High frequency of IgM antiphospholipid antibodies in young Iranian patients with stroke

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ABSTRACT

Objective: To investigate the presence of IgG and IgM types of anticardiolipin (aCL) and antiphospholipid (aPL) antibodies in younger Iranian patients with ischemic stroke.

Methods: Both IgG and IgM types of aPL (cardiolipin, anti phosphatidyl inositol, anti phosphatidyl serine, anti phosphatidic acid and beta 2-glycoprotein I [B2-GPI]) and aCL alone (cardiolipin and B2-GPI) were measured in 117 patients with ischemic stroke (aged <45 years) during an 18-month period from September 2002 to March 2004 in Al-Zahra Hospital, Isfahan, Iran. The demographic, clinical, and laboratory characteristics of patients with a positive titer were recorded.

Results: Seven men and 16 women (23 patients, 19.6%) had increased IgG types of aPL antibodies. Increased titers of IgM and IgG were found in 19 (82.6%) and 6 (26%) patients for aPL antibodies and in 15 (83.3%) and 8 (44.4%) cases for aCL alone.

Conclusion: Despite European studies, high titers of IgM aPL antibodies found in a large number of patients can be caused by the presence of unknown triggering factors (infections or poisons), that are more prevalent in developing countries compared to developed countries. This hypothesis remains to be investigated further.

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During recent years, with advances in recognition of complex pathologic stages of stroke and developing new diagnostic laboratory methods, many risk factors such as antiphospholipid (aPL) antibodies have been identified in patients with stroke.[1] In fact, many studies have showed the relation of anticardiolipin (aCL) antibodies and lupus anticoagulants (LA) with stroke. The diagnosis of antiphospholipid antibody syndrome (APS) can be assumed when these antibodies are present for more than 8 weeks. Although the mentioned antibodies are not detectable in some patients with clinical manifestations of this syndrome, other types of non-cardiolipin antibodies (non aCL) such as anti phosphatidyl inositol antibody and anti phosphatidyl serine antibody can be found in them.[2-9] In recent years, it has been shown that anti B2-GPI (human B2-glycoprotein) could distinguish between autoimmune aCL and benign alloimmune aCL,[10,11] and could be a more specific factor compared to aCL in thrombosis mechanism.[12-14] Indeed, in some cases, it is the only antibody known to be responsible for APS.[15,16] With regard to the role of aPL antibodies as risk factors for ischemic strokes (especially recurrent strokes), detection of these antibodies, in younger patients with ischemic stroke is essential for prevention of subsequent strokes. Meanwhile, according to European studies,[17-21] many patients with APS and stroke had higher levels of IgG antibodies in contrast to Indian studies,[22] which have shown increased levels of IgM antibodies. Thus, for identifying the profile of these antibodies in developing countries, further studies are mandatory. Considering the lack of sufficient information on this field in Iran, we investigated the characteristics of patients with ischemic stroke aged less than 45 years (with undetermined cause), and the prevalence of aPL antibodies, as well as the type of these antibodies (IgG or IgM), in Al-Zahra Hospital of Isfahan, Iran.

Methods. In this descriptive study, 117 young patients (<45 years old) with ischemic stroke diagnosed by CT-scan were selected consecutively during an 18-month period from September 2002 to March 2004 at Al-Zahra Hospital, Isfahan, Iran. All patients were clinically examined and after recording the results, blood samples were obtained

to measure serum aCL and aPL. The LA was measured only in the last 28 patients (as the diagnostic kit became available). Serum titers of aCL and aPL were measured by the ELISA method, and we used ORG515 (Orgentec, Diagnostica, Germany, with cardiolipin- and B2GPI-coated microplate) and ORG522 (Orgentec, Diagnostica, Germany, with cardiolipin-, phosphatidyl serine-, phosphatidyl inositol-, phosphatidic acid- and B2GPI-coated microplate) diagnostic kits. Serum levels of IgG >10 IgG antiphospholipid (GPL) units, IgM >7 IgM antiphospholipid (MPL) units for aCL and IgG >10 GPL, IgM >10 MPL for aPL were considered positive. The LA titer was tested by dilute Russell viper venom technique (DRVVT). The results of other laboratory tests including anti-neutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), rheumatoid factor, complete blood count differential, partial thromboplastin time, c-reactive protein, venereal disease research laboratory and erythrocyte sedimentation rate (to determine autoimmune disease and also abnormal laboratory values accompanied with aPL antibodies), demographic characteristics, clinical findings of patients with positive antibody titers, previous thrombotic attack, past medical history and treatments were recorded. Data were analyzed using SPSS Version 10 software.

Results. Twenty-three out of 117 young patients with stroke (7 males, 16 females, 19.6%) were positive for both aPL and aCL antibodies (ORG522) and 18 patients (15.3%) had raised aCL antibody titer (ORG515). The LA was negative in 28 patients for whom antibody titers were measured. The mean age in the 23 patients was 32.5 ± 9.5 years. According to the findings, 15 (83.3%) and 8 (44.4%) patients with positive aCL antibody had IgM >7 MPL and IgG >10 GPL, as compared to 19 (82.6%) and 6 (26%) of patients with positive aPL and aCL antibodies who had IgM >10 MPL and IgG >10 GPL. The IgM antibody titers >40 MPL and serum IgG antibody levels >40 GPL were present in 3 and one patients positive for aCL antibody and in one and 4 patients with raised aPL antibody titer. Also 21% of patients who were negative for aCL-antibody had increased titers (positive) of non-aCL antibody (raised titer of IgM or IgG of aPL with ORG522 kit but normal levels of IgM or IgG of aCL with ORG515 kit). One of the studied patients had a history of systemic lupus erythematosus (SLE) and in 3 of them, SLE was diagnosed simultaneously with occurrence of stroke. The ANA–ANCA were positive in 3 patients without clinical manifestations of SLE, therefore they were classified as cases with latent lupus. Among studied patients, history of previous cerebrovascular accident was positive in 7, of Amaurosis Fugax in one, of migraine headache in 9 and of mesenteric emboli and deep vein thrombosis in one. From 23 patients with raised aPL and aCL titers, 21 and 2 of them had been admitted to hospital with the diagnosis of infarction and transient ischemic attack. Further evaluations revealed that 7 patients had embolic infarction and in 16 patients, thrombotic stroke was found. Fifteen patients had middle cerebral artery involvement, and in 2, 2 and 4 of them posterior cerebral artery, vertebrobasilar and multiple vessel involvement was observed. In addition, circulating antibody titers in patients with multiple vascular involvement were higher than 20 (MPL, GPL) (2 patients >20 and 2 patients > 40).

Discussion. According to the findings of this study, 19.6% of patients were positive for aPL antibodies and from these patients, 13% had raised level of aCL antibodies. Previous studies in this field have reported varying results (from 44-10%) concerning the prevalence of these antibodies in young patients with stroke.[1,17,22-24] Nagarraja et al[22] showed that 23% of patients had high serum aCL titers as compared to 10% in another study in Europe.[1] In Toschi et al's study,[17] 44% of patients were positive for one or more aPL antibodies and from these patients, 23% had higher titer of aCL.[17] These differences may be due to the various normal ranges considered for aPL antibodies or because of the difference in assay methods in studied populations. Therefore, further analytic studies with larger sample size are recommended to investigate the reason. In our study, LA testing was not carried out in all patients. This was a limitation for this study, and as a result, many patients were missed because of incomplete overlap between aCL and LA. Although in this study, 83.3% and 82.6% (from 18 and 23 patients) of cases had higher titer of aCL-IgM and aPL-IgM, IgG types of both aCL and aPL were positive in 44.4% and 26% of patients. So, the prevalence of raised IgM type of aPL or aCL is higher in our patients as compared to the IgG type. These findings are similar to the results of Nagarraja et al,[22] in India and in spite of the European reports.[17,21,23] The above mentioned differences can be explained through 2 hypotheses: aPL antibodies have been detected in malignancies, infections, and drug ingestions.[25-31] Considering the lower quality of health care services, higher prevalence of infectious diseases, and more frequent exposure to toxins in developing countries, infections or poisons and drugs can trigger the acute increase of IgM aPL antibodies through a "molecular mimicry" mechanism analogous to acute rheumatic fever. Some unknown racial or geographical differences make the people from developing countries susceptible to develop stroke earlier in the phase of acute IgM aPL rising. These hypotheses should be investigated carefully in future studies.

In conclusion, our study shows predominance of female gender, higher rate of ischemic thrombotic stroke and high titers of IgM aPL antibodies in a large number of patients, among young Iranian adults with stroke. Despite European studies, high titers of IgM aPL antibodies in a large number of our stroke patients can be caused by the presence of unknown triggering factors (infections or poisons) or undetermined racial or geographical differences.

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