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RECURRENT HEADACHE AND MIGRAINE HERITABLITY - TWIN STUDY -

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The aim of the study was to determine recurrent headache (migraine and non-migraine) heritability, among the twin pairs. Headache hritability was investigated among 396 twin pairs (42.4% monozygotic and 57.6% dizygotic) aged 3 to 21 years, on north part territory of Serbia -Vojvodina, during the 20 years period. Within the group of tested twin persons, 30.2% had recurrent headaches, 9.2% migraine headache and 21% other recurrent non-migraine headaches. Heritability quotient of all recurrent headaches was 0.3882. For non-migraine headaches heritability quotient of 0.2286 confirmed that the external factors influence is higher than heritability. Migraine headache heritability quotient 0.8598 clearly proved the heritability of the migraine headache. Both, correlation and determination quotient of the migraine headache of all the twins (r_{12} 0.7498; r^2_{12}56.12%), monozygotic (r_{12}0.8458; r_{12}71.54%) and dizygotic (r_{12}0.6342; r^2_{12}40.22%), show high degree of migraine headache twin siblings dependence, and higher correlation and significance of the difference with monozygotic twins.

Key words: children, twins, headache, migraine, heritability

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INTRODUCTION

Recurrent headache is a common complain, occurring in over 90% of general population. Migraine is the most frequent recurrent headache in children (KNEŽEVIĆ-POGANČEV 2008). The mechanisms underlying the recurrent headache are largly unknown (GARGUS 2009). Recurrent headache seem to be a complex disorder caused by influence of multiple genes and environmental factors (MONTAGNA *et al* 2010; SCHURKS 2008; BASBAUM *et al* 2009; CREGG *et al* 2010). No empirical study has explicitly examined how genetic and environmental factors influence the recurrent headache (DE VRIES *et al* 2008; MONTAGNA 2008; VAN DEN MAAGDENBERG 2010; HERSHEY 2008).

A history of headaches in a family is very frequently noted when evaluating a child for recurrent, headaches. Oftentimes, these headaches have migraine features, although the family may not recognize migraine headache among other family members. Many migraine sufferers have a family history of migraine but the exact hereditary nature of migraine is still being determined. Since the exact cause of migraine is unknown and there are no laboratory based diagnostic tests to identify those who suffer from the disorder, research is vital to migraine sufferers. Although most scientists seem to agree that migraine is caused, in part, by defective genes, the actual types of genes responsible are still not fully understood. Family and twin studies show that there is a genetic component, but no genes predisposing to common forms of the recurrent headache (migraine and non-migraine) have been identified (WESSMAN *et al* 2007; BIGAL 2010). Certain authors take the positive family anamnesis to be one of the diagnostic criteria of the recurrent headache syndrome (CATARCI and CLIFORD-ROSE 1992; WESSMAN *et al* 2007; CHUBAR 1991).
The modern genetic heredity concept suggests multifactor heredity in which several genes take place (RUSSELL 2007; VICTOR *et al* 2010; NATOLI *et al* 2010). This investigation should give a better understanding of migraine and clarification of the diagnostic subtypes for a genotype-phenotype association.

The aim of this research was to determine heritability of recurrent headache (migraine and non-migraine) among the twin pairs, on the territory of Vojvodina.

MATERIALS AND METHODS

A questionnaire study of recurrent headaches (migraine and non-migraine) was carried out in the territory of Vojvodina, Serbia's Northern Province, which has a total population of 2,031,992, according to the last census (in 2002). By the method of random sampling 792 twins (396 twin pairs) aged 7 to 21 years were surveyed. Twin pairs (42.4% monozygotic and 57.6% dizygotic) was tested during the 20 years period (1988-2008), independent of the place of birth, and nationality. During the study, this lasts from 1988 to 2008 the questionnaire was given to the participants in 9 cities in Vojvodina (Novi Sad, Subotica, Kikinda, Zrenjanin, Vrsac, Bela Crkva, Melenci, Futog and Temerin). Children were notified according to their month and year of birth, and the first 3 letters of their first name and surname. This ensured that children could not enter the study twice during the long research period.

The subjects and/or their parents were asked to fill out a questionnaire in their places of residence. Questionnaires were distributed to children and/or their parents. The semi structured questionnaire, which was developed for this study by the author, was designed according to the International Headache Society criteria. It was a screening questionnaire, which was completed by children aged 15–17 years and by parents of younger subjects. It included 3 sections: (1) items about the child's socio demographic characteristics and his/her family; (2) items about the child's development, and (3) items about headaches.

The questionnaire was developed in 3 phases. In the first, semi structured interviews with pediatricians, researchers, teachers and nurses were organized to select relevant domains. The domains for the section about headaches were selected, based on criteria of the International Classification of Headache Disorders – II.
More than 150 possible items were identified. Precise, comprehensive and appropriate items were included in the first form. The possible responses were open-ended options or categorical judgments.

In the second phase, the questionnaire was pretested in semi structured interviews on a small group of children who either did or did not suffer from headaches (16 families were included). This phase aimed to evaluate the face and content validity of the questionnaire. Additionally, the sensitivity was evaluated by correlating the data from the questionnaire and the medical records of the children who had headaches. This phase resulted in a revised version, which was evaluated only on healthy children. Fifty children and adolescents completed the questionnaire twice in 3 weeks. The non response rate, response distributions, graphical response presentation (response inconsistency) and questionnaire burdens (time to complete, formatting, etc.) were analyzed. A number of items were modified or eliminated and the final form included 93 items which required 20 min to complete.

The inclusion criteria were: age 3–17 years, signed informed consent from parents of children to their fifteenth birthday. After 15th birthday children signed informed consent too. The exclusion criterion was a previous diagnosis of a disease that could have headache as a symptom.

The mean age of the study subjects was 9 years and 2.5 months [range 7–21 years, standard deviation (SD) 3.62]. The large number of children surveyed allowed for definite conclusions. The study was conducted in 2 phases: completion of the questionnaire and, for those with recurrent headache a face-to-face interview. Based on data gathered by the questionnaire, children who had according to questionnaire more than 4 episode of head pain during 2 years underwent an extended interview and neurological examination.

The accuracy of the questionnaire used in this survey was based on International Headache Society criteria. Using the society's classification codes, migraine was accepted as 1.1–1.7, migraine with aura was 1.2.2–1.2.6, migraine without aura was 1.1 and other migraine syndromes were 1.3–1.7. Recurrent headache was accepted as all headache types that appeared 1 to 3 times per month, without separating them due to specific characteristics. All types of recurrent

headache (idiopathic or cryptogenic recurrent headaches) that were not migraine were considered as non-migraine headaches (OLESEN 2005).

Prevalence data of the general population for migraine and tension-type headache was obtained from our previous reports (KNEŽEVIĆ-POGANČEV 2006; KNEŽEVIĆ-POGANČEV *et al* 2010). Zygosity was determined according to gender and pregnancy and delivery data obtained from medical documentation.

No one questionnaire has been biased. Separate data according to recurrent headache were analyzed for children who had completely answered the questionnaire.

The demographic, clinical and social characteristics were described by age and sex according to headache presence and type. The Hi ^{2} test, Levin test and ANOVA were used as statistical methods. In corrlative regressive analysis it was determined by calculating the correlation quotient (r_{12}) and the determination quotient (r^2_{12}), for the pairs of data where the number of tested with the migraine headache was taken as a subordinate variable, and a number of tested with someone in the family with the migraine, was taken as an insubordinate variable. A significance level of 5% was used ($p < 0.05$). All statistical analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, Ill., USA).

RESULTS

Within the group of 792 tested twins (396 twin pair: 42.4% (336 of 792) monozygotic and 57.6% (456 of 792) dizygotic) 30.2% (239 of 792) had recurrent headaches, 21% (166 of 792) non-migraine recurrent headaches and 9.2% (73 of 792) migraine syndrome. Within the group of tested twins 9.2% of them have the migraine syndrome (10.1% monozygotic and 8.3% dizygotic).

Table 1 - Presence of headache among twin pairs

Twin // Twin	Without headache		Migraine headaches		Non-migraine headaches	
Type of headache	f	%	f	%	f	%
Without headache	140	**35.4**	77	19.4	100	25.3
Migraine headaches	8	2.0	27	**6.8**	1	0.3
Non-migraine headaches	6	1.5	13	3.3	24	**6.1**
SUM TOTAL	154	38.9	117	29.5	125	31.6

Pearson Chi-Square: V 5732100, DF 4, Sig 0.000001

Likelihood Ratio: V 5747381, DF 4, Sig 0.000001

None of the siblings from the twin pair suffers from the recurrent headaches in 35.4%. Both siblings from the twin pair have the migraine syndrome in 6.8%, and non-migraine headaches in 6.1%. (Table 1. Presence of headache among twin pairs)

Table 2 – Concordance of the twins for headaches, according to types of headaches

Headaches - Twins	Migraine headaches				Non-migraine headaches			
Identical twins	MZ		DZ		MZ		DZ	
Headaches - Twins	f	%	f	%	f	%	f	%
Without headache	16	11.9	61	33.5	43	31.9	57	31.3
Migraine headaches	**16**	**94.1**	**11**	**57.9**	-	-	1	5.3
Non-migraine headaches	8	50.0	5	18.5	**8**	**50.0**	**16**	**59.3**
SUM TOTAL	40	23.8	77	33.8	51	30.4	74	32.5

MZ- monozygotic twins - Likelihood Ratio: V 72.79549, DF 4, Sig 0.000001

MZ- monozygotic twins - Mantel-Haenszel test for linear asocciation: V 10.29850, DF 1, Sig 0.00133

DZ- dizygituc twins - Likelihood Ratio: V 17.85186, DF 4, Sig 0.00132

DZ- dizygotic twins - Mantel-Haenszel test for linear association: V 3.24775, DF 1, Sig 0.07152

The concordance for the migraine syndrome is 94.1% for monozygotic twins and 57.9% for dizygotic ones, a significant difference ($p<0.05$). The heritability quotient for the migraine syndrome with monozygotic twins was calculated by using Holzinger`s formula and it is 0.8598. The concordance for the non-migraine headaches is 50.0% for monozygotic and 59.3% for dizygotic twins. The heritability quotient is 0.2285, and it clearly negates the influence of heredity on the non-migraine headaches.

The concordance for the recurrent headaches was 64.7% for monozygotic and 42.3% for dizygotic twins. Holzinger`s formula was used to calculate the heritability quotient which was 0.3882.

Viewing the twin pairs separately the highest concordance (45.5%) is recorded in the group of monozygotic twins where none of the siblings from the twin pair has recurrent headache. In the group of dizygotic twins, the highest concordance is recorded for siblings from the twin pair where one of them does not have headache while the other one has the migraine headache (29.7%), non-migraine (27.9%) or does not have the headache at all (27.9%)

The probability of appearance of a headache according to type with the other sibling was calculated by analyzing the twin sample structure. The probability that one of the siblings will not have the recurrent headache if the other sibling does not have it as well, is 0.72 for monozygotic and 0.50 for dizygotic twins. If one of the siblings does not have the migraine syndrome, probability that the other one will not have it either, is 0.91 for monozygotic, and 0.79 for dizygotic twins. Probability that the child, whose twin sibling does not have the non-migraine headaches, will not have them either is 0.81 for monozygotic, and 0.68 for dizygotic twins.

Table 3. Concordance of twins according to types of headaches

Twins according to zygotes	The relation of the types of headaches (I : II twin)	Headache group f	%
MZ – presence and type of headache	there isn't – there isn't	76	45.5
	there isn't – non migraine	17	10.2
	migraine - migraine	16	9.6
	migraine - others	8	4.8
	others – there isn't	42	25.1
	others - others	8	4.8
DZ-presence and type of headache	there isn't – there isn't	64	27.9
	there isn't - migraine	68	**29.7**
	migraine - migraine	11	4.8
	migraine - others	6	2.6
	others – there isn't	64	27.9
	others - others	16	7.0
SUM TOTAL – presence and type of headache	there isn't – there isn't	140	35.4
	there isn't - migraine	85	21.5
	migraine - migraine	27	6.8
	migraine - others	14	3.5
	others – there isn't	106	26.8
	others - others	24	6.1

Table 4 – Twin headaches demonstration probability in headaches structure (% of probability within the structure= 1/100)

Probability of demonstration of headaches in structure	1st twin	2nd twin	Recurrent headaches		Migraine headaches		Non-migraine headaches	
	Headache presence		f	%	f	%	f	%
MZ-demonstration of headaches	**+**	**+**	152	**0.72**	254	**0.91**	218	**0.81**
	-	**-**	64	**0.52**	32	**0.56**	16	**0.24**
DZ-demonstration of headaches	**+**	**+**	128	**0.50**	286	**0.79**	286	**0.68**
	-	**-**	66	**0.34**	22	**0.23**	32	**0.32**
SUM – demonstration of headaches	**+**	**+**	280	**0.6**	540	**0.85**	504	**0.81**
	-	**-**	130	**0.4**	54	**0.35**	48	**0.28**

Dependence of the migraine syndrome of one twin on the migraine syndrome of the other was calculated through the correlation (r_{12}) and determination (r^2_{12}) quotient, by method of covariant. The correlation quotient (cq) of the migraine syndrome of all the twins is 0.7498; 0.8458 for monozygotic and 0.6342 for dizygotic. The determination quotient (dq) of the migraine syndrome for the twins in general is 56.12%; 71.54% for monozygotic, and 40.22% for dizygotic twins (Table 5. Results of correlation analysis).

Table 5. Results of correlation analysis

Twins	All twins	Monozygotic	Dizygotic
Correlation quotient r_{12}	0.7498	0.8458	0.6342
Determination quotient r^2_{12}	56.12%	71.54%	40.22%

DISCUSSION

It is very hard to study genetics of the recurrent headache and migraine syndrome. In the family anamnesis data, there are no precise data on types of headaches within the family. We do not recognize headaches in family data or they are defined as "recurrent headaches similar to ones found among the members of the tested group". Comparison and analysis of the twin pairs give us the complete genetic analysis, having in mind that clear data on headaches, as well as precisely defined type of headache, exist for both siblings in the twin pair. Genetic-heritability of the migraine syndrome can be investigat by analyzing the headaches of the twin pairs

All existing studies have been characterized by one or more of the following methodologic shortcomings: selection of probands from clinic populations, information obtained by questionnaire, family history obtained through probands, insufficient description of the attacks, and lack of distinction between headache types. Useful strategies for future studies of migraine genetics shell be discussed.

Svenston in the group of 372 twins with recurrent headache did not find zygosity as a significant predictor for migraine, as we did. He did not find twin-singleton or monozygotic-dizygotic difference for the risk of migraine. In tension-type headache, he described twins seem to have a lower risk than singletons, and this is especially true for monozygotic twins (SVENSSON *et al* 2002). Zeigler et al suggested that approximately 50% of the variance in liability to migraine was attributable to genetic factors with nonshared environmental factors and measurement errors responsible for the remaining variance (ZIEGLER *et al* 1998). Autor determined probandwise concordance rates. Assuming that liability to migraine has a multifactorial etiology involving a number of genetic and environmental risk factors acting additively, they described tetrachoric correlations in the four groups of twins (monozygotic raised together, monozygotic raised apart, dizygotic raised together, and dizygotic reised apart) were then calculated. Tetrachoric correlations for migraine were consistently higher in monozygotic than

in dizygotic twins, for both reared together and reared apart samples, with a heritability estimate of 52%.

A family history of migraine is very frequently noted when evaluating a child for recurrent headaches. This implies an inherited or genetic basis as a component to the underlying pathophysiology. A variety of techniques have begun to elucidate this contribution, including historical observation, population-based studies including family and twin studies, gene polymorphism association studies, and specific gene identification for isolated migraine subtypes. VIBEKE *et al* by analyses of twins described environmental influence as of major importance for episodic tension-type headache and a genetic factor, if it exits, as minor, as well as we found it in our group of non-migraine headaches (VIBEKE *et al* 2004). Their data clearly separate episodic tension-type headache from migraine without aura where the phenotypic variation consists of non-shared environmental effects of 39% and of 61% additive genetic effects. Although tension-type headache and migraine are the two most common types of headache in children and adolescents, most articles address migraine headache. ANTILLA found prevalence of non-migrainous headache is 10–25% in childhood and adolescence (ANTILLA 2006). Our results are very simillar.

RUSSELL *et al* (2007) investigated the importance of genetic and environmental factors in tension-type headache using a genetic modeling analysis, in twins 12–41 years of age, from the population based Danish Twin Registry. They also used a validated posted questionnaire about tension-type headache and migraine. Their quantitative genetic modeling included 2,437 monozygotic, 2,720 same gender dizygotic, and 2,203 opposite gender dizygotic twin pairs without co-occurrence of migraine. They found polychoric correlations were significantly higher in monozygotic than same gender monozygotic twin pairs analyzed separately by gender, while polychoric correlation were higher in same gender than opposite gender monozygotic twin pairs, although this was not significant in the comparison with male same gender monozygotic twin pairs. In Russell et al study heritability estimates of 48% in men and 44% in women were obtained (RUSSELL *et al* 2007). In our twin grpup concordance rates for migraine in Monozygotic (MZ) twins was 94.1% and in Dizygotic (DZ) twins 57.9%, a significant difference ($p < 0.05$). The concordance rate for migraine in male and female twins was not significantly different.

Concordance rates for individual symptoms (e.g. unilaterality, vomiting) did not reveal any particular feature with a markedly higher genetic loading. Results from inter-twin comparisons, taken with family history data, suggested that in some cases migraine may be significantly associated with recurrent childhood vomiting, eczema and travel sickness, but not with epilepsy or asthma (KNEŽEVIĆ-POGANĆEV 2003).

The primary recurrent headaches (migraine with and without aura and cluster headache) all carry a substantial genetic liability. Migraine with and migraine without aura are considered multifactorial genetic disorders, and familial hemiplegic migraine has been usually proposed as a model for migraine aetiology. Familial

hemiplegic migraine genes are not involved in the typical migraines and that familial hemiplegic migraine should be considered as a syndromic migraine rather than a subtype of migraine with aura (MONTAGNA 2010).

When viewed as a whole, the migraine syndrome is more present within the twin group. Most often only one of the sibling from the same twin pair has the recurrent headache (48.2%). In 16.4% of twin pairs, both siblings have the recurrent headaches (migraine syndrome in 6.8%, and non-migraine headaches in 6.1%). Individually, 108 twin siblings (13.64%), have the migraine syndrome. By comparing the same age groups (aged 3 to 17 years), according to data obtained by (KNEŽEVIĆ-POGANČEV 2003), for the territory of Vojvodina, higher presence of the migraine syndrome among the twin pairs was detected (9.2%), in comparison to the rest of the observed population (8.63%), which speaks in favor of the genetic determination of the migraine syndrome. Within the group of tested twins 9.2% of them have the migraine syndrome (10.1% monozygotic and 8.3% dizygotic). Among monozygotic twins where one of them has the migraine syndrome, the other one does not have the headaches in 0.6%, and in 9.5% has the migraine syndrome. Among dizygotic twins where one of them has the migraine syndrome and the other one has not headaches in 3.1%, and in 4.8% has migraine headaches. All recurrent headache, especially migraine in twins shows stronger ties between monozygotic than dizygotic twins. When viewing the twin pairs separately, there are no statistical differences in relation of migraine to non-migraine headaches according to degree of being identical (Sig 0.7). The probability of appearance of a headache according to type with the other sibling was calculated by analyzing the twin sample structure. The probability that one of the siblings will not have the recurrent headache if the other sibling does not have it as well is statistic significant higher for monozygotic twins, with widest distance for migraine (072:0.50 for all recurrent headaches; 0.91: 0.77 for migraine syndrome; 0.81:0.68 for non-migraine headaches). This also clearly confirms very high hereditability of the migraine syndrome.

CONCLUSION

The migraine syndrome of one twin is directly dependent on the migraine syndrome of the other. This mutual dependence is different for monozygotic and dizygotic twins. The analysis of such mutual influence was calculated through the correlation (r_{12}) and determination (r^2_{12}) quotient, by method of co-variant. The very high correlation quotient of the migraine syndrome of all twins 0.7498 the is (0.8458 of monozygotic and 0.6342 of dizygotic) and the determination quotient of the migraine syndrome for all the twins 56.12% (71.54% for monozygotic, and 40.22% for dizygotic twins) show that the high degree of mutual dependence between the migraine syndromes of twin siblings, is more important with monozygotic twins.

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NASLEDLJIVOST REKURENTNIH GLAVOBOLJA I MIGRENE - STUDIJA BLIZANACA-

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I z v o d

Cilj istraživanja je determinisanje nasledljivosti rekurentnih glavobolja (migrenskih i drugih primarnih rekurentnih (nemigrenskih) glavobolja) u populaciji blizanaca. Nasledljivost glavobolja je ispitivana u grupi od 396 blizanačkih parova (42.4% jednojajčanih i 57.6% dvojajčanih), uzrasta od 3 do 21 godine. Istraživanje je sprovedeno u severnoj pokrajini Srbije - Vojvodini u dvadesetogodišnjem periodu. U grupi ispitanih blizanaca 30.2% je imalo rekurentne glavoobolje, 9.2% migrenskog tipa i 21% druge primarne rekurentne glavobolje. Koeficijent nasledljivosti svih rekurentnih glavobolja je bio 0.3882. Koeficijent nasledljivosti nemigrenskih glavobolja 0.2286 potvrđuje viši značaj spoljašnjih faktora od naslednih faktora na pojavu nemigrenskih glavobolja. Koeficijent nasledljivosti migrenskih glavobolja 0.8508 jasno potvrđuje značaj nasleđivanja za pojavu migrenskih glavobolja. Koeficijenti korelacije i determinacije migrenskih glavobolja u grupi opserviranih blizanaca (r_{12} 0.7498; r^2_{12}56.12%), kao i grupi jednojajčanih (r_{12}0.8458; r_{12}71.54%) i dvojajčanih blizanaca (r_{12}0.6342; r^2_{12}40.22%) jasno pokazuju visoku međuzavisnost pojave migrenskih glavobolja u grupi blizanaca u celini, sa značajno višom korelacijom i signifikantnom značajnošću razlike u grupi jednojajčanih blizanaca.

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