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Vertebral Artery Hypoplasia – Sex-Specific Frequencies in 36 Parent-Offspring Pairs

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ABSTRACT

The major interest in vertebral artery (VA) hypoplasia comes from its possible connection to migraines with aura as well as from the fact that it is one of the risk factors for a stroke. Therefore, the aim of this preliminary study was to investigate the mode of inheritance of VA hypoplasia. Initially, color Doppler of VA was performed in 64 first- and second-degree relatives of 33 probands, and the presence of VA hypoplasia was confirmed according to the already established criteria. Since a higher prevalence of VA hypoplasia (15.6%) in probands' relatives in comparison with 2.34% in the general population of Croatia was indicative of a strong familial predisposition for this condition, an analysis of family data by means of Pearson's chi-square statistics has been performed. In this analysis, the observed sex-specific frequencies of 36 parent-offspring pairs composed only of affected parent and his/her (affected or non-affected) offspring are compared to the frequencies as expected under eight proposed models. For both – autosomal and X-linked monogenetic inheritance – four hypotheses have been chosen, assuming that the individuals having the affected allele (in combination with a healthy one) have 100%, 50%, 40% and 0% chances of developing VA hypoplasia. Out of eight tested models only two – completely dominant and completely recessive X-linked models – were rejected. But, from the six non-rejected models, goodness-of-fit statistics showed that the hypothesis of X-linked inheritance of VA hypoplasia with the »healthy« allele being stronger (60% effect on phenotype) – almost perfectly fit the data ($\chi^2 = 2.0023$; $df = 7$; $p = 0.9597$). Further research encompassing a more enlarged family sample is needed to confirm the present findings.

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Introduction

There are few categories of cerebral arteriovenous diseases in relation to possible genetic factors. Some cerebral arteriovenous malformations show a relationship with the inherited diseases where a genetic support is clearly identified, such as hereditary hemorrhagic teleangiectasia¹. On the other side, there are other types of malformations where several family members harbor the pathology without clear evidence of any genetic basis¹. Some data place an emphasis on intracranial aneurysmal inheritance².

Different familial patterns indicate that migraine with aura and migraine without aura have different etiologies³. While the migraine with aura is probably determined largely or exclusively by genetic factors, migraine without aura seems to be caused by a combination of genetic and environmental factors³. We have noticed⁴ a higher frequency of hypoplastic vertebral arteries (VA) in migraines with aura than in migraines without aura or in controls. Such observation led to the assumption that VA hypoplasia might also be an inheritable condition. Genetics of VA hypoplasia was found to be additionally important because hypoplastic VA poses a risk factor for a stroke^{5–7}.

Vertebral artery embryogenesis differs from that of any other vessel, and is characterized by a great variety of malformations and anomalies. Earlier reports on VA diameters were based on cadavers, rarely on angiographic findings. Recently, a possibility of non-aggressive insight in to brain circulation by means of color Doppler ultrasound makes possible a non-invasive assessment of VA diameter in two or three generations of the same family^{8,9}.

In an epidemiological investigation encompassing 596 vertebrobasilar symptom-free individuals from Croatia, VA hypo-

plasia was found in 2.34% (limit: VA 2.0 mm) and a VA asymmetry in 15% of the investigated subjects⁸. Criteria for VA hypoplasia differ between ultrasound laboratories, but not a single investigation found a hypoplastic VA in more than 10% of symptom-free individuals^{4,9–11}. Since in the investigated extended families of individuals with already established hypoplasia (probands) 15.6% prevalence of VA hypoplasia was found, we considered this finding indicative of a strong familial predisposition for this condition. Thus, the aim of the present study was to investigate the mode of inheritance of VA hypoplasia, by testing the concordance of observed (measured) frequencies of the affected and the healthy offspring of affected parents (sex-specific) and the frequencies as expected under the assumption of both autosomal and X-linked inheritance.

Subjects and Methods

According to the already established criteria for vertebral artery (VA) hypoplasia, diameter 2 mm, PSV 40 cm/s and higher resistance pattern^{8,12}, VA color Doppler have been performed in 64 first- and second-degree relatives of 33 individuals (probands) with already established VA hypoplasia, amounting to a total of 97 individuals (40 males and 57 females). From this initial family sample it was possible to extract 36 affected persons that had measured offspring. Since it turned out that 9 (or 25%) out of 36 offspring had hypoplastic VA, the analysis of family data under the assumption of monogenetic inheritance of VA hypoplasia was performed.

The hypotheses of autosomal as well as X-linked monogenetic inheritance of VA hypoplasia were assumed and four variants of each model have been designed and tested: i.e. the hypotheses assuming that an individual having affec-

TABLE 1
 ALLELE AND GENOTYPE FREQUENCIES AS WELL AS THE FREQUENCIES OF AFFECTED INDIVIDUALS AND OF INDIVIDUALS CARRYING ALLELE A_A , CALCULATED FOR 8 SUGGESTED MODELS ON THE BASIS OF THE PREVALENCE OF 2.34% OF VA HYPOPLASIA IN GENERAL POPULATION IN CROATIA

Type of inheritance	Allele frequency (%)	Genotype frequency (%)	Frequency of individuals carrying allele A_A (%)	Frequency of affected individuals (VA hypoplasia) (%)
AUTOSOMAL				
Dominance of A_A	$A_A = 1.18$	$A_A^2 = 0.0139$	2.34% (= $A_A^2 + 2A_A A_H$)	2.34% (= $A_A^2 + 2A_A A_H$)
	$A_H = 98.82$	$A_H^2 = 97.6599$ $2A_A A_H = 2.3263$		
Recessiveness of A_A	$A_A = 15.30$	$A_A^2 = 2.34$	28.26% (= $A_A^2 + 2A_A A_H$)	2.34% (= A_A^2)
	$A_H = 84.70$	$A_H^2 = 71.74$ $2A_A A_H = 25.92$		
Co-dominance: A_A has 50% effect	$A_A = 2.340$	$A_A^2 = 0.0548$	4.63% (= $A_A^2 + 2A_A A_H$)	2.34% (= $A_A^2 + 0.5 * 2A_A A_H$)
	$A_H = 97.66$	$A_H^2 = 95.3748$ $2A_A A_H = 4.5705$		
Co-dominance: A_A has 40% effect	$A_A = 2.90$	$A_A^2 = 0.0841$	5.72% (= $A_A^2 + 2A_A A_H$)	2.34% (= $A_A^2 + 0.4 * 2A_A A_H$)
	$A_H = 97.10$	$A_H^2 = 94.2841$ $2A_A A_H = 5.6318$		
X-LINKED				
Dominance of A_A	$A_A = 0.78$	$A_A^2 = 0.0061$	M+F = 2.34%	M+F = 2.34%
	$A_H = 99.22$	$A_H^2 = 98.4401$ $2A_A A_H = 1.5537$	M = 0.78% (= A_A) F = 1.56% (= $A_A^2 + 2A_A A_H$)	M = 0.78% (= A_A) F = 1.56% (= $A_A^2 + 2A_A A_H$)
Recessiveness of A_A	$A_A = 2.29$	$A_A^2 = 0.0523$	M+F = 6.81%	M+F = 2.34%
	$A_H = 97.71$	$A_H^2 = 95.4763$ $2A_A A_H = 4.4713$	M = 2.29% (= A_A) F = 4.52% (= $A_A^2 + 2A_A A_H$)	M = 2.29% (= A_A) F = 0.05% (= A_A^2)
Co-dominance: A_A has 50% effect	$A_A = 1.17$	$A_A^2 = 0.0137$	M+F = 3.50%	M+F = 2.34%
	$A_H = 98.83$	$A_H^2 = 97.6737$ $2A_A A_H = 2.3126$	M = 1.17% (= A_A) F = 2.33% (= $A_A^2 + 2A_A A_H$)	M = 1.17% (= A_A) F = 1.17% (= $A_A^2 + 0.5 * 2A_A A_H$)
Co-dominance: A_A has 40% effect	$A_A = 1.30$	$A_A^2 = 0.0169$	M+F = 3.88%	M+F = 2.34%
	$A_H = 98.70$	$A_H^2 = 97.4169$ $2A_A A_H = 2.5662$	M = 1.30% (= A_A) F = 2.58% (= $A_A^2 + 2A_A A_H$)	M = 1.30% (= A_A) F = 1.04% (= $A_A^2 + 0.5 * 2A_A A_H$)

A_A = »affected« allele (VA hypoplasia); A_H = »healthy« allele; M = males; F = females

ted allele – in combination with a healthy one – has 100%, 50%, 40% and 0% chances of developing vertebral hypoplasia. The observed frequencies of sex-specific pairs of affected parent and his(her) affected/ non-affected offspring were compared, by means of χ^2 statistics, with the frequencies that were expected under assumptions of autosomal and X-linked mono-

genetic inheritance. Thus, four different effects of affected allele (A_A) on phenotype have been proposed and tested, assuming:

- A) complete dominance of »hypoplastic« allele (100%:0%);
- B) complete recessiveness of »hypoplastic« allele (0%:100%);
- C) co-dominance with equal strength of both alleles (50%:50%);

TABLE 2
SIDE OF THE SMALLER (HYPOPLASTIC OR NORMAL) VERTEBRAL ARTERY (VA) IN AFFECTED PARENTS AND THEIR OFFSPRING

Side of hypoplastic VA in parents	Side of smaller (hypoplastic or normal) VA in offspring			
	Right	Left	Rigt = left	Total
Right	14	12	–	26
Left	2	7	1	10
Total	16	19	1	36

D) co-dominance with »hypoplastic« allele being weaker than the »healthy« one in ratio (40%:60%).

For all 8 hypotheses, the estimated allele and genotype frequencies as well as the frequencies of affected individuals (VA hypoplasia) and of individuals carrying allele A_A in the population with 2.34% prevalence of VA are shown on Table 1.

From these estimations, the expected frequencies of affected offspring (of affected parents) have been calculated with respect to each proposed model, which included:

1. Estimation of the risk that offspring receives the affected allele from his/her measured (affected) as well as non-measured parent (affected or non-affected);
2. Estimation of the risk that the offspring who received the affected allele (from one or both parents) develop VA hypoplasia; and
3. Calculation of the expected proportion of the affected and non-affected offspring in each sex-specific parent-offspring pair.

All calculations are sex-specific and the proportion of heterozygotes and homozygotes are incorporated in calculations for each model as well. Goodness-of-fit statistics has been performed on Statistica 5 (1997) program package.

Results

As it is shown in Table 2, the side of hypoplastic vertebral artery differs in parents and children. Therefore, the ge-

netic analysis has been performed using, as the investigated value, the diameter of the smaller VA (left or right). The characteristics of smaller VA distributions in daughters and sons of affected parents are shown on Figure 1. In contrast to a more normal distribution of the smaller VA in daughters, in the sons of affected parents an additional peak of the distribution of VA is visible within the limits defining the hypoplasia of the VA, indicating a possibility of contribution of X-linked inheritance in this condition.

Goodness-of-fit statistics of measured and expected frequencies of affected and healthy daughters and sons of affected parents under four different hypotheses (A, B, C and D) of autosomal and X-linked monogenetic inheritance of VA hypoplasia is presented in Tables 3 and 4.

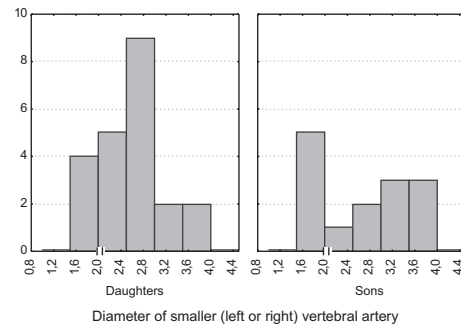


Fig. 1. Diameter of the smaller (left or right) vertebral artery in daughters (n = 22) and sons (n = 14) of affected parents (mother or father).

TABLE 3
 AUTOSOMAL INHERITANCE OF VA HYPOPLASIA: χ^2 -TEST OF OBSERVED (O) AND EXPECTED (E)
 FREQUENCIES OF AFFECTED AND HEALTHY OFFSPRING OF AFFECTED PARENTS UNDER
 FOUR DIFFERENT HYPOTHESES (A, B, C, D)

Parent-offspring pairs	O	A		B		C		D	
		Dominant effect of A _A vs. A _H (100%:0%)		Recessive effect of A _A vs. A _H (0%:100%)		Co-dominant effect of A _A vs. A _H (50%:50%)		Co-dominant effect of A _A vs. A _H (40%:60%)	
		E	(O-E) ² / E	E	(O-E) ² / E	E	(O-E) ² / E	E	(O-E) ² / E
M _A _D _A	2	6.1760	2.8237	1.8360	0.0147	3.1761	0.4355	2.6438	0.1568
M _A _D _H	10	5.8240	2.9943	10.1640	0.0027	8.8239	0.1568	9.3562	0.0443
M _A _S _A	5	5.1467	0.0042	1.5300	7.8699	2.6467	2.0924	2.2032	3.5505
M _A _S _H	5	4.8533	0.0044	8.4700	1.4216	7.3533	0.7531	7.7969	1.0033
F _A _D _A	2	5.1467	1.9239	1.5300	0.1444	2.6467	0.1580	2.2032	0.0187
F _A _D _H	8	4.8533	2.0402	8.4700	0.0261	7.3533	0.0569	7.7969	0.0053
F _A _S _A	0	2.0587	2.0587	0.6120	0.6120	1.0587	1.0587	0.8813	0.8812
F _A _S _H	4	1.9413	2.1831	3.3880	0.1106	2.9413	0.3811	3.1188	0.2490
Sum	36	36	14.0325	36	10.2018	36	5.0924	36	5.9092
		$\chi^2 = 14.0325$; df = 7 p = 0.0506		$\chi^2 = 10.2018$; df = 7 p = 0.1775		$\chi^2 = 5.0924$; df = 7 p = 0.6487		$\chi^2 = 5.9092$; df = 7 p = 0.5504	

A_A = »affected« allele (VA hypoplasia); A_H = »healthy« allele; M = mother, F = father; D = daughter; S = son; A = affected; H = healthy

TABLE 4
 X-LINKED INHERITANCE OF VA HYPOPLASIA: χ^2 -TEST OF OBSERVED (O) AND EXPECTED (E)
 FREQUENCIES OF AFFECTED AND HEALTHY OFFSPRING OF AFFECTED PARENTS UNDER
 FOUR DIFFERENT HYPOTHESES (A, B, C, D)

Parent-offspring pairs	O	A		B		C		D	
		Dominant effect of A_A vs. A_H (100%:0%)		Recessive effect of A_A vs. A_H (0%:100%)		Co-dominant effect of A_A vs. A_H (50%:50%)		Co-dominant effect of A_A vs. A_H (40%:60%)	
		E	(O-E) ² / E	E	(O-E) ² / E	E	(O-E) ² / E	E	(O-E) ² / E
M_A-D_A	2	6.1170	2.7709	0.2746	10.4833	3.1584	0.4249	2.5717	0.1271
M_A-D_H	10	5.8833	2.8812	11.7254	0.2539	8.8416	0.1518	9.4283	0.0347
M_A-S_A	5	5.0193	0.0001	9.9990	2.4993	5.0300	0.0002	5.0327	0.0002
M_A-S_H	5	4.9807	0.0001	0.0010	24990.0000	4.9700	0.0002	4.9673	0.0002
F_A-D_A	2	9.9990	6.3990	0.2288	13.7113	5.0580	1.8488	4.0776	1.0586
F_A-D_H	8	0.0010	6.3984.0000	9.7712	0.3211	4.9420	1.8922	5.9224	0.7288
F_A-S_A	0	0.0313	0.0313	0.0915	0.0915	0.0468	0.0468	0.0520	0.0520
F_A-S_H	4	3.9687	0.0002	3.9085	0.0021	3.9532	0.0006	3.9480	0.0007
Sum	36	36	63.996.0800	36	25017.7225	36	4.3654	36	2.0023
		² = 63,996.0800; df = 7 p < 0.0001		² = 25,017.7225; df = 7 p < 0.0001		² = 4.3654; df = 7 p = 0.7369		² = 2.0023; df = 7 p = 0.9597	

A_A = »affected« allele (VA hypoplasia); A_H = »healthy« allele; M = mother, F = father; D = daughter; S = son; A = affected; H = healthy

As it was expected, the X-linked model assuming a complete dominance of the affected allele, as well as the one assuming complete recessiveness – were rejected ($p < 0.0001$, in both). Namely, both models are incoherent with the observed data where the pairs of »affected father-healthy daughter« and »affected mother-healthy sons« occurs, which is in contrast with X-linked dominant and X-linked recessive model, respectively. For those two parent-offspring pairs the expected frequency are arbitrarily denoted as different from zero ($= 0.001$) in respective models, assuming new mutations and/or the occurrence of adoptive or non-genetic parent-offspring situations.

On the other hand, the expected frequencies as calculated under other six hypotheses proved not to be significantly different from the observed ones, so not a single model could be statistically rejected. However, it is interesting to note that two co-dominant X-linked models showed a better fit to the data than all four autosomal ones.

Models testing the autosomal inheritance of VA hypoplasia showed the following concordance with the observed data: A) dominant variant $\chi^2 = 14.0325$; $p = 0.0506$; B) recessive $\chi^2 = 10.2018$; $p = 0.1775$; C) co-dominant (50%) $\chi^2 = 5.0924$; $p = 0.6487$; and D) partial recessive (40%) $\chi^2 = 5.9092$; $p = 0.5504$.

The results of the chi-square statistics of the two accepted models of the X-linked inheritance showed that co-dominant (50%) variant C) had $\chi^2 = 4.3654$; $p = 0.7369$, and the variant D), assuming partial recessiveness of the affected allele (40%), shows the smallest differences from the observed ones and had $\chi^2 = 2.0023$; $p = 0.9597$.

Out of all eight proposed models, the expected frequencies of the affected and non-affected offspring (of affected parents) calculated under variant D) of the

X-linked inheritance – assuming the situation where the »healthy« allele is stronger and has a 60% effect on phenotype – almost perfectly describes the observed data.

Discussion

According to our knowledge, this is the first genetic analysis of the VA hypoplasia up to date. Until recently, the head and neck blood vessels could not be non-invasively imaged. The introduction of the color Doppler flow imaging enabled a non-invasive insight into vertebral arteries and the first results of the mean diameters and blood flow were published only in the last decade^{8–11,13}. Such easy and non-aggressive evaluation enabled a visualization of vertebral arteries in the symptom-free population, including the relatives of patients with established VA hypoplasia.

The aim of this preliminary investigation was to try to subject the family data of VA hypoplasia, as a discriminative trait, to various genetic models. According to the previously published ultrasonographic diagnostic criteria of hypoplastic VA, in the sample of 36 affected parents and their affected and non-affected offspring, the mode of monogenetic VA hypoplasia inheritance was assumed, and both autosomal and X-linked inheritance were tested.

However, the observed frequencies of the affected and non-affected sex-specific family pairs (especially the absence of »affected father-affected son« pairs) in addition to the observed distribution of the smaller VA in sons and daughters, pointed to a possible influence of the X-linked inheritance in VA hypoplasia. On the other hand, the presence of 8 healthy daughters of affected fathers under dominant assumption or 5 healthy daughters of affected mothers under recessive one (and in either case there should be none!) could not be disregarded. Thus, it was

clear that if the putative allele determining this condition was located at X chromosome, its effect should be co-dominant. Therefore, four various effects of a putative »hypoplastic« allele (in heterozygous condition) have been proposed (100%, 50%, 40% and 0%) and the same four variants have been tested under the assumption of autosomal inheritance. Calculations of the expected number of sex-specific »affected parent-affected child« pairs have been performed on the basis on the 2.34% prevalence of VA in the Croatian population⁸.

According to the results of the present study, only completely dominant and completely recessive X-linked models could be rejected. However, the presented results also show that VA hypoplasia could be viewed as a condition determined by X-linked allele with a partially recessive major gene effect, since this hypothesis showed the smallest difference from the observed data. The presented findings need to be confirmed by a new analysis that should include a larger family sample and more complete families.

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Conclusion

According to the sample of 36 affected parents and their affected and non-affected offspring, the hypotheses assuming complete dominant and complete recessive X-linked inheritance of an allele determining VA hypoplasia were strongly rejected. However, the hypothesis assuming vertebral artery hypoplasia as a condition determined by an X-linked allele having partially recessive effect showed the best fit to the observed data. Further research encompassing a more complete family sample is needed to confirm the present findings.

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HIPOPLAZIJA VERTEBRALNE ARTERIJE – PO SPOLU SPECIFIČNA UČESTALOST U 36 PAROVA RODITELJA I DJECE

SAŽETAK

Veliki interes za hipoplaziju vertebralne arterije (VA) proizlazi iz njene moguće povezanosti s migrenom s aurom kao i zbog činjenice kako je riječ o jednom od čimbenika rizika za moždani udar. Stoga je cilj ovog preliminarnog istraživanja bio ispitati način nasljeđivanja hipoplazije VA. Početno je Color Doppler VA primijenjen kod 64 člana obitelji 33 probanda (srodnici prvog i drugog stupnja) pri čemu je hipoplazija VA dijagnosticirana prema unaprijed utvrđenim kriterijima. Kako je kod ispitanih članova šire obitelji probanada utvrđena veća prevalencija hipoplazije VA (15,6%) u usporedbi s prevalencijom od 2,34% u općoj populaciji Hrvatske, to je upućivalo na snažnu obiteljsku predispoziciju za razvoj ovog stanja. Stoga je izvršena analiza obiteljskih podataka (Pearsonovom χ^2 statistikom) i to korištenjem po-spolu specifičnih frekvencija 36 parova roditelj-dijete koje su tvorili samo aficirani roditelji (utvrđena VA hipoplazija) i njihova mjerena djeca bez obzira na aficiranost. U ovoj analizi uspoređene su mjerene frekvencije zdrave i aficirane djece aficiranih roditelja te one koje se očekuju pod pretpostavkom 8 predloženih modela. I za autosomno i X-vezano nasljeđivanje pretpostavljen je različiti stupanj dominantnosti aficiranog alela, te su testirane hipoteze koje pretpostavljaju kako osoba koja ima aficirani alel (uz prisutnost zdravog alela) ima: 100%, 50%, 40% te 0% šanse razvoja hipoplazije vertebralne arterije. Među 8 testiranih modela samo su dva odbačena: model koji pretpostavlja potpuno dominantno X-vezano i potpuno recesivno X-vezano nasljeđivanje. Međutim, od 6 modela koji nisu odbačeni, »goodness-of-fit« statistika je pokazala kako X-vezano nasljeđivanje VA hipoplazije pri čemu je »zdravi« alel snažniji (60% učinka) – gotovo savršeno opisuje obiteljske podatke ($\chi^2 = 2.0023$; $df = 7$; $p = 0.9597$). Daljnja istraživanja koja bi uključila veći uzorak obitelji potrebna su kako bi ovdje prikazani nalazi dobili svoju čvršću potvrdu.