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Acute Peripheral Vertigo: Involvement of the Hemostatic System

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Abstract: Viral infection is the most frequent cause of unilateral acute peripheral vestibulopathy (APV). Another possible cause is a vascular disorder in the labyrinth area associated with alterations in hemostasis. In a group of 45 patients with APV and in a series of 25 patients with Ménière's disease (control group), we evaluated blood parameters, including total cholesterol, triglycerides, apolipoprotein A and B, lipoprotein (a), homocysteine, folate, prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen, antithrombin III, protein C, protein S, activated protein C resistance, and anticardiolipin antibodies. In the acute phase of their disease, the patients with APV exhibited increased plasma levels of fibrinogen (341.5 ± 136.8 standard deviation [SD] versus 268.1 ± 72.6 SD mg/dl; $p = .05$); increased plasma levels of D-dimer (305 ± 158 SD versus 201 ± 106 SD ng/dl; $p = .008$); enhanced plasma levels of lipoprotein (a) (42.6 ± 38.5 SD versus 16.9 ± 17.7 SD mg/dl; $F = 5.67$, $p = .02$); high leukocyte count (9.2 ± 2.7 SD versus 6.4 ± 1.2 SD × $10^3/\mu l$; $F = 8.42$, $p < .006$); and low serum folate concentration (5.1 ± 1.7 SD versus 7.2 ± 2.6 SD ng/ml; $F = 4.34$, $p = .04$). During follow-up, the prothrombin time was prolonged ($p = .04$), and leukocyte count was decreased ($p < .019$) in the patients with APV, whereas fibrinogen, D-dimer, lipoprotein (a), and folate were unchanged. In this study, we demonstrated that patients with APV exhibit significant involvement of the hemostatic system.

Key Words: acute unilateral vestibular dysfunction; D-dimer; fibrinogen; hemostatic system; leukocyte count; lipoprotein (a)

Unilateral acute peripheral vestibulopathy (APV) is one of the most frequent causes of peripheral acute vertigo. The etiology of the disorder has yet to be clearly defined [1,2]; possible causes include a vascular disorder in the labyrinth area associated with alterations in hemostasis or even a viral infection (adenovirus, cytomegalovirus, herpesvirus, rubella) [3–8]. In some patients, it has been possible to demonstrate a traumatic origin or even one of a toxic nature deriving from the use of ototoxic drugs, such as aminoglycoside antibiotics, sulfur anhydride, or carbon dioxide [1].

The clinical features of APV are distinct: intense objective and rotatory vertigo lasting longer than a day and associated with intense neurovegetative symptoms and persistent, horizontal, spontaneous nystagmus but with no signs of cochlear involvement. Affected patients are ataxic; neurological examination show no signs of central involvement [2], and otoneurological tests reveal the presence of canal paresis.

The possibility of a vascular origin for APV is linked to the actual vascularization of the labyrinth, which is very poor in anastomotic circuits and, therefore, prone to possible thrombotic or embolic events. Various authors have reported alterations in the lipid metabolism of APV patients [3,9].

In this study, we assessed the presence of alterations in hemostasis as being predictors of the risk of ischemia

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in patients who were referred to our department because of APV. We compared blood test results with patients suffering from Ménière's disease in which the etiopathogenetic mechanism is known to be traceable to endolymphatic hydrops.

SUBJECTS AND METHODS

We studied 45 patients (21 male and 24 female; age range, 23–72 years; mean age, 56.2 ± 15.8 SD) who were suffering from APV and were referred to us over a period during the acute stage of their disorder (within 1–6 hours of the onset of the symptoms). They were admitted to the Ear, Nose, and Throat Unit of the Department of Neurosciences of Pisa University because of the severity of their vertigo and neurovegetative symptoms. The clinical features were intense, objective vertigo with nausea or spontaneous vomiting (or both), ataxic postural behavior, and persistent, horizontal, spontaneous nystagmus. The results of the otoscopic examinations performed were all within normal limits, and no other neurological symptoms or signs were detected.

We excluded from the study those patients with a positive anamnesis or positive laboratory data revealing present or past viral infections (antiviral antibody titer versus cytomegalovirus, herpes simplex, Epstein-Barr virus, rubella, adenovirus, and influenza); recent head trauma; uncontrolled diabetes mellitus; liver disease with impairment of protein synthesis; history of cerebral ischemia (transient ischemic attacks, stroke); or atrial fibrillation. The control group was made up of 25 patients (11 male and 14 female; age range, 22–70 years; mean age, 55.8 ± 14.6 SD) suffering from monolateral Ménière's disease that was previously diagnosed according to the criteria proposed by the Committee on Hearing and Equilibrium Guidelines (1995) [10]. These patients also were being treated in our Ear, Nose, and Throat Unit and were referred again to us because of the onset of new acute episodes of vertigo.

Within 3 days of the onset of their attacks, all patients were submitted to an otoneurological examination that included such tests as vestibulo-oculomotor reflex with a video-nystagmographic Ulmer 1.3 system and vestibular-spinal reflex with static posturography (S.Ve.P. 2.5 Amplifon). Liminal-tone audiometry and evoked auditory potentials also were performed.

Other examinations, including neurological and ophthalmological examinations, were carried out. The following blood tests also were performed: hemocytometric analysis including platelet count and mean platelet volume; prothrombin time (PT); activated partial thromboplastin time (aPTT); levels of fibrinogen, D-dimer, total cholesterol, high-density lipoproteins (HDLs), triglycerides, lipoprotein (a), apolipoprotein-A_1, apolipoprotein-B, homocysteine, folates, anticardiolipin antibodies IgG and IgM (ACLA), antithrombin III, protein C, and protein S; and resistance to activated protein C (APC).

When the general health of the patients permitted it, we performed an echocardiographic Doppler test of the cerebroafferent vessels and neuroradiological examinations (brain computed tomography or magnetic resonance imaging or both).

After a period of 4–6 weeks of pharmacological washout, the patients in both the study group and the control group repeated the otoneurological and liminal-tone audiometric tests and the specific blood tests for evaluating hemostasis. The liminal-tone audiometric examination revealed that 32 of the total 45 patients (71.1%) demonstrated normal hearing, whereas 13 (28.9%) showed signs of slight or moderate symmetrical, bilateral perceptive hypoacusis at the higher frequencies, which was a recent occurrence and could be classified as presbycusis. Tinnitus was absent in 40 patients (88.9%).

In all 45 patients (100%), the vestibular examination showed signs of spontaneous horizontal nystagmus: 29 cases (64.4%) with second-degree nystagmus and 16 (35.6%) with third-degree, whereas the head-shaking test revealed an increase of nystagmus in all patients (100%). Twenty-five (55.5%) had positional geotropic nystagmus, which was a sign of intensified spontaneous nystagmus. We detected one case (2.2%) of benign paroxysmal positional nystagmus.

During the days after these tests and when their conditions permitted it, the patients were submitted to the caloric test after the Fitzgerald-Hallpike procedure, and evaluation of the vestibular response was expressed in terms of labyrinthine preponderance (LP) and directional preponderance (DP), calculated with the Jonkees formula. In the cases of areflexia, we performed the ice-water test. Our reference values for normal subjects were less than 20% and less than 24% for LP and DP, respectively. We found that 100% of patients had canal paresis: 23 (51.1%) with pathological LP, 13 (28.9%) with pathological LP and DP, and 9 (20%) with areflexia.

The evoked auditory potentials did not reveal signs of retrocochlear involvement in any of the patients. The results of the echocardiographic Doppler test of the cerebroafferent vessels were within normal in 32 of the 45 patients (71.1%), whereas the test showed alterations in the walls (thickening of the intima) in 8 patients (17.8%) and calcific-fibrous plaques that were not hemodynamically significant in 5 (11.1%). The neuroradiological investigations (34 computed tomography and 11 magnetic resonance imaging) produced negative results in all the patients.

Clinical assessment (performed on admission to the hospital) of the patients in the control group, all of whom were affected with acute, monolateral Ménière's disease, revealed that all had undergone worsening of the hearing threshold during the attack (pure-tone average ≥10 dB; 15 exhibited unilateral, flat, sensorineural hypoacusis, and 5 demonstrated up-sloping hypoacusis). Tinnitus had increased in intensity in all the patients.

The vestibular examination revealed horizontal spontaneous nystagmus in all patients. Canal paresis was present in 100% of the 25 control patients: 16 patients (64%) with pathological LP, 6 (24%) with pathological LP and DP, and 3 (12%) with areflexia. The head-shaking test (HST) resulted in an increase in nystagmus in all the patients (100%); 11 (44%) manifested positional geotropic nystagmus, which was an indication of intensified spontaneous nystagmus.

Results of the neuroradiological investigations (computed tomography or magnetic resonance imaging or both) were negative in all patients. A statistical analysis was performed by analyzing the variance in repeated measurements, taking into account such factors as time, group, and their interaction. The Student's *t*-test was used to calculate the difference in D-dimer between the genders, and Pearson's correlation coefficient was employed to correlate the age variable with the D-dimer.

RESULTS

The results of the blood tests are summarized in Table 1. The higher leukocyte count observed in the 16 APV patients (35.5%) was due to an increase in neutrophil count, with a statistically significant difference ($p < .0001$) in comparison with the control group. Of the 45 APV patients, 8 (17.7%) had fibrinogen plasma levels above the upper limit of normality (i.e., 400 mg/dl); 23 (51.1%) had abnormally increased D-dimer levels (i.e., >300 ng/ml); and 19 (42.2%) had abnormally high concentrations of serum lipoprotein (a) (i.e., >30 mg/dl; Fig. 1). During the acute episodes, the homocysteine, protein C, protein S, and antithrombin III levels of the APV patients all were within the normal range. APC/aPTT, D-dimer, and total cholesterol proved to be increased in 23 patients (51.1%), with HDL levels reduced in 9 (20%). Triglycerides were increased in 11 patients (24.4%), and lipoprotein (a) in 19 (42.2%), whereas apolipoprotein-B results showed an increase in only 6 (13.3%) and apolipoprotein-A_1 in only 1 (2.2%).

Table 1. Blood Test Results (Mean ± SD) in Patients with APV or Ménière's Disease in the Acute Phase and During Follow-Up

	Acute Phase		Follow-Up		
Blood Test	**APV**	**Ménière's Disease**	**APV**	**Ménière's Disease**	**Healthy Subjects**
Fibrinogen (mg/dl)	341.5 ± 136.8	268.1 ± 72.6	318.8 ± 80.9	313.7 ± 83.9	285 ± 57
Lipoprotein (a) (mg/dl)	42.6 ± 38.5	16.9 ± 17.7	35.7 ± 29.6	16.1 ± 15.9	15.2 ± 13.1
D-Dimer (ng/dl)	305 ± 158	201 ± 106	304 ± 211	222.7 ± 133	120.7 ± 59.2
Apolipoprotein-A_1 (mg/dl)	151 ± 43.8	157.2 ± 12.8	159.6 ± 29.4	192 ± 111	156.3 ± 13.5
Apolipoprotein-B (mg/dl)	111.8 ± 37.5	105.3 ± 35.4	108.9 ± 30.4	101.2 ± 33.0	95 ± 30
Total cholesterol (mg/dl)	218.5 ± 51.3	211.1 ± 32.3	215.2 ± 33.4	203.9 ± 30.3	190 ± 30
High-density lipoprotein cholesterol (mg/dl)	49.3 ± 15.9	44.2 ± 5.2	49.3 ± 17.5	46.7 ± 7.9	45.2 ± 6.9
Triglycerides (mg/dl)	150 ± 77.6	134.9 ± 44.5	148.4 ± 77.8	128.2 ± 43.5	123 ± 37.2
Folates (ng/ml)	5.1 ± 1.7	7.2 ± 2.6	5.1 ± 1.4	6.2 ± 2.2	7.2 ± 2.1
Antithrombin III (%)	104 ± 12.1	106 ± 12.6	109 ± 13	103 ± 14.1	104.6 ± 13.4
APC resistance (sec)	133 ± 45.8	136.5 ± 23.7	146.6 ± 38.6	130.5 ± 27.4	130 ± 25
APC/aPTT	4.4 ± 1.5	4.6 ± 1.1	4.8 ± 1.4	4.2 ± 1.3	4.3 ± 1.2
PT (ratio)	0.85 ± 0.22	0.93 ± 0.08	0.9 ± 0.15	0.96 ± 0.09	1.02 ± 0.07
aPTT (sec)	31.1 ± 8.8	29.9 ± 2.8	30.7 ± 4.4	28.9 ± 2.1	29.8 ± 2.3
Leukocyte count ($\times 10^3/\mu l$)	9.2 ± 2.7	6.4 ± 1.2	7.2 ± 1.87	6.5 ± 1.27	6.6 ± 1.34
Hematocrit (%)	42.8 ± 3.7	41.6 ± 3.4	43.3 ± 3.7	42.3 ± 2.9	41.5 ± 2.9
Platelet count ($\times 10^3/\mu l$)	228.2 ± 45.1	221.3 ± 45.5	238 ± 41.9	222.9 ± 47.5	220 ± 40
Mean platelet volume (fl)	9 ± 0.9	9 ± 0.7	8.9 ± 0.7	9 ± 0.7	9 ± 0.7
Homocysteine (μM/dl)	5.8 ± 1.2	6.7 ± 1.7	6 ± 1.2	6.4 ± 1.4	6.5 ± 1.3
Protein C (%)	110 ± 21.1	111.4 ± 10	106.9 ± 24.1	110.8 ± 16.7	105 ± 12
Protein S (%)	95.5 ± 17.9	97 ± 12.1	90.5 ± 16.3	101.3 ± 18.1	98 ± 14
ACLA IgM	Negative	Negative	Negative	Negative	Negative
ACLA IgG	Negative	Negative	Negative	Negative	Negative

ACLA = anticardiolipin antibodies; APC = activated protein C; aPTT = activated partial thromboplastin time; APV = acute peripheral vestibulopathy; PT = prothrombin time; SD = standard deviation.

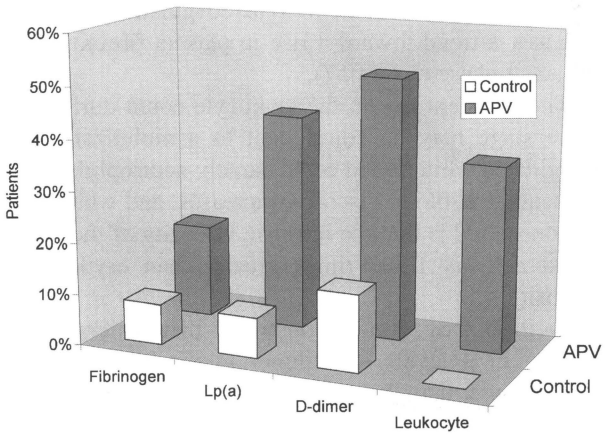

Figure 1. Percentage of patients affected with acute peripheral vestibulopathy (gray columns) and of those with Ménière's disease (white columns) having altered levels of fibrinogen, lipoprotein (a) [*Lp(a)*], D-dimer, and leukocyte during acute phase.

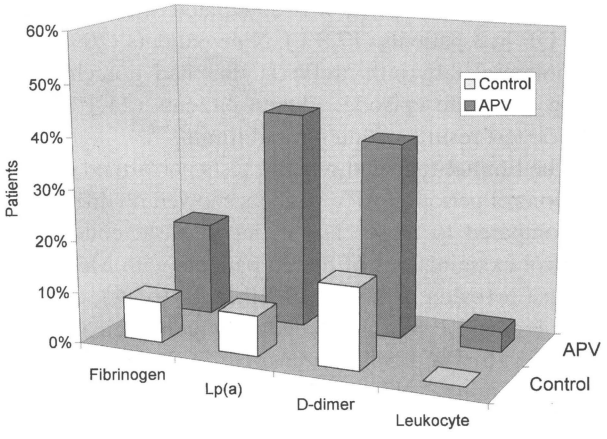

Figure 2. Percentage of patients affected with acute peripheral vestibulopathy (gray columns) and those with Ménière's disease (white columns) having altered levels of fibrinogen, lipoprotein (a) [*Lp(a)*], D-dimer, and leukocytes after a 4- to 6-week period of pharmacological washout.

Of the patients with Ménière's disease (i.e., control group), the acute phase of the disease produced an increase of total cholesterol in 12 of the 25 subjects (48%), of D-dimer in 4 (16%), of lipoprotein (a) and fibrinogen in 2 (8%), and of APC/aPTT in 5 (20%). The other parameters were within the normal range (see Fig. 1).

A comparison of the results obtained in the APV patients during their acute episode and of those seen in the controls showed that the mean rate of fibrinogen was significantly higher in the APV group than in the control group (341.5 ± 136.8 SD mg/dl versus 268.1 ± 72.6 SD mg/dl; $F = 4.3$; $p = .05$); the same was the case for lipoprotein (a) (42.6 ± 38.5 SD mg/dl versus 16 ± 18.2 SD mg/dl; $F = 5.67$; $p = .02$) and for the leukocyte count (9.2 ± 2.7 SD × $10^3/\mu l$ versus 6.4 ± 1.2 SD × $10^3/\mu l$; $F = 8.42$; $p < .006$). A comparison of the mean D-dimer levels obtained during acute episodes in the APV patients and those in the controls showed that these were significantly higher in the APV group (305 ± 158 SD versus 201 ± 106 SD; $F = 7.48$; $p = .008$). Folate concentration was significantly lower in the APV patients as compared to that in the controls (5.1 ± 1.7 SD ng/ml versus 7.2 ± 2.6 SD ng/ml; $F = 4.34$; $p = .04$), even though it remained within the normal range in both groups. The mean PT values were statistically shorter in the APV patients (84.6 ± 21.5 SD versus 93 ± 8 SD) during the acute episode (see Table 1). APC resistance increased in 12 of the 45 APV patients (26.7%) and in 2 of the 25 controls (8%); PT decreased in 14 APV patients (31.1%) but in just 2 of the controls (8%); and aPTT was increased in 8 APV patients (17.7%), whereas it remained normal in all the controls.

The follow-up tests carried out after 4–6 weeks showed that in the APV patients, the fibrinogen, lipoprotein (a), and folate measurements were unchanged, whereas PT was significantly longer in comparison with PT during the acute phase ($F = 4.34$; $p = .04$), and the leukocyte count was significantly lower than the previous count ($F = 7.39$; $p < .01$). During the follow-up, 17 APV patients (37.8%) had D-dimer levels that exceeded the normal range, whereas the number of patients in the control group with higher-than-normal levels remained at 4 (16%; Fig. 2). The statistically significant difference was still present during the follow-up when the mean plasmatic level was higher in the APV group (304 ± 211 SD ng/ml versus 192 ± 111 SD ng/ml; $F = 6.06$; $p = .016$). High APC/aPTT levels persisted in 25 APV patients (55.5%), just as the APC resistance rate persisted in 16 (35.6%). This latter measurement also showed a statistically significant difference between the measurements taken during the acute episode and those taken during the follow-up, which were higher and behaved differently as compared with those in the 25 controls with Ménière's disease ($F = 4.81$; $p < .03$). The levels of cholesterol in the blood remained high in 30 APV patients (66.7%; see Table 1).

The otoneurological examinations performed on the APV patients 4–6 weeks after the end of treatment showed persistent spontaneous nystagmus in two cases (4.4%), although it was less intense as compared to that found on admission, whereas nystagmus was revealed only with Frenzel glasses in six patients (13.3%). The HST result was positive in 24 APV patients (53.3%), whereas positional geotropic nystagmus persisted in 2 (4.4%). Caloric tests revealed 17 patients (37.8%) with

pathological LP, which was associated with homolateral DP in 8 patients (17.8%). Nine patients (20%) had monolateral labyrinth areflexia that had not changed since the acute episode. Eleven patients (24.4%) had caloric test results within normal limits.

The liminal-tone audiometric tests performed during the control period in APV patients showed no difference as compared to those carried out in basal conditions. Control examinations of the 25 patients with Ménière's disease revealed pathological LP in 16 (64%), and the pathological LP was associated with pathological DP in 5 of the 16. The HST was positive in 21 cases (84%), and the liminal audiometric test showed improvement (PTA $\geq$ 10 dB) in 11 cases (44%).

DISCUSSION

The etiology of APV is still a matter of debate. One of the principal etiopathological factors is viral infection [4,5]. Some authors suggest that ischemia plays a pathogenetic role in patients affected with blood hyperviscosity [3], such as those with primary or secondary polycythemia, other myeloproliferative disorders, macroglobulinemia, and hypergammaglobulinemia [3,6,9,11], or during the course of metabolic disorders [9,12]. The ischemic etiology might be part of a more extensive vertebrobasilar insufficiency and, in this case, neurological signs of posterior cranium fossa involvement will also be seen, or it might be limited to a selective impairment of the labyrinth [7,8]. Nevertheless, the forms with multiple signs of neurological involvement no longer come under the heading APV, as they are not limited exclusively to labyrinth involvement.

To date, the literature contains no reports of studies aimed at detecting the presence of alterations in hemostasis, either genetic or acquired, which might support the hypothesis of ischemia being at the root of APV; therefore, the majority of cases are diagnosed on a presumptive basis. In our study, we considered patients with APV but lacking either head trauma or present or past viral infection, confirmed by laboratory data. We analyzed this group of patients with idiopathic APV for possible alterations to hemostasis.

The results we obtained show that most patients with APV have multiple important alterations in hemostasis, whereas hemostatic alterations were seen in only 26% of the patients in the control group and were of a lesser degree. The short PT in the acute phase indicates an acceleration of the blood coagulation extrinsic pathway, possibly related to increased plasma concentrations of factors VII, II, or X [13]. The significantly greater increase in APC resistance in the acute phase, compared with that found in the follow-up, may be due to increased plasma levels of factor II or factor VIII (or both) and may contribute to hypercoagulation [13]. We also saw a trend toward a rise in plasma fibrinogen in the acute phase ($p = .057$).

The transient rise in the leukocyte count during the acute stage may be consequent to a mobilization of marginated white blood cells, namely neutrophils. As a consequence, blood viscosity increases, and what must be considered is that the intrinsic viscosity of the white blood cells is 1,000 times greater than erythrocyte viscosity.

In this study, we demonstrated that patients with APV exhibit levels of D-dimer in the blood significantly higher than those in patients with Ménière's disease, both during acute episodes of their respective disorders and in the follow-up period ($F = 7.48$, $p = .008$ and $F = 6.06$, $p = .016$, respectively). The increase in D-dimer in cases of APV provides further laboratory evidence of long-lasting hypercoagulation that might favor the acute events [14–16].

We also compared the APV patients with the Ménière's controls to detect any changes in laboratory data that persisted beyond the acute stage. The higher fibrinogen plasma levels, which remained unchanged during follow-up, indicate a prothrombotic condition: fibrinogen is well-known to be an independent risk factor for cardiovascular disorders [17]. The higher lipoprotein (a) serum concentration the APV patients, which persisted in the follow-up period, can indicate a predisposition for thrombosis [18]. Our results provide evidence that alterations in the hemostatic system can be considered an important pathogenetic factor in APV, in patients with negative anamnesis and negative laboratory data about viral infection.

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