

Neurological manifestations in the anti-phospholipid syndrome

[Anti-fosfolipid sendromda gözlenen nörolojik bulgular]

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ABSTRACT

Neurological manifestations are prominent and common in patients with autoimmune condition anti-phospholipid (Hughes) syndrome (APS) which can affect people of any age and involves production of antibodies against phospholipid, a component of cell membranes. Diagnosis of APS requires presence of anti-phospholipid antibodies and a history of specific health problems related to the disorder. Anti-phospholipid antibodies (aPL) are common among children or young adults with ischemic stroke, but other manifestations have also been associated with aPL. An important question that remains unanswered is why the brain and central nervous system (CNS) seem to be particularly vulnerable in patients with APS. This review summarizes recent data regarding the neurological manifestations associated with anti-phospholipid antibodies.

Key words: immunologic factors, thrombosis, anti-phospholipid antibodies

ÖZET

Hücre zarı bileşeni fosfolipide karşı antikor oluşan anti-fosfolipid (Hughes) sendromu, her yaşta kişileri etkileyebilen ve nörolojik bulguların belirgin ve sık olduğu oto-immün bir hastalıktır. Anti-fosfolipid sendrom tanısı için anti-fosfolipid antikorlarının varlığı ve hastalığa ait sağlık problemleri hikayesi olması gerekmektedir. Anti-fosfolipid antikorları iskemik inme geçiren çocuklar veya gençlerde sıklıkla gözlenir ancak bu durum ile ilgili başka bulgularda ilişkilendirilmiştir. Cevaplanması gereken önemli bir soru da Anti-fosfolipid sendromlu kişilerin beyin ve merkezi sinir sisteminin risk altında olduğudur. Bu derleme Anti-fosfolipid antikorları ile ilişkilendirilen nörolojik bulguları özetlemektedir.

Anahtar Kelimeler: immünolojik etkenler, tromboz, anti-fosfolipid antikorlar

Anti-phospholipid (Hughes) syndrome (APS) is considered to be one of the most frequent acquired thrombophilias [1]. In APS, thrombocytopenia occurs because platelets are used up by the clotting process or because antibodies destroy them. Anti-phospholipids antibodies (aPL) may interfere with endothelial cell function and promote the pro-coagulant activity of endothelial cells [2]. APS is an autoimmune disorder [3] defined by a clinical vascular event or pregnancy morbidity and the presence of aPL [4,5]. aPL is directed against serum proteins bound to anionic phospholipids and may be detected by lupus anticoagulant tests, anti-cardiolipin antibody ELISA, or anti- β_2 -glycoprotein 1 ELISA. In APS, the body mistakenly makes antibodies that attack phospholipids—a type of fat [6,7].

aPL activate the inner lining of blood vessels leading to the formation of blood clots in arteries or veins. In particular, the disease is characterized by antibodies against cardiolipin (anti-cardiolipin antibodies) and β_2 -glycoprotein 1 [8].

The symptoms of APS are due to the abnormal blood clotting that occurs in veins in approximately two thirds of the cases. APS is diagnosed by the presence of a positive aPL and either a history of blood clots in an artery or vein or a history of multiple miscarriages or other pregnancy problems [9,10].

Central nervous system (CNS) involvement is prominent in APS. It includes arterial and venous thrombotic events, psychiatric features and a variety of non-thrombotic neurological syndromes [11].

APS can occur as a primary disorder or secondary to a connective tissue disease, most frequently systemic lupus erythematosus (SLE). aPL is associated with a variety of neurologic manifestations [12].

There is an association between aPL and transverse myelitis (TM). The prevalence of aPL had been shown to be higher in SLE patients with transverse myelitis compared with SLE patients in general. Several cases of TM associated with aPL have been published, most of them in patients with SLE. A growing body of evidence supports an association between aPL and ischemic stroke not only in SLE and/or APS but in unselected populations as well [13].

One of the most serious complications of APS occurs when a clot forms in the brain and causes a stroke. Episodes of cerebral ischemia, mainly focal, can be transient or permanent. Recurrent disease often leads to multifocal deficits. Amaurosis fugax, transient paraesthesias, motor weakness, vertigo and transient global ischemia can all be expressions of transient ischemic attacks (TIAs). TIAs are often recurrent and may precede cerebral infarction by weeks or months. The risk for recurrent stroke appears to be increased in APS patients and multiple events can occur after the first cerebral ischemic episode. Some people have APS antibodies, but do not ever have signs or symptoms of the disorder. [14-16].

Studies on the prevalence of aPL in ischemic stroke have been mainly focused on anti-cardiolipin antibody (aCL) rather than lupus anticoagulant (LA) or both aCL and LA. Several studies suggest that the presence of high titers of aCL immunoreactivity correlate with an increased risk of thrombosis. IgG and IgM are the aCL isotypes mainly implicated in thrombosis. The titer and isotype of aCL were important in determining the presence of clinical complications. Moderate-to-high titers of IgG aCL were the most strongly implicated in relation to the appearance of seizures, while the IgM isotype appeared to be less specific. IgM isotype aCL was found to be associated with future stroke but did not constitute an independent risk factor after adjusting for conventional vascular risk factors. It is well known that aCL and LA can fluctuate over time [17,18].

Some of the studies tested aPL within 48 h after the ischemic event. It has been reported that aCL titers can decrease during the acute phase of the thrombotic event. The presence of aPL should be confirmed at least from 1 to 3 months after the thrombotic event. A well designed study, demonstrated an association between β_2 -GPI-dependent, aCL and incidence of ischemic stroke and myocardial infarction. Patients with IgG β_2 -GPI-dependent and aCL had a 2-fold increase in the odds of stroke within 15 years of follow-up when compared with aCL-negative individuals. Anti-phospholipid antibodies syndrome has emerged as an important entity responsible for stroke in young. However, aPL are identified in 2% to 7% of healthy young people and in higher rates among the elderly, complicating interpretation of associations with different neurological manifestations [19-21].

In addition to the lupus anticoagulant (LA) and aCL, antibodies against anti-phosphatidylserine, anti-phosphatidylinositol, and anti- β_2 -GPI were also associated with increased risk of ischemic stroke. Anti-phosphatidylserine antibodies were associated with increased risk for ischemic stroke. [22-25].

It was confirmed the association between aCL and epilepsy. Epilepsy may be a primary neuropsychiatric event associated with high titers of aCL in SLE patients. Epilepsy (and stroke) was more common in patients with SLE and aPL, suggesting that these antibodies increase thrombotic and non-thrombotic brain injuries. aCL can play a role in pathophysiology of epilepsy. The prevalence of aPL was shown to be greater in patients with epilepsy, including newly diagnosed seizure disorder. Newly diagnosed patients had a significantly greater prevalence of IgG aCL than the controls [26].

A strong relationship between aPL and chorea had been reported in retrospective studies. Chorea is a well-known phenomenon in SLE, shown to be strongly related to the presence of aPL antibodies [27].

Anti-phospholipid antibodies were found in sera of patients with the Guillain-Barré syndrome. Guillain-Barré syndrome patients produce auto-antibodies to vario-

us phospholipid and nuclear antigens. Clinical syndromes mimicking multiple sclerosis (MS), mainly in its relapsing-remitting pattern, are reported to occur in association with aPL [28].

Transient global amnesia has been associated with aPL. An association between dementia and aPL is probably explained mostly by multiple brain infarcts. A chronic multifocal disease, defined as a recurrent or progressive neurological deterioration attributable to cerebrovascular disease, can produce multi-infarct dementia. One of the most prominent features in patients with APS is headache. This symptom, a common complaint of APS patients in clinical practice, can vary from classic intermittent migraine to almost continuous incapacitating headache. Cognitive dysfunction varies from global dysfunction in the context of multi-infarct dementia to subtle cognitive deficits in otherwise asymptomatic patients with aPL. One of the most common complaints in these patients is of poor memory, difficulty in concentrating or difficulty in keeping their attention for a long time, indicating a probable preclinical phase of neurological involvement. Although depression and psychosis have been associated with aPL, it had been postulated that auto-antibodies, and specifically aPL, may represent an adverse response to neuroleptic treatment. Transient global amnesia, a syndrome of sudden unexplained short-term memory loss in association with aPL was reported [29].

Idiopathic intracranial hypertension is frequently associated with aCL and can be the presenting symptom of APS. Ocular vaso-occlusive disease is frequently found in patients with APS. Amaurosis fugax is one of the most common manifestations. Optic neuropathy is a well-known ocular manifestations occurring in patients with SLE, and it remains one of the major causes of blindness in these patients. Bilateral optic neuropathy in SLE occurs more frequently than monolateral optic neuropathy, and the associated main neurological manifestation seen in these patients is transverse myelitis, particularly in SLE patients with bilateral optic nerve disease (Devic's syndrome). On the other hand, optic neuropathy is less frequently described in APS patients without SLE and tends to be unilateral in these cases. Although basal ganglia involvement is often confirmed on magnetic resonance imaging, extrapyramidal disorders such as Parkinsonism and dystonia are unusual in APS [30,31].

Dystonia and Parkinsonism may be associated with APS as well as other movement disorders. A link between sensorineural hearing loss and autoimmune disease has been postulated by many authors who described the association of sensorineural hearing loss with aPL [32].

Conclusion

There is compelling evidence for a strong association between aPL and neurological manifestations in patients with the primary or secondary APS. Symptoms vary

and can include blood clots, miscarriage, rash, chronic headaches, dementia, and seizures.

We conclude that physicians should look for the presence of aPL antibodies in patients with ischemic neurologic disease (such as recurrent miscarriages, venous thrombosis, and livedo reticularis), in young patients after stroke, after recurrent stroke, and in thrombo-occlusive events of undetermined origin.

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