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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

INTRACEREBRAL HEMATOMA AND CERVICOCEPHALIC DOLICHOARTERIOPATHY

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ABSTRACT

INTRODUCTION: Prediction of expansion is of critical importance in intracranial hematoma (ICH) management. Cervicocephalic dolichoarteriopathy (CCDAP) may be a readily available marker of ICH expansion (ICHE) given its possible association with cerebral microvascular dysfunction.
METHODS 104 ICH patients (mean age: 64±12 years, 45% female) who had brain CT within first 12 hours, follow-up CT during first 72 hours, and CT angiography during this period were included. Basilar artery (BA) dolichoarteriopathy was graded with Smoker's criteria; cervical carotid artery (CCA) dolichoarteriopathy with modified Wiebel-Fields & Metz scoring. ICHE criteria were absolute volume increase ≥12.5cc and ≥6cc, or percent increase ≥33% and ≥26%.
RESULTS: ICHE ≥12.5 cc was detected in 10.5%; ≥6 cc in 21%, ≥33% percent increase in 20% and ≥26% in 27%. There was no significant correlation between enlarged BA diameter (>4.5 mm) and ICHE (≥12.5cc in 18%; ≥6cc in 18%, ≥33% in 19%, ≥26% in 14%). A high (≥1) Smoker's score does not correlate significantly with ICHE (≥12.5cc in 45%; ≥6cc in 50%, ≥33% in 38%, ≥26% in 39%) ICHE was not significantly, albeit numerically lower, correlated with ≥1 score of ipsilateral modified Wiebel-Fields & Metz (≥12.5cc in 71%; ≥6cc in 80%, ≥33% in 77%, ≥26% in 82%) No dolichoarteriopathy parameters were found to be linked with functional outcome and mortality.
DISCUSSION AND CONCLUSION: Although none reached statistical significance, ICHE tends to occur at a lower numerical rate as degree of CCDAP increases. The role of hypertension-induced parent artery remodeling in ICHE and its association with hypertensive microvascular adaptation may be the operating mechanism underlying this speculative protective effect.
Keywords: "Remodeling", microcirculation, hypertension, angiopathy, cerebral hematoma, avalanche hypothesis.

İNTRASEREBRAL HEMATOM VE SERVİKOSEFALİK DOLİKOARTERİOPATİ

ÖZ

GİRİŞ ve AMAÇ: İntraserebral hematom ekspansiyonunun (İHE) tahmin edilmesi intraserebral hematom (İSH) yönetiminde önemlidir. Serebral mikrovasküler disfonksiyon temelinde servikosefalik dolikoarteriopati (SSD) ile İHE arasında nedensel bir ilişki bulunabilir.
YÖNTEM ve GEREÇLER: İlk kraniyel BT incelemesi <12 saat, kontrol kraniyel BT incelemesi <72 saat ve BT anjiografi incelemesi bu periyotlar arasında yapılabilmiş olan toplam 104 hasta (ortalama yaş: 64±12 yıl, %45 kadın) çalışmaya dahil edildi. Baziler arter (BA) dolikoarteriopatisi, Smoker's kriterleri; SSD tayini ise modifiye Wiebel-Fields&Metz skoru ile değerlendirildi. İHE mutlak olarak, hacimsel ≥12,5 ml ve ≥6 ml artış veya yüzdesel ≥%33 ve ≥%26 artış kriterleriyle tanımlandı.
BULGULAR: İHE ≥12,5 ml artış %10,5, ≥6 ml artış %21, ≥%33 artış %20, ≥26 artış %27 hastada saptandı. Genişlemiş BA çapı (>4,5 mm) ile İHE arasında anlamlı korelasyon izlenmedi (≥12,5 cc artış %18; ≥6 cc artış %18, ≥33% artış %19, ≥26% artış %14). Yüksek Smoker's (≥1) skoru ile İHE arasında anlamlı korelasyon izlenmedi (≥12,5cc artış %45; ≥6cc artış %50, ≥33% artış %38, ≥26% artış %39). İpsilateral ≥1 modifiye Wiebel-Fields&Metz skoru da İHE ile, değeri göreceli daha

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düşük olmakla beraber, ilişkili saptanmadı (≥12,5cc artış %71; ≥6cc artış %80, ≥33% artış %77, ≥26% artış %82). Hiçbir dolikoarteriopati parametresi ile fonksiyonel sonlanım ve mortalite arasında anlamlı bağlantı tespit edilemedi.
TARTIŞMA ve SONUÇ: İstatistiksel anlamlılığa ulaşmamış olsa da, SDD skoru arttıkça İHE daha düşük oranlarda oluşmaya meyilli gibi gözükmektedir. Hipertansiyon ile indüklenen parent arter "remodeling"i ve bu durumun hipertansif mikrovasküler adaptasyon ile ilişkisi, bu spekülatif koruyucu etkinin altta yatan mekanizması olabilir.
Anahtar Sözcükler: "Remodelling", mikrosirkülasyon, hipertansiyon, anjiopati, serebral hematom, çığ hipotezi.

INTRODUCTION

Cervicocephalic dolichoarteriopathy (CCDAP) is an elongation anomaly of the relevant arteries (1). There are two fixation points of the internal carotid artery (ICA) in the cervical region, and if the relevant vessel is longer than the distance between these two points, CCDAP may occur (2). CCDAP can be in tortuous, kinking, and completely coiling types, or in the form of combinations of these (3-5).

The anatomical transition from the common carotid artery to ICA also histologically involves the transition from an elastic vascular structure to a muscular artery. In CCDAP, a metaplasia-like transformation of the ICA occurs (1). This metaplastic transformation is associated with genetic-embryological developmental problems and/or aging-associated vascular wall rarefaction (loosening and reduced density) and loss of elasticity (6, 7). Although there are some papers reporting that CCDAP is associated with atherosclerotic risk factors such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), and smoking; (8-11) there are also other papers not supporting those (12-14) findings.

Intracerebral hematoma enlargement (IHE) is associated with both poor prognosis and increased mortality; therefore, it is an important marker in the follow-up of intracerebral hematoma (ICH) (15). In this context, the parameters associated with IHE are important in the management of ICH.

In our study, whether there is a relationship between CCDAP and IHE was investigated on the basis of cerebral microvascular dysfunction.

METHODS

The study was conducted in accordance with the Helsinki Declaration ethical standards and approved by the Hacettepe University Faculty of Medicine Noninterventional Clinical Studies Ethics Committee (Number: 2019/08-43, Date: 07.03.2019).

Patient and Definitions: Demographic data, comorbid diseases, admission and subsequent laboratory values (platelet count, INR, etc.), admission NIHSS value of ICH patients followed up between 2004-2019 were collected retrospectively from our recorded database and hospital electronic information system. The time from the onset of symptoms to the first cranial computed tomography (CT) was defined as the $duration_{first}$, and the time from the first cranial CT to the second (follow-up) cranial CT was defined as the $duration_{second}$. Neuroimaging of patients who fell under the criteria of $duration_{first}$ <12 hours and $duration_{second}$ <72 hours were evaluated in terms of IHE. In patients whose cranial CT angiography (CTa) examination could be performed within this period ($duration_{first}$ and $duration_{second}$), basilar artery dolicoarteropathy was determined by Smoker's criteria (16) and CCDAP was determined by the modified Wiebel-Fields/Metz score (3-5, 17, 18). Since a basilar artery diameter of >4.5 mm is included in the terminology of dolichoectasia, patients meeting this criterion were further categorized as patients with 'a large basilar artery vs. without a large basilar artery'. In addition, the angles of bilateral ICA origin were recorded. To briefly touch on the scores, the Smoker's criteria are a scale that assesses the laterality of the basilar origin and the height of the rostral bifurcation in addition to the measurement of the diameter of the basilar artery (BA) in millimeters (mm) at the mid-pons level (Normal: BA ≤4,5 mm), while the basilar is a scale that evaluates the laterality of the root and the height of the rostral bifurcation, the Wiebel-Fields/Metz classification is a scale that assesses the extracranial ICA as normal (0), tortuous (1), mild kinking (2), moderate kinking (3), severe kinking (4) and complete coiling (5) (see reference 18 for sample figure). The primary result was used in the form of volumetric (≥12.5 ml and ≥6 ml) and percentage (≥33% and ≥26%) IHE in accordance with the literature. The secondary results were determined as good functional outcome and mortality at discharge.

A good functional outcome was defined as mRS ≤2 at discharge.

Neuroimaging: CTa was performed with a multi-detector sequential scanner (SOMATOM® Sensation 16, Erlangen, Germany). Source and maximum intensity projection (MIP) reformat analysis were used to evaluate the CTa images. Contrast administration was carried out by dynamic contrast bolus detection and helical scanning methods during the delivery of 100-130 ml non-ionic contrast agent through the antecubital vein at a rate of 3-4 ml/sec.

Statistics: SPSS 23 IBM® software provided by Hacettepe University Faculty of Medicine was used for the statistical analyses. The mean values of the groups were expressed as "mean ± standard deviation (SD)" or "median ± interquartile range (IQR)". In intergroup comparisons, the Student's t-test or Mann-Whitney U test was used for numerical data and the Chi-Square test was used for categorical data. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 104 patients (age: 64±12 years (mean ± SD), 45% female) were included in the study. It was found that there was an IHE increase of ≥ 12.5 ml in 10.5%, ≥6 ml increase in 21%, ≥33% increase in 20%, and ≥26 increase in 27% of the patients. All IHE subgroups had similar characteristics in terms of sociodemographic characteristics, comorbidities, drug use, and admission blood pressures (Table I). There was no significant correlation between admission hematoma volume, follow-up hematoma volume and IHE change at the interval, and basilar artery dolichoectasia, Smoker's scale, and ipsilateral or contralateral Metz Score (Figure I).

A significant correlation between enlarged BA diameter (>4.5 mm) and IHE was not observed (IHE (+) vs IHE (-): ≥12.5 cc increase 18% vs. 15%, p=0.78; ≥6 cc increase 18% vs. 14%, p=0.68, ≥33% increase 19% vs. 16%, p=0.87, ≥and 26% increase 14% vs. 16%, p=0.85, respectively).

There was no significant correlation between high Smoker's (≥1) score and IHE (≥12.5 cc increase 45% vs. 38%, p=0.61; ≥6 cc increase 50% vs. 35%, p=0.21, ≥33% increase 38% vs. 39%, p=0.96, ≥26% increase 39% vs. 38%, p=0.91).

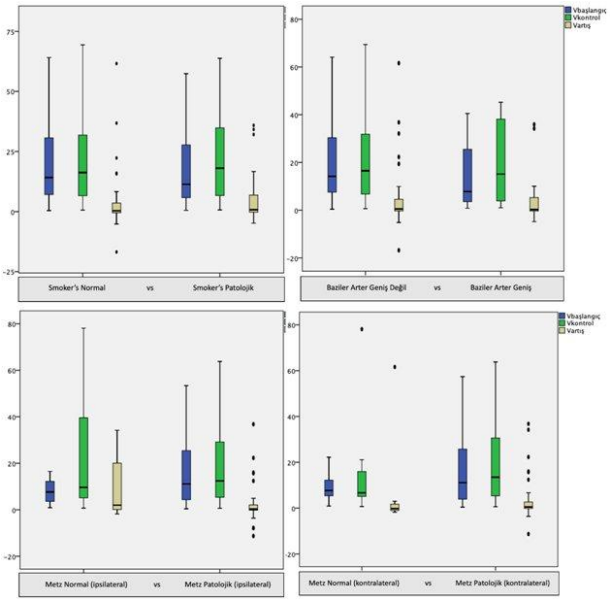

Figure I. The relationship between dominant hematoma changes at admission, follow-up, and interval and basilar artery dolichoectasia, the Smoker's and Metz scores.

The correlation between the ipsilateral ≥1 modified Wiebel-Fields & Metz score and IHE was not statistically significant, although the p-value was relatively low (≥12.5 cc increase 71% vs. 90%, p=0.15; ≥6 cc increase 80% vs. 90%, p=0.39, ≥33% increase 77% vs. 91%, p=0.16, ≥ and 26% increase 82% vs. 90%, p=0.40). The branching angle of ICA (ipsilateral); which was not included in the respective scoring systems, was significantly larger in the IHE (+) patients compared to the IHE (-) group in all IHE subtypes based on either the volume of the percentage (Table I).

When the global (Smoker's scores of not zero) or subcriteria criteria of basilar artery dolichoectasia were not normal, a numerical increase in the rates of good functional outcome rates (mRS 2 or less) was notable (p=0.08 for Smoker's score and p>0.1 for all of the remaining ones; Table II; Figure II- blue arrows). As for the anterior cervicocerebral circulation and Metz scores; the rates of good functional outcome tended to be numerically low in the dolichoectatic patients; however, the mortality was noted to be numerically low (p=0.08 for ipsilateral Metz scores; p=0.15 for contralateral Metz scores; Table III for survival rates, and Figure II for mortality - red arrows).

Table I. IHE(+) vs IHE(-) features.

	IHE(+) vs IHE(-) (33%) n= 21/83 (20%/80%)	p	IHE(+) vs IHE(-) (26%) n= 28/76 (27%/73%)	p	IHE(+) vs IHE(-) (12,5 ml) n= 11/93 (10,5%/89,5%)	p	IHE(+) vs IHE (-) (6 ml) n= 22/82 (21%/79%)	p
Age* (year)	67±13 vs 63±13	0,27	66±12 vs 63±13	0,42	69±11 vs 64±13	0,20	64±11 vs 64±13	0,98
Gender (%)(W)	16 (76 %) vs 31(37%)	0,001	19(68%) vs 28(37%)	0,005	8(72%) vs 39(42%)	0,052	14(64%) vs 33(40%)	0,05
Hemphill Score**	1(0-3) vs 1(0-2)	0,27	1(0-3) vs 1(0-3)	0,74	1(0-4) vs 1(0-3)	0,34	1(0-3) vs 1(0-3)	0,41
NIHSS**	13(2-24) vs 10(0-22)	0,43	14(2-26) vs 10(0-22)	0,12	14(0-29) vs 10(0-22)	0,12	15(3-28) vs 9(0-19)	0,002
SystolicBP* (application) (mmHg)	169±26 vs 173±36	0,63	166±30 vs 173±35	0,27	155±31 vs 174±34	0,11	171±34 vs 172±34	0,91
Diastolic BP*(application) (mmHg)	94±24 vs 95±21	0,79	94±23 vs 95±20	0,87	89±19 vs 95±21	0,36	100±27 vs 94±20	0,22
HT (%)	16(76%) vs 45(54%)	0,06	19(68%) vs 42(55%)	0,24	9(82%) vs 52(56%)	0,09	14(64%) vs 47(57%)	0,59
DM (%)	6(29%) vs 14(17%)	0,22	6(21%) vs 14(18%)	0,73	1(9%) vs 19(20%)	0,36	3(14%) vs 17(21%)	0,45
HL (%)	8(38%) vs 13(16%)	0,02	9(32%) vs 12(16%)	0,06	6(54%) vs 15(16%)	0,003	7(32%) vs 14(17%)	0,12
AF (%)	3(14%) vs 5(6%)	0,20	4(14%) vs 4(5%)	0,12	2(18%) vs 6(7%)	0,16	2(9%) vs 6(7%)	0,78
CAD (%)	4(19%) vs 14(17%)	0,81	6(21%) vs 12(16%)	0,50	2(18%) vs 16(17%)	0,93	2(9%) vs 16(20%)	0,25
Anti-aggregant usage (%)	3(14%) vs 24(29%)	0,17	7(25%) vs 20(26%)	0,89	3(27%) vs 24(26%)	0,91	5(23%) vs 22(27%)	0,69
Anti-coagulant usage (%)	6(29%) vs 10(12%)	0,06	7(25%) vs 9(12%)	0,09	3(27%) vs 13(14%)	0,24	3(14%) vs 13(16%)	0,79
Platelet count* (x10^3/mm^3)	236±70 vs 232±71	0,80	243±74 vs 229±70	0,39	240±105 vs 232±66	0,74	236±85 vs 232±67	0,82
Metz Score ≥1 (ipsi) (%)	10(77%) vs 49(91%)	0,16	14(82%) vs 45(90%)	0,40	5(71%) vs 54(90%)	0,15	8(80%) vs 51(90%)	0,39
ICA diameter* (ipsi) (mm)	4,9±0,9 vs 5,0±0,8	0,69	4,8±0,7 vs 4,9±0,8	0,37	4,5±0,8 vs 5±0,8	0,04	4,6±0,8 vs 5±0,8	0,08
ICA divergence angle* (ipsi) (°)	159±15 vs 154±15	0,26	158±13 vs 153±16	0,32	153±13 vs 155±15	0,55	156±13 vs 154±16	0,93
Metz Score ≥1 (cont) (%)	11(85%) vs 48(89%)	0,67	15(88%) vs 44(88%)	0,97	6(86%) vs 53(88%)	0,84	9(90%) vs 50(88%)	0,83
ICA diameter*(cont) (mm)	5±0,8 vs 4,8±0,9	0,68	4,8±0,7 vs 4,8±0,9	0,84	4,5±0,6 vs 4,9±0,9	0,10	4,6±0,8 vs 4,9±0.9	0,15
ICA divergence angle* (cont) (°)	165±11 vs 149±18	0,003	163±11 vs 147±19	0,003	166±10 vs 150±18	0,01	165±12 vs 150±18	0,01
Smoker's (≥1) (%)	8(38%) vs 32(39%)	0,96	11(39%) vs 29(38%)	0,91	5(45%) vs 35(38%)	0,61	11(50%) vs 29(35%)	0,21
Basillary diameter (≥4,5 mm) (%)	3(19%) vs 13(16%)	0,87	4(%14) vs 12(%16)	0,85	2(18%) vs 14(15%)	0,78	4(18%) vs 12(14%)	0,68
Basillary laterality (%)	2(10%) vs 16(19%)	0,29	4(14%) vs 14(18%)	0,62	1(9%) vs 17(18%)	0,44	5(23%) vs 13(16%)	0,44
Basillary height (%)	4(19%) vs 20(24%)	0,62	4(19%) vs 20(26%)	0,19	2(18%) vs 22(24%)	0,68	4(18%) vs 20(24%)	0,53
LoS* (day)	17±15 vs 21±29	0,96	26±32 vs 18±25	0,25	25±33 vs 20±26	0,94	24±32 vs 19±25	0,39
mRS**	5(2-6) vs 3(0-6)	0,04	5(2-6) vs 3(1-5)	0,01	5(3-6) vs 3(0-6)	0,007	5(3-6) vs 3(1-5)	<0,001
Survivability (%)	15(71%) vs 73(83%)	0,06	21(75%) vs 67(88%)	0,09	6(55%)vs 82(88%)	0,003	13(59%) vs 75(92%)	<0,001

AF: Atrial Fibrillation, DM: Diabetes Mellitus, HL: Hyperlipidemia, HT: Hypertention, LoS: length of stay, ICA: Internal Carotid Artery, ipsi: Ipsilateral, CAD: Coronary Artery Disease, BP: Blood Pressure, cont: Contralateral, NIHSS: National Institutes of Health Stroke Score, *Mean±SD and **Median± interquartile range (IQR).

Table II. The association between good functional outcome and CCDAP parameters*.

Criteria	mRS ≤2	P
Smoker's	15(%38) vs 14(%22)	0,08
Basillary diamemter (>4,5mm)	6(%38) vs 23(%26)	0,35
Basillary laterality	6(%33) vs 23(%27)	0,57
Basillary height	9(%38) vs 20(%25)	0,23
Metz≥1 (ipsilateral)	20(%34) vs 4(%50)	0,37
Metz ≥1 (contralateral)	19(%68) vs 5(%63)	0,09

*with vs without criteria.

Table III. The association between mortality and CCDAP parameters*.

Criteria	Survivability	p
Smoker's	34(%85) vs 54(%84)	0,93
Basillary diamemter (>4,5mm)	14(%88) vs 74(%84)	0,72
Basillary laterality	16(%89) vs 72(%84)	0,58
Basillary height	22(%92) vs 66(%83)	0,27
Metz≥1 (ipsilateral)	56(%92) vs 5(%63)	0,08
Metz ≥1 (contralateral)	59(%92) vs 6(%75)	0,15

**with vs without criteria.

Figure II. The correlation of each CCDAP parameter with mRS distribution.

DISCUSSION AND CONCLUSION

It was found that the coexistence of CCDAP with cerebral small vessel disease (CSVD) was more frequent than normal in the rostral vascular system (19), its coexistence with an abdominal aortic aneurysm was more frequent than normal in the caudal vascular system (20). When this issue is evaluated in terms of ICH, particular attention should be paid to cerebral microbleeds, which are one of the indirect neuroimaging features of CSVD (21). It has been reported that cerebral microbleeds can be observed in up to 70% of patients with ICH (22). It has been found out that the absence of microbleeding on neuroimaging increases the risk of IHE by approximately 2-folds (23).

Although not statistically significant; IHE, which may tend to be less common in cases with anterior system CCDAP, may be partially protective against IHE through common pathways with CSVD, especially on the grounds of chronic hypertension. In this context, the development of rarefaction in vascular structures on the grounds of chronic hypertension can be given as an example as it parallels to the rarefaction observed in the pathology of CCDAP (1). Furthermore, reduced cerebral dilator capacity on the grounds of hypertension, (24) vascular "inward" remodeling, (25), and changes in matrix metalloproteinases (MMP) may represent common pathways between the issues concerning their effects on vascular wall integration.

MMP is known to be associated with vascular rupture and blood-brain barrier (BBB) destruction (26). It has been determined that in animal models of CCDAP, the MMP3 level is lower compared to controls, and there is a relationship between increased MMP3 and increased hematoma volume and poor functional outcome in humans (26).

Moreover, it has been found that the MMP2 level is higher in CCDAP patients than in controls (27), and this protein has been shown to be associated with increased BBB dysfunction and perihematomal edema (28). Considering in the light of the increasing literature knowledge starting with Fisher's "Avalanche" theory, the hematoma progressing after vascular rupture creates IHE by causing secondary vascular ruptures with increasing volume, (29) the high MMP2 level present in CCDAP patients may be protective against IHE due to the compression effect of more perihematomal edema. Other supports of this protective expression are that mortality is lower in the presence of dolicoectasis and that dolichoectasia detected in the posterior circulation seems to be associated with numerically good functional outcomes.

Finally, time is also an important factor in the development of this process (30). CCDAP, which shows development over time, may be serving to create an environment in favor of patients with CCDAP in terms of the development of cerebral hematoma and perhaps large IHE, especially in the event of acute hypertension, as a result of the reflection of changes in the parent artery.

In summary, despite being statistically insignificant in our study, CCDAP may indicate the improvement of the clinical course of intracerebral hematoma through mechanisms that have not been clarified yet but should be investigated in the future.

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Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Faculty of Medicine Noninterventional Clinical Studies Ethics Committee (Number: 2019/08-43, Date: 07.03.2019).

Informed Consent: It was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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