures (2). Persistent high titer aPL antibodies are detected in less than 2% of healthy adults.

Author for correspondence:
Radu Tanasescu, MD, PhD, AFS, "Carol Davila" Medicine and Pharmacy University, Neurology Department, Colentina Clinical Hospital, 19-21 Stefan cel Mare Blvd, District 2, Bucharest, Romania
email: neuradutanasescu@yahoo.com

The antiphospholipid syndrome (APS), or Hughes syndrome, is an acquired autoimmune disorder defined by the persistence of procoagulant autoantibodies and clinical evidence of vascular thrombosis or pregnancy morbidity (3). Several APL have been described, but positive APS diagnosis implies at least two moderate to highly positive anticardiolipin (ACL), anti-beta-2-glycoprotein 1 (antiβ2GPI) or lupus anticoagulant (LA) tests (separated by 12 weeks) in the presence of arterial, venous or small vessel thromboses that are confirmed by imaging or histopathology and are not explained by vasculitis, or pregnancy losses (4). LA and high ACL titers (IgG or IgM isotype) are best associated with thrombo-occlusive events (5). APS can occur in association with other autoimmune disease (secondary APS), most frequently systemic lupus erythematosus (SLE), or as an isolated disorder (primary APS), and may affect any size of vessel and any organ of the body in patients of both sexes and all ages. APS account for 20% of recurrent thromboses in young adults (2,6).

From APS description in 1983, a broad spectrum of clinical features was described, including peripheral venous and arterial thrombosis, obstetric, skin, cardiac, pulmonary, renal, hematological and neurological involvement. Patients may also present with catastrophic APS (CAPS) characterized by a multi-organ thrombotic microangiopathy with high mortality (6).

Several neurological manifestations have been described associated with APL (Table 1).

Cerebrovascular ischemia is the most common arterial manifestation of APS. Numerous mechanisms have been proposed to explain the thrombotic tendency of patients with APL, but the pathogenesis seems to be multifactorial.

There are a substantial number of gaps in our knowledge about stroke and APL. Many of these were reviewed in a consensus meeting in Taormina in 2002 (7).

Stroke or TIA can occur in any cerebral arterial territory, most often in middle cerebral artery, and can be the initial presentation in 20% of adults with APS (8).

It is accepted that APL are a risk factor for incident stroke, but the evidence to support the role of aPL in recurrent stroke is conflicting and, therefore, inconclusive (9,10). The same situation is for older populations, who often associate many vascular risk factors, other than APL, and there is unclear if the demonstrated risk for recurrent thromboses between APS in LES patients can be found in subjects with isolated APS features (11,12).

The relative predictive value of each specific type of APL needs further study, as does the question of whether the long-term risk, if it exists, is dose-related or a threshold effect. Also, studies are needed to define a risk profile, having impact to secondary prevention (13).

Some of the conflicting data on associations between stroke and APL may be due to study methodologies, with different protocols (only baseline APL testing, lack of LA dosing, different patient populations with lack of APS classification criteria) (14).

The role played APL in pediatric strokes and coagulopathies is unclear, but is believed that isolated pediatric APS is a rare entity due to less prominent childhood prothrombotic risks (15).

There are no studies that address the issue of disappearing APL in patients with a single ischemic event, and thus no strong and clear therapeutic recommendations concerning the type and duration of treatment can be strongly made. Probably there is a need to stratify these patients as a subgroup for separate analysis, but again further study is needed.

Of great importance is the role of coagulopathy and cerebral ischemia in the occurrence of additional APS neurological features, as seizures, cognitive impairment and dementia. Chronic small vessel ischemic events predispose patients to early-onset multi-infarct dementia, and recurrent seizures are more prevalent in SLE patients with high titer ACL ischemic changes (8). Nevertheless, cognitive dysfunction and demyelination associated with APL can involve also non-vascular mechanisms (16). In SLE patients, prospective studies shown APL positive titers associated with cognitive impairment, and a small cross-sectional study revealed similar impairments in primary APS patients (14). Other clinical features involving APL associated mechanisms are movement disorders as chorea, hemibalismus and parkinsonism (17).

Demyelination is frequently encountered in inflammatory systemic diseases, and indeed, the clinical presentation and lesions evidenced by MRI may be similar. Moreover, MS patients can have APL. These associations have been reviewed (18). There is not clear evidence supporting a definite attitude concerning anticoagulation in a MS-like patient with high APL titers, but the most part of these patients who present other additional features like livedo reticularis, thrombocytopenia, Raynaud's phenomenon, photosensitivity, rash,

arthritis/arthralgia, Sicca syndrome, necessit careful differential diagnosis and follow-up, in order to circumscribe a systemic disorder mimicking MS (19,20). There is no high class evidence for the management of the MS patient with APL. Present data strongly suggest that MS patients who fulfill MS 2005 criteria should be treated as MS, since there is no other features suggesting an associated or underlain autoimmune or system disorder, which can be unmasqued by appropriate biological and clinical follow-up.

Transverse Myelitis is a rare (0.4%) manifestation encountered with APS. However, the association of TM and APS is not well established and the exact mechanisms are not clearly known. Data on the management of these patients is based on small series or case reports, being not well established, and these patients must be followed-up for SLE sometimes several years (21).

Other non-ischemic manifestations in the presence of APL are controversial. The presence in Guillain-Barre patients of positive titers of APL can be explained by cross-reaction with myelin phospholipids, but recent data on other proteins involved in apparition of conduction block suggest that further study is needed (22,23).

Migraine is more prevalent in the SLE population. However, it has no clear relationship with APL in general population, even both can be coincident in SLE patients (24,25,26).

It must be emphasized that only ischemia is accepted with certainty as criterion for APS. The neurological manifestations unrelated to stroke listed in Table 1 are, as are the nephropathy, valvular heart disease, thrombocytopenia and livedo reticularis, not included in the specific classification criteria, but are important in clinical practice. However, it is important to precise that is difficult to make recommendations for the management of patients with non-ischemic neurological manifestations and APL, since there is scant data on the subject and it exists important case-to-case variability of clinical contexts and pathogenical mechanisms. The difficulty of decision-making is even higher in patients with transient APL, or with persistent low titers of APL, or with a specific type of APL positive in only one laboratory method of testing and negative by another, since is desired "that laboratories perform multiple tests with differing assay principles" (4).

Further study is needed for all these issues, new data having to integrate new emerging concepts of probable APS and microvascular and microangiopathic APS antiphospholipid-associated syndrome (27).

Table 1. *APL-associated neurological manifestations (modified after* ***Muscal E, Brey RL.*** *– Neurological manifestations of the antiphospholipid syndrome: risk assessments and evidence-based medicine.* Int J Clin Pract. *2007; 61(9):1561-1568)*

APL – associated neurological manifestations for which ischemic mechanism is certain
Stroke
Transient ischemic attack (TIA), including
Amaurosis fugax
Ocular ischemia
Cerebral venous sinus thrombosis
Acute ischemic encephalopathy
APL – associated neurological manifestations with different potential mechanisms: ischemic, immune, neurotransmitter-related, etc.
Seizures
Cognitive impairment and dementia
Optic atrophy
Transverse myelopathy
Chorea
Hemidystonia, parkinsonism, hemiballismus
Migraine
Psychiatric disturbances
Sensory-neural hearing loss
"Multiple sclerosis-like disease"
Guillian-Barré syndrome

MANAGEMENT OF APS NEUROLOGICAL ASSOCIATED MANIFESTATIONS

As APL are risk factor for incident stroke, primary prevention is important in those who have persistently elevated APL levels, also by reducing the total vascular risk by controlling other vascular risk factors (28).

For primary prevention, the optimal treatment remains unclear in the absence of well-designed randomized clinical trials. Antigenecity carries a low absolute risk of thrombosis of less than 1% per year (6). Even the expert consensus found that aspirin has to be recommended in primary profilaxys in APL carriers (29), recently, the Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study showed no benefit for prophylactic antithrombotic therapy with low-dose aspirin in asymptomatic individuals who had circulating APLs in the absence of prior thrombotic events (30). It was previously recommended that aspirin therapy should be prescribed in patients with additional stroke risk factors such as lupus, hypertension, diabetes and hyperlipidemia (31).

For secondary prevention, the optimal duration and intensity of anticoagulation are disputable.

Actual recommendations for the treatment of venous and non-cerebral arterial thrombosis is Warfarin (INR 2-3); for cerebral arterial thrombosis, Warfarin (INR 1.4-2.8) or aspirin (4). The treatment duration is indefinite. If there are recurrent thrombotic episodes while on therapy, Heparin (LMW or unfractionated), Warfarin with higher INR or Warfarin plus antiplatelet therapy may be used (4). These recommendations does not clarify some points of controversy, raised by the recent prospective and randomized trials on cerebral thrombosis treatment who served for the recommendations (32-34).

Single antibody measurement may not offer clear answer for APS patients with persistent and severe disease (14). The trials had not clarified if the morbidity and mortality can be decreased by high-intensity warfarin (INR 3-4) in patients being at high risk by having history of lupus, recurrent thromboses or initial arterial event (14). Also, there is no evidence of optimal treatment of patients with recurrent thromboses while anticoagulated, and the recommendations have not been validated by clinical trials. Also, there are no expert opinions or trials that have examined anticoagulants in children with APS (14). Alternative treatments (ACE inhibitors, adenosine uptake inhibitors, statins, hydroxychloroquine, thrombin inhibitors) seem theoretically justified, but their places have not been clearly settled by study results.

DISCUSSION

According to the EFNS recommendations, the aim of a neurological management guideline "is to provide evidence-based guidance for clinical neurologists, other health care professionals and health care providers about important aspects of management of neurological disease" (35). It must offer "a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence", in order to implement "measures of prevention and treatment that are scientifically proven" (35).

The same recommendations states that, for "important clinical areas for which no high class evidence is available or likely to become available in the near future", "it may be possible to recommend best practice based on the experience of the guideline development group". Nevertheless, EFNS instructions emphasize that such cases "should be marked as exceptional", and they imply "large clinical uncertainty" (35).

It must be emphasized that on most of the problems and controversies regarding APL and neurological manifestations, actual data can not offer much support for grade I – III evidence recommendations, but only Class IV (Evidence from uncontrolled studies, case series, case reports, or expert opinion).

From a practical point of view, there are several settings in which the attitude regarding APL and neurological manifestations can be discussed: a) the confirmed APS with cerebral thrombotic manifestations; b) patients not fulfilling APS criteria but having cerebral ischemia; c) patients with non-ischemic neurological manifestations and APL.

Firstly, for confirmed APL (arterial or venous stroke due to persistent APL medium/high titers), the practical attitude is a antithrombotic treatment, as already recommended (9). This attitude is already accepted in clinical practice; therefore a guideline will only reconfirm it, bringing nothing new. Controversy reigns as for the duration of treatment in these patients, since controversy is on the risk of recurrence. Here, the lack of studies will bring the task force to elaborate "good practice points", as for other controversial issues regarding APL, but this kind of recommendations already exists (4).

In what concerns the associations of APL with MS or TM, who need sometimes laborious and long time follow-up in order to finalize the diagnostic demarche, the attitude of correct differentials in controversial cases is already done in practice, and it is questionable if a Guideline for APL is needed in order to emphasize the need for a correct differential diagnosis of MS and other CNS inflammatory diseases.

The discussion on the opportunity of a guideline of APL management in neurology at the present moment must ask to the question: is actual literature data already providing evidence-based approach to the management of APL in neurological settings, and if yes, can the guideline provide more accurate recommendations on the subject? In other words, can a guideline give answers to the problems raised by the subject, others than the already known and applied rules, or the guideline will only reproduce, instead of analyzing, the current conclusions and uncertainties?

It must be emphasized that APL related neurological manifestations and their management were already reviewed, evidence was analyzed and information is accessible (36, 7, 4, 6, 14, 28, 37).

It is clear that a guideline on APL and neurological manifestations can offer correct

information on the state of knowledge and "good practice points" for the general neurologist, when higher class evidence lacks. But, in this setting, at the moment a guideline is 'in danger' to be only another *review* on the subject, and can not replace the need for further studies for controversy points.

The questions are neither whether the subject deserves special attention, nor if exists the necessity to have an expert point of view on the multiple controversies regarding APL-related neurology: the answer is positive to both questions.

The problem raised is if a Guideline realized at this stage of the scientific knowledge can offer pertinent answers at those controversies, and can therefore be more than a review of the literature emphasizing and popularizing the state of knowledge in the field. If it is the case, it will be maybe appropriate to still wait new data to emerge, therefore to be able to elaborate a material that offers scientifically and therapeutically practical positions in order to develop scientifically sound, clinically relevant guidelines to aid specialists and non-specialists in the management of APL related neurological disease.

It is no doubt that it is necessary a common point of view with pragmatic implications aiming to harmonize the practical attitude of the general neurologist for the APL patients. The question remains *when* a guideline is more appropriate to be realized, in order to fulfill its purposes, since data that is already available will be only repeated, and data that is still missing will wait further study.

Of course, as physicians, we have to be trained to be able to make decisions in the face of uncertainty, but on the other hand, we are increasingly challenged to make our decisions based on evidence. In elaborating a guideline, one can take into account both the evidence and the lack of evidence to support decisions that we make all the time. Since the clear evidence is, or should be, already known, and the lack of evidence needs further study, I believe that all initiative that should encourage and facilitate the design and performance of large, appropriately stratified studies in order to produce answers to the questions posed here, is justified. Meanwhile, maybe a guideline on APL may wait more evidence in order to avoid making the majority of recommendations as "good practice points", as is the risk today with an important part of the current data on APL. Therefore, debate is opened to Neurological community and especially EFNS Neuroimmunology Panel where this issues was raised by us, in order to decide if existing consensus provide some efficient tools for practice and on the moment of a new guidelines.

REFERENCES

1. **Gharavi AE, Harris EN, Asherson RA, et al.** – Anticardiolipin antibodies: isotype distribution and phospholipid specificity. *Ann Rheum Dis* 1987; 46(1):1-6
2. **Hanly JG** – Antiphospholipid syndrome: an overview. *CMAJ* 2003; 168:1675-1682
3. **Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al.** – International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999; 42:1309-1311
4. **Miyakis S, Lockshin MD, Atsumi T et al.** – International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome. *J Thromb Haemost* 2006; 4:295-306
5. **Galli M, Luciani D, Bertolini G et al.** – Lupus anticoagulants are stronger risk factors for thrombosis than antocardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood* 2005; 101:1827-1832
6. **Lim W, Crowther MA, Eikelboom JW.** – Management of the antiphospholipid antibody syndrome: a systemic review. *JAMA* 2006; 295:1050-1057
7. **Brey RL, Chapman J, Levine SR, Ruiz-Irastorza G, Derksen RHWM, Khamashta M, et al.** – Stroke and the antiphospholipid syndrome: consensus meeting Taormina 2002. *Lupus* 2003; 12:508-513
8. **Sanna G, Bertolaccini ML, Cuadrado MJ et al.** – Central nervous system involvement in the antiphospholipid (Hughes) syndrome. *Rheumatology* 2003; 42:200-213
9. **Brey RL.** – Management of the neurological manifestations of APS – what do the trials tell us? *Thromb Res* 2004; 114:489-499
10. **Tanasescu R, Ticmeanu M, Nicolau A et al.** – Anticardiolipin antibodies, recurrent stroke and vascular events: a prospective study on 210 patients. *Rom J Intern Med.* 2005; 43(1-2):79-88
11. **Janhardan V, Wolf PA, Kase CS et al.** – Anticardiolipin antibodies and risk of ischemic stroke and transient ischemic attacks: the Framingham cohort and offspring study. *Stroke* 2004; 35:736-741
12. **Cervera R, Khamashta MA, Font J et al.** – Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine* 2003; 82:299-308
13. **Gatenby PA** – Controversies in the antiphospholipid syndrome and stroke. *Thromb Res.* 2004; 114(5-6):483-488
14. **Muscal E, Brey RL** – Neurological manifestations of the antiphospholipid syndrome: risk assessments and evidence-based medicine. *Int J Clin Pract.* 2007; 61(9):1561-1568
15. **Berkun Y, Padeh S, Barash J et al.** – Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum* 2006; 55:850-855
16. **Chapman J, Cohen-Armon M, Shoenfeld Y et al.** – Antiphospholipid antibodies permeabilize and depolarize brain synaptoneurosomes. *Lupus* 1999; 8:127-133
17. **Katzav A, Chapman J, Shoenfeld Y** – CNS dysfunction in the antiphospholipid syndrome. *Lupus* 2003; 12:903-907.
18. **Theodoridou A, Settas L** – Demyelination in rheumatic diseases. *J. Neurol. Neurosurg. Psychiatry* 2006; 77:290-295
19. **Ruiz-Irastoza G, Khamashta MA** – Warfarin for multiple sclerosis? *Q J Med* 2000; 93:497-499
20. **Cuadrado MJ, Khamashta MA, Ballesteros A et al.** – Can neurologic manifestations of Hughes' (antiphospholipid) syndrome be

distinguished from multiple sclerosis. Analysis of 27 patients and review of the literature. *Medicine* (Baltimore) 2000; 79:57-68
21. **Theodoridou A, Settas L** – Demyelination in rheumatic diseases. *J. Neurol. Neurosurg. Psychiatry* 2006; 77:290-295
22. **Jackson C, Brey RL, Barohn R et al.** – Anticardiolipin antibodies in Guillain-Barre syndrome. *Clin Exp Rheumatol* 1992; 10:657
23. **Shavit E, Beilin O, Korczyn A** – Thrombin receptor PAR-1 on myelin at the node of Ranvier: a new anatomy and physiology of conduction block. *Brain* 2000; 131:1113-1122
24. **Tanasescu R, Nicolau A, Caraiola S et al.** – Antiphospholipid antibodies and migraine: a retrospective study of 428 patients with inflammatory connective tissue diseases. *Rom J Intern Med* 2007; 45(4):355-363
25. **Sanna G, Bertolaccini ML, Khamashta MA** – Neuropsychiatric involvement in systemic lupus erythematosus: current therapeutic approach. *Curr Pharm Des* 2008; 14(13):1261-1269
26. **Williams FM, Cherkas LF, Bertolaccini ML et al.** – Migraine and antiphospholipid antibodies: no association found in migraine-discordant monozygotic twins. *Cephalalgia* 2008; 28(10):1048-1052
27. **Asherson RA, Cervera R** – Microvascular and microangiopathic antiphospholipid-associated syndromes ("MAPS"): semantic or antisemantic? *Autoimmun Rev* 2008; 7(3):164-167
28. **Dafer RM, Biller J** – Antiphospholipid syndrome: role of antiphospholipid antibodies in neurology. *Hematol Oncol Clin North Am* 2008; 22(1):95-105
29. **Alarcon-Segovia D, Boffa MC, Branch W et al.** – Prophylaxis of the antiphospholipid syndrome: a consensus report. *Lupus* 2003; 12:499-503
30. **Erkan D, Harrison MJ, Levy R et al.** – Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum* 2007; 56(7):2382-2391
31. **Brey RL** – Management of the neurological manifestations of APS – what do the trials tell us? *Thromb Res* 2004; 114:489-499
32. **Crowther MA, Ginsberg JS, Julian J et al.** – A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med* 2003; 349:1133-1138
33. **Finazzi G, Marchioli R, Brancaccio V et al.** – A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost* 2005; 3:848-853
34. **The APASS Writing Committee.** – Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA* 2004; 291:576-584
35. **Brainin M, Barnes M, Baron J-C et al.** – Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol* 2004; 11:577-581
36. **Chapman J, Rand JH, Brey RL et al.** – Non-stroke neurological syndromes associated with antiphospholipid antibodies: evaluation of clinical and experimental studies. *Lupus* 2003; 7(12):514-517
37. **Hughes** – Syndrome: Antiphospholipid Syndrome. Khamashta M.A. (Editor). Springer; 2nd ed. 2005. ISBN 978-1-85233-873-2. *Neurologic manifestations:* pg. 53-86