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Relevance of plasma D-dimer measurement in patients with acute peripheral vertigo

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Abstract

The aetiopathogenesis of acute unilateral peripheral vestibular dysfunction (APV), also known as vestibular neuritis, is still debated: the principal cause is viral infection with vascular factors second in importance.

Plasmatic D-dimer, considered a plasmatic index of hypercoagulation, was measured in a group of 45 APV patients and in a group of 25 patients suffering from Ménière's disease. Measurements were taken both during the acute stage and after a four to six week period of pharmacological washout. The mean D-dimer levels were significantly higher than those measured in the controls both during the acute phase (301 SD161 *vs* 202 SD113 ng/mL) and after follow up (304 SD211 *vs* 192 SD111 ng/mL) ($p = 0.008$). Moreover, during the acute stage 23 of the APV patients (51.1 per cent) had plasmatic D-dimer levels above the upper normal limit (i.e.: <300 ng/mL), compared to four of those with Ménière's disease (16 per cent).

Our results lead us to postulate an involvement of the haemostatic system in APV.

Key words: Vestibular Neuronitis; Ménière's Disease; Blood Coagulation

Introduction

Acute unilateral peripheral vestibular dysfunction (APV) is one of the most frequent causes of peripheral acute vertigo and is more commonly called vestibular neuritis. The aetiology of the disorder has yet to be clearly defined:[1] the main cause is attributable to a viral infection (adenovirus, cytomegalovirus, herpes virus, rubella) capable of damaging the receptor cells of the ampullar crests and the maculae;[2,3] the second most frequent cause is the presence of disorders in the labyrinth area associated with altered haemostasis.[4,7] 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 aminoglucoside antibiotics, sulphur anhydride, or carbon dioxide.[1]

The clinical features of APV are distinct: there is intense, objective and rotatory vertigo lasting longer than one day, associated with intense neurovegetative symptoms; persistent, horizontal direction-fixed spontaneous nystagmus, but with no signs of cochlear involvement. The patient is ataxic and the Romberg test reveals lateropulsion towards the damaged side.[8] Neurological examinations show no signs of central involvement and otoneurological tests reveal the presence of canal paresis when the patient is submitted to the caloric test, whereas pure tone audiometry is within normal limits. Tinnitus and/or hearing-loss are present in only a few APV patients and it is impossible to demonstrate a direct association with vestibular disorders.[9]

The possibility of APV having a vascular origin 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.[7,10] In one of our recent studies on APV, we reported significant alterations in the haemostatic system, such as an abnormal increase in fibrinogen level and a shorter prothrombin time.[11]

In this study we evaluated plasmatic D-dimer, a stable end-product of the cross-linked fibrin degradation, in a group of patients suffering from APV both during the acute stage and after a four to six weeks pharmacological washout.

As a control group we used patients with Ménière's disease, a disorder that similarly manifests with acute episodes of peripherally located vertigo but which has a clearly defined aetiopathogenesis traceable to endolymphatic hydrops.

Materials and methods

We studied 45 patients (21 males and 24 females) whose ages ranged from 23 to 72 years (mean 56.2 SD15.8) suffering from APV and referred to us

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consecutively during the acute stage of their disorder (within one to six hours of the onset of the symptoms); these patients were admitted throughout the span of one year to the ENT Unit of the Department of Neurosciences of Pisa University because of the severity of the vertigo and neuro-vegetative symptoms.

The study group did not include those APV patients in whom anamnesis revealed recent viral infection and/or positive laboratory results (antivirus antibody titres) for infections such as adenovirus, cytomegalovirus, herpes simplex, Epstein-Barr virus, influenza virus and rubella.

We also excluded from the study any patient affected with disorders known to be associated with higher D-dimer plasma levels, namely fever, phlogosis, cirrhosis of the liver, malignancies, nephrotic syndrome, chronic uraemia, pancreatic diseases, previous cerebral ischaemia (TIA or stroke), recent venous thromboembolism, atrial fibrillation or uncontrolled arterial hypertension.

The clinical features were intense, objective vertigo with nausea and/or spontaneous vomiting, ataxic postural behaviour and persistent, horizontal, direction-fixed spontaneous nystagmus. The results of the otoscopic examinations performed were all within normal and there were no other neurological symptoms or signs.

The control group was made up of 25 patients (11 males and 14 females) whose ages ranged from 22 to 70 years (mean 55.8 SD14.6) suffering from monolateral Ménière's disease, previously diagnosed according to the criteria proposed by the Committee on Hearing and Equilibrium Guidelines (1995);[12] these patients were being treated in our ENT Unit and were once more referred to us consecutively throughout a one-year span (like the study group patients) because of the onset of new acute episodes of vertigo.

The number of patients in the study group is different from that in the control group because the number of APV and Ménière's patients with acute attacks examined over our one-year period of study was different. We considered a sample size of 70 patients to be sufficient for achieving an α error = 0.05 and a β error = 0.2 (power of the test = 0.8). Within three days of the onset of the attack, all patients were submitted to an otoneurological examination which included tests such as vestibular-oculomotor reflex (VOR) with a videonystagmographic Ulmer 1.3® system and postural attitude was studied with static posturographic (S.Ve.P. 2.5 Amplifon®). Pure tone audiometry and auditory evoked brainstem responses were also performed.

Other examinations were carried out, namely neurological and ophthalmological examinations, and blood tests, using both routine parameters and those specifically indicated to assess the haemostatic condition of the patients. D-dimer in the blood was measured with an enzyme-linked immunosorbent assay (ELISA) technique.

When the general health of the patients permitted it, we performed an Echo-Doppler of the cerebro-afferent vessels and neuroradiological examinations (brain computed tomography (CT) and/or magnetic resonance image (MRI)). After a period of four to six weeks pharmacological washout, both the patients in the study group and those in the control group repeated the otoneurological and liminal tone audiometric tests, as well as the specific blood tests for evaluating haemostasis.

Clinical assessment of the APV patients on admission to the hospital revealed 11 cases (24.4 per cent) of pharmacologically controlled arterial hypertension, five cases (11.1 per cent) of non-insulin-dependent, compensated mellitus diabetes; 10 patients (22.2 per cent) had instrumentally diagnosed heart disease (one case of left ventricular hypertrophy, four cases of right bundle branch block and one with incomplete left bundle branch block, two cases of mitral valve prolapse, one of aortic valve stenosis and one with steno-deficiency of the aorta). Twenty-three subjects (51.1 per cent) had no signs of other diseases (Table I).

The pure tone audiometry revealed 32 patients (71.1 per cent) with normal hearing while 13 (28.9 per cent) showed signs of slight or moderate symmetric, bilateral sensorineural hypoacusia at the higher frequencies, diagnosed several years previously and proving to be substantially unvaried at the pure tone audiometry examinations performed at check-up.

Tinnitus was absent in 40 patients (88.9 per cent) while in five (11.1 per cent) it was present before the acute episode and did not increase during it.

Thirty-nine patients (86.7 per cent) had never suffered from episodes of vertigo in the past while six (13.3 per cent) referred to having had another episode of acute rotatory vertigo during the past four to five years.

In all patients (100 per cent), the vestibular examination showed signs of spontaneous horizontal nystagmus (29 cases – 64.4 per cent – with IInd degree nystagmus and 16–35.6 per cent – with IIIrd degree), while the head-shaking test revealed an increase in nystagmus in all patients (100 per cent). Twenty-five (55.5 per cent) had positional geotropic nystagmus, which was a sign of intensified spontaneous nystagmus. There was one case (2.2 per cent) of benign paroxysmal positional nystagmus (Table II).

During the days following these tests, and when their conditions permitted it, the patients were submitted to the caloric test, following the Fitzgerald-Hallpike procedure, and the evaluation of the vestibular response was expressed in terms of labyrinthine preponderance (LP) and directional preponderance (DP), calculated with the Jongkees formula.[13] In the cases of unilateral areflexia, we performed the iced-water test. Our reference values for normal subjects were <20 per cent and <24 per cent for LP and DP, respectively. We found 100 per cent cases of canal paresis: 23 (51.1 per cent) with pathological LP, 13 (28.9 per cent) with pathological LP and DP and nine (20 per cent) with unilateral areflexia.

The auditory evoked brainstem responses did not reveal signs of retro-cochlear involvement in any of the patients. The Echo-Doppler of the cerebro-

TABLE I

D-DIMER LEVELS (μG/ML) IN THE INDIVIDUAL APV AND MÉNIÈRE'S (CONTROL GROUP) PATIENTS DURING THE ATTACKS AND FOLLOW-UP

APV	Sex	Age	D-dimer acute phase (μg/mL)	D-dimer end follow-up (μg/mL)	Clinical assessment	Ménière's disease	Sex	Age	D-dimer acute phase (μg/mL)	D-dimer end follow-up (μg/mL)	Clinical assessment
1	F	60	0.50	1.00	Normal	1	F	66	0.50	0.50	Normal
2	F	68	0.40	0.40	CAH-CMD	2	F	62	0.30	0.30	Normal
3	M	23	0.50	1.00	Normal	3	M	71	0.50	0.50	CAH
4	M	54	0.70	0.50	AVS	4	M	66	0.10	0.10	Normal
5	M	33	0.50	0.50	Normal	5	F	22	0.10	0.10	Normal
6	F	46	0.50	0.50	CAH	6	F	36	0.20	0.10	Normal
7	F	76	0.50	0.50	RBBB	7	M	70	0.20	0.26	CAH
8	M	79	0.50	0.50	CAH	8	F	66	0.10	0.22	Normal
9	F	65	0.10	0.10	Normal	9	M	67	0.10	0.20	LBBB
10	M	63	0.20	0.10	CAH-CMD	10	M	45	0.20	0.16	Normal
11	F	30	0.10	0.20	Normal	11	M	68	0.40	0.30	MVP
12	M	74	0.10	0.10	Normal	12	F	65	0.20	0.20	Normal
13	F	30	0.20	0.10	MVP	13	F	25	0.20	0.10	Normal
14	F	50	0.50	0.20	Normal	14	M	43	0.10	0.10	Normal
15	F	67	0.70	0.70	LBBB	15	F	47	0.20	0.20	Normal
16	M	51	0.20	0.30	Normal	16	M	36	0.15	0.10	Normal
17	F	78	0.20	0.20	CAH-LVH	17	F	70	0.10	0.10	MVP
18	M	56	0.10	0.20	Normal	18	F	64	0.20	0.15	CAH
19	M	51	0.10	0.20	CMD	19	M	52	0.21	0.16	Normal
20	M	52	0.40	0.50	CAH-RBBB	20	M	56	0.10	0.10	Normal
21	F	46	0.10	0.10	CMD	21	F	68	0.15	0.15	CMD
22	F	43	0.10	0.10	CAH	22	M	53	0.16	0.16	Normal
23	F	59	0.16	0.10	CMD	23	F	36	0.18	0.16	Normal
24	F	68	0.30	0.25	Normal	24	F	69	0.20	0.18	RBBB
25	M	52	0.30	0.30	Normal	25	F	72	0.20	0.20	CMD
26	F	59	0.30	0.21	Normal						
27	M	80	0.26	0.22	CAH						
28	F	62	0.35	0.35	Normal						
29	M	54	0.30	0.24	SDA						
30	M	42	0.30	0.21	RBBB						
31	F	58	0.50	0.50	CAH						
32	F	82	0.37	0.35	Normal						
33	M	35	0.16	0.16	Normal						
34	M	65	0.17	0.20	Normal						
35	F	42	0.20	0.16	Normal						
36	F	77	0.47	0.50	Normal						
37	M	79	0.30	0.24	CAH						
38	F	65	0.20	0.16	Normal						
39	M	27	0.16	0.15	MVP						
40	M	32	0.28	0.21	Normal						
41	F	53	0.20	0.19	Normal						
42	F	75	0.20	0.18	RBBB						
43	F	56	0.30	0.25	CAH						
44	M	50	0.28	0.25	Normal						
45	M	60	0.30	0.30	Normal						

CAH = Controlled arterial hypertension; CMD = Compensated mellitus diabetes; RBBB = Right bundle branch block; LBBB = Left bundle branch block; MVP = Mitral valve prolapse; AVS = Aortic valve stenosis; SDA = Steno-deficiency of the aorta; LVH = Left ventricular hypertrophy

TABLE II

OTONEUROLOGICAL INVESTIGATION

	Acute phase		Follow up	
Vestibular investigation	APV	Ménière's disease	APV	Ménière's disease
Spontaneous nystagmus	64.4% (II°) 35.6% (III°)	68% (II°) 32% (III°)	4.4% (I°)	Absent
Positioning nystagmus	2.2%	Absent	4.4%	Absent
Positional nystagmus	55.5%	44%	4.4%	Absent
Head-shaking nystagmus	100%	100%	53.3%	84%
Caloric test	LP 51.1% LP + DP 28.9% Unilateral Areflexia 20%	LP 64% LP + DP 24% Unilateral Areflexia 12%	LP 37.8% LP + DP 17.8% Unilateral Areflexia 20% Normal 24.4%	LP 64% LP + DP 20% Normal 16%

LP = Labyrinth preponderance; DP = Directional preponderance

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afferent vessels resulted to be within normal in 32 cases (71.1 per cent), while it showed alterations in the walls (thickening of the intima) in eight subjects (17.8 per cent) and calcific-fibrous plaques which were not haemodynamically significant in five (11.1 per cent).

The neuroradiological investigations (34 CT and 11 MRI) gave negative results in all the patients, as did also the neurological examination, which did not reveal any further signs of neurological impairment. The ophthalmological examination showed that six patients (13.3 per cent) had signs of sclerosis of the retina vessels.

The clinical assessment of the patients in the control group who were all affected with acute, monolateral Ménière's disease, performed on their admission to the hospital, revealed anamnesis positive for arterial hypertension in three cases (12 per cent), compensated non-insulin-dependent mellitus diabetes in two cases (eight per cent), right bundle branch block in one (four per cent), incomplete left bundle branch block in one (four per cent) and prolapse of the mitral valve in two cases (eight per cent). Sixteen patients (64 per cent) had no signs of other associated diseases. The pure tone audiometry test performed during the attack showed that all patients had undergone worsening of the hearing threshold (PTA $\geqslant$ 10 dB; 15 of which were unilateral flat sensorineural hypoacousia and five were up-sloping hypoacousia). Tinnitus had increased in intensity in all the patients.

The vestibular examination revealed horizontal fixed gaze spontaneous nystagmus in all patients, in 17 subjects (68 per cent) it was IInd degree and in eight (32 per cent) it was IIIrd degree. There was a 100 per cent presence of canal paresis: 16 cases (64 per cent) with pathological LP, six (24 per cent) with pathological LP and DP, and three cases (12 per cent) with unilateral areflexia. The head-shaking test resulted in an increase in nystagmus in all the patients (100 per cent); 11 (44 per cent) manifested positional geotropic nystagmus, which was an indication of intensified spontaneous nystagmus (Table II).

The neurological investigations were negative regards further lesions and ophthalmological examinations revealed one case (four per cent) of sclerosis of the retina vessels. Examination of the cerebro-afferent vessels with Echo-Doppler showed normal findings in 19 cases (76 per cent), slight thickening of the intima in five (20 per cent) and with non-dynamically significant calcific-fibrous plaques in one subject (four per cent).

The neuroradiological investigations (CT and/or MRI) were negative in all patients. Statistical analysis was performed by using analysis of variance for repeated measures where time was the repetition factor, and groups and the interaction group per time were the class factors.

Two tailed Fisher's exact test was used to compare the proportions of the pathological D-dimer values ($\geqslant$300 ng/mL) with those of the associated diseases in the two groups being studied.

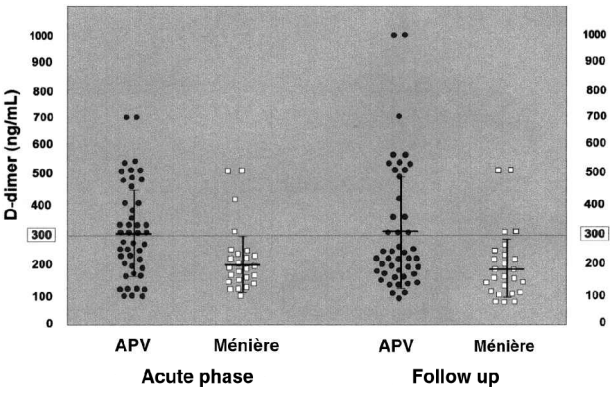

FIG. 1

Plasma levels of D-dimer in the individual APV patients (black dot) and Ménière's disease patients (white squares), during both the attacks and the follow-up. Horizontal bars: the mean values; Vertical bars: Standard Deviation.

A multifactor analysis, the log-linear model, was used to test the relationship between associated diseases and D-dimer considered as a binary variable. Log-linear models are methods that make it possible to describe the effects and the interactions between the various factors in multidimensional categorical data.

Results

The plasmatic levels of D-dimer measured in APV patients during attacks exceeded normal limits in 23 cases (51.1 per cent), whereas these levels were higher than normal in four (16 per cent) Ménière's disease subjects (i.e. <300 ng/mL), with a statistically significant difference between the two groups (Fisher's exact test $p = 0.005$). After four to six weeks of pharmacological wash-out, 17 APV patients (37.8 per cent) had D-dimer levels which were over the normal range, while the number of patients in the control group with higher than normal levels stayed at four (16 per cent) (Fisher's exact test $p = 0.065$) (Figure 1).

Mean D-dimer levels found during acute episodes in the APV patients versus those found in the controls showed that these were significantly higher in the APV group (301 SD161 *vs* 202 SD113 ng/mL). This statistically significant difference was still present at the end of the follow-up period, when the mean plasmatic level was higher in the APV group (304 SD211 *vs* 192 SD111 ng/mL) (Figure 1).

No significant time differences ($F = 0.07$; $p = 0.79$) were found while there was a significant difference between the D-dimer mean levels in the two groups ($F = 7.4$; $p = 0.0083$), both during the acute attacks and at the end of the follow-up period. No significant interaction was found between time and group factors ($F = 0.22$; $p = 0.64$). Moreover, the D-dimer resulted to have no relationship with either age or sex in both groups, whether at the acute stage or after the follow-up (data not shown).

There was a 48.9 per cent incidence of associated diseases in the study group while in the control group the percentage was 36 per cent. The two percentages are not significantly different. The otoneurological examinations performed in the APV patients four to

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six weeks after the end of treatment showed persistent spontaneous nystagmus in two cases (4.4 per cent), although less intense compared to that found on admission, whereas nystagmus was only revealed with Frenzel glasses in six patients (13.3 per cent). The HST was positive in 24 subjects (53.3 per cent) while positional geotropic nystagmus persisted in two cases (4.4 per cent). Caloric tests revealed 17 patients (37.8 per cent) with pathological LP, which was associated with homolateral DP in eight cases (17.8 per cent). Nine patients (20 per cent) had monolateral labyrinth areflexia, which had not changed since the acute episode. In two cases (4.4 per cent), it was found that benign positional paroxysmal vertigo of the posterior semicircular canal had arisen a few days after discharge from hospital, and was associated with homolateral canal paresis. In 11 patients (24.4 per cent) the caloric test was within normal limits.

The pure tone audiometry tests performed during the control showed no differences compared to those carried out in basal conditions.

Control examinations of the Ménière's disease patients revealed pathological LP in 16 cases (64 per cent), whereas this was associated with pathological DP in five (20 per cent): the HST was positive in 21 cases (84 per cent), and the pure tone audiometry showed improvement (PTA $\geqslant$10 dB) in 11 cases (44 per cent) (Table II).

Discussion

The principal aetiopathogenetic factor of APV, also known as vestibular neuritis, is a viral infection.[1–3] Nevertheless, this diagnosis is often an assumption since it is not always possible to demonstrate, by means of anamnesis and/or laboratory tests, that there is or has been a viral infection. In these cases, various authors have postulated the possibility of circulation disorders playing an important aetiopathogenetic role.[1,3,11] In a previous investigation it was reported that patients with APV in the acute phase, as compared to patients with Ménière's disease, displayed significantly increased blood levels of fibrinogen (mean: 338.3 SD135.9 mg/dl), enhanced blood levels of lipoprotein (a) (41.4 SD38.6 mg/dl), and high leukocyte counts (9.1 SD2.7 $\times$ $10^3/\mu L$), suggesting an involvement of the haemostatic system in APV.[11]

In this investigation the D-dimer levels in the blood of APV patients were studied during acute attacks and after a period of pharmacological washout, since there have been many accounts in the literature of this peptide being implicated in the aetiopathogenesis of diseases of a definite thromboembolic nature.[14–27] D-dimer is a stable end-stage degradation product of cross-linked fibrin, which considerably increases in the blood both in hypercoagulation conditions and in acute thrombotic events,[14] and is correlated with the processes of coagulation alteration that occur during normal ageing.[15,16] Elevated D-dimer levels have been reported in cases of pulmonary embolism,[17,18,24,25,27] disseminated intravascular coagulation (DIC),[19] venous thrombosis (DVT),[20,26] myocardial infarction and particularly in ischaemic heart disease,[21] acute ischaemic stroke[22,28] and, to a lesser degree, in cases of retinal artery thrombosis.[29,30] D-dimer also appears to be an important factor in the prediction of arterial thromboembolic events.[23,31] Plasma D-dimer levels are therefore highly sensitive and moderately specific for diagnosing hypercoagulation conditions. Hence, an increased concentration of D-dimer in the blood indicates that there is, or has been, coagulation activity, an event that leads to an increase in the risk of thrombosis.[24–27]

- **A previous study has shown increased levels of fibrinogen, lipoproteins and leucocytes in vestibular neuronitis**
- **This study presents the levels of D-dimer, a proxy for hypercoagulation, in vestibular neuronitis and Ménière's disease**
- **The level of D-dimer was raised in patients with vestibular neuronitis when compared to Ménière's disease, and that this was so in both the acute and recovery phases of the disease**
- **It is not clear from this study whether this finding is of clinical and practical significance or merely an epiphenomenon. Further studies are required**

Certain authors claim that D-dimer, in contrast to such coagulation activation markers as fibrinopeptide A, prothrombin fragment 1+2, and thrombin-antithrombin complex, tends to remain high for a long time (several months) after a thrombotic event.[30]

Increased levels of D-dimer have also been reported in patients with disorders associated with an increased incidence of thromboembolism, such as malignancies and particularly those with metastatic involvement[32,33] nephrotic syndrome[34] and chronic uraemia.[35]

In this study we have demonstrated that patients with APV exhibit significantly higher levels of D-dimer in the blood than patients with Ménière's disease, both during acute episodes of their respective disorders and in the follow-up period ($F = 7.48$; $p = 0.008$). Using multi-factor analysis, no statistically significant correlation between D-dimer levels in the blood and the concomitant diseases (arterial hypertension, mellitus diabetes, heart diseases) was found manifested in the two study groups. Moreover, neither sex nor age influenced the increase in the D-dimer levels in the blood (data not shown).

In the patients examined in this study, the persistent high levels of D-dimer indicated the presence of hypercoagulation; since all those patients affected with conditions associated with high D-dimer levels had been excluded from the study, an increase in D-dimer can be considered an interesting factor for predicting APV.

In view of this, it can be maintained that in APV patients in whom no viral infection can be demonstrated to be at the root of the disease it would be

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useful to measure the level of D-dimer in their blood, on the suspicion of there being a thromboembolic condition behind the disease, and thus to determine which treatment to administer during the acute attack and which regimen to follow for prevention thereafter.

It cannot be stated whether the hypercoagulation demonstrated in our series of patients with APV represents a pathogenic mechanism or rather a mere epiphenomenon. Controlled clinical trials will be required to test the efficacy of anti-thrombosis agents in the management of APV.

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