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RECURRENT HEADACHE AND MIGRAINE WITHIN THE FAMILY

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The aim of this research was to determine risk for family appearance of the recurrent headache (non-migraine and migraine). The recurrent headache can be understood as being a heterogeneous state, consisting of some more, still not found, hereditary disposition factors which altogether, interacting with surrounding factors give the recognizable clinical picture. The current heredity concept suggests multifactor heredity. The research was conducted in Vojvodina, the Northern Province of Serbia. The population of Vojvodina is around 2 million people belonging to more than 20 different ethnic groups. During the 20 years period (1988-2008), 30363 children aged 3 to 17 years were tested, independent of the place of birth. The presence of headaches similar to those tested was compared among all the members of the family within three generations.

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Positive family data of the recurrent headaches was detected among 98,6% children with migraine headaches, 64,7% children with non-migraine headaches, and 32,4% children without recurrent headaches. The relation among the members of the nuclear family (contingency quotient of 0,429) is significantly stronger than the relation to the members of wider family (contingency quotient of 0,338).

The probability of a child having the migraine headache, and not the non-migraine one, is 0,664 for a mother, 0,644 for a father, 0,411 for a father`s mother, - 0,175 for a mother`s mother, 0,165 for a mother`s father, and - 0,102 for a father`s father having similar recurrent headaches.

Key words: family, migraine, recurrent headache.

INTRODUCTION

The recurrent headache syndrome can be understood as being a heterogeneous state, consisting of some more, still not found, hereditary disposition factors which altogether, interacting with other surrounding factors, give the recognizable clinical picture (KNEŽEVIĆ-POGANČEV 2008). 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 current hereditary concept suggests multifactor heredity (SVENSON *et al.,* 2004; GARDEN 2006).A positive family headache anamnesis among the first degree cousins is described in 56-90% children with recurrent headache, but among 18% children without recurrent headache as well (RUSSELL and OLESEN, 1995). Prensky finds the positive migraine family anamnesis among 44-87%, Bille 78.1%, Barlow 79,5%, and Congdon and Forsythe 17,8% (BILLE, 1962; KNEŽEVIĆ-POGANČEV, 2006). In 1930, Allen described the migraine among 83% children coming from families where both mother and father suffer from migraine, while Baier and Doose found it among 28% of children whose siblings suffer from migraine (ALLEN, 1939). In 90% of the cases, children with migraine have parents and either a brother or/and a sister suffering from the migraine. Therefore, the negative family anamnesis questions the validity of the diagnose (MARJANOVIĆ et a.,l 1988; KNEŽEVIĆ-POGANČEV, 2003). The existence of the positive family anamnesis is not really helpful in diagnosing the migraine, knowing that even up to 50% of children have the positive migraine family anamnesis both with the first and second degree relatives (RUSELL et al., 1993; 1995;1996). Goodell and Wolf wrote about the somatic recessive heredity in 1954th, Barolin and Linet wrote in 1991. about the dominant heredity with higher probability of penetration among womens (GOODELL and MOTULSKY, 1982; RUSSELL, 2007). The modern genetic heredity concept suggests multifactor heredity in which several genes take place (RUSSELL, 2007; VICTOR et al., 2010; NATOLI et al., 2010).

MATERIALS AND METHODS

This research 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). During the study, this lasts from 1988 to 2008 the questionnaire have been given to the participants, drawn from 23 preschools and 42 grade schools in 9 cities in Vojvodina (Novi Sad, Subotica, Kikinda, Zrenjanin, Vrsac, Bela Crkva, Melenci, Futog and Temerin). In total, 30,636 children aged 3–17 years were surveyed (15,202 girls and 15,434 boys). Children were sampling by multistage, stratified, clustered sampling procedure. 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 3–17 years, standard deviation (SD) 3.44]. 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).

Of the questionnaires, 4.5% may have been biased, due to possible double interview and missing data in the questionnaires. Separate data according to recurrent headache were analyzed for children who had completely answered the questionnaire.Heredity of the recurrent headache was investigated by analyzing and comparing the presence of the recurrent headache similar to those of the children examined, within their families. The family was analyzed through three generations. The headaches were defined as "recurrent headaches similar to ones found among the members of the tested group". Out of 30,636 questionaries, complete data for headache presence in family members of three generations have been reported from 10616 questionaries. Only questionaries having clear data about headaches in family members of three generation have been further analyzed, to avoid wrong conclusion reporting "not known data" as "not hawing headaches".

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

Positive family anamnesis for the recurrent headaches similar to those of the tested, was found among 98,6% of children with the migraine headaches, 64,7% of children with non-migraine headaches, and 32,4% of children without headaches. Recurrent headaches similar to those of the tested children were found for children with migraine headaches among 50,5% of father`s sister daughter's and 43,7% of mother`s brother daughter's. Mothers of children with migraine headaches have similar headaches among 42,4% children, father`s sister among 41,2%, fathers in 40,7%, mother`s sisters in 36,5%, and mother`s sister's daughters in 29,4%. Recurrent headaches similar to those of the tested children were found for children

with non-migraine headaches among 30,3% of father's sisters, 25,2% of mother's fathers, 22,2% of mother's mothers, and 19,4% of mothers (Table 1).

Table 1. Headaches according to headache types in the family (group table)

Headaches within family		No headaches		Migraine headaches		Non-migraine headaches	
	f	f	%	f	%	f	%
Family	10616	5642	32,4	2045	98,6	2929	64,7
Father	1449	436	2,5	844	40,7	169	3,7
Mother	3114	1355	7,8	880	42,4	879	19,4
Brother	37	20	0,6	9	1,4	8	0,4
Sister	100	35	0,5	31	2,9	34	2,3
Mother`s brother	153	35	0,3	93	13,2	25	1,2
Mother`s brother son	84	20	0,3	60	11,9	4	0,3
Mother`s brother daughter	284	116	40,8	124	43,7	44	15,5
Father`s brother	15	1	0,0	13	1,7	1	0,0
Father`s brother son	41	7	0,4	30	4,3	4	0,1
Father`s brother daughter	94	12	0,6	69	11,9	13	1,3
Father's sister	2260	816	7,1	531	41,2	913	30,3
Father's sister son	293	18	0,2	104	8,2	171	7,3
Father's sister daughter	372	120	3,2	203	50,5	49	4,1
Mother's sister	890	108	1,4	567	36,5	215	10,8
Mother's sister son	164	41	0,8	100	8,3	23	1,5
Mother's sister daughter	451	90	2,5	273	29,4	88	10,2
Father's father	592	495	2,8	60	2,9	37	0,8
Mother`s father	1206	1013	5,8	106	5,1	87	1,9
Father's mother	3377	2212	12,7	416	20,1	993	22,0
Mother`s mother	3501	1945	11,2	172	8,3	1140	25,2

Family- Pearson Chi Square: V 4254.30333, DF 2,p< 0.000001

Father-Pearson Chi Square: V 4824.25269, DF 2, p< 0.000001

Mother- Pearson Chi Square: V 2181.56353, DF 2, p< 0.000001

Brother- Pearson Chi Square: V 9.93742, DF 2, p< 0.000001

Sister- Pearson Chi Square: V 70.35145, DF 2, p< 0.000001

Mother`s brother - Pearson Chi Square: V 1025.68103, DF 2, p< 0.000001

Mother`s brother son - Pearson Chi Square: V 672.23356, DF 2, p< 0.000001

Mother`s brother daughter - Pearson Chi Square: V 755.61174, DF 2, p< 0.000001

Father`s brother - Pearson Chi Square: V 94.78743, DF 2, p< 0.000001

Father`s brother son - Pearson Chi Square: V 132.12956, DF 2, p< 0.000001

Father`s brother daughter - Pearson Chi Square: V 236.62961, DF 2, p< 0.000001

Father's sister - Pearson Chi Square: V 1721.28723, DF 2, p< 0.000001

Father's sister son - Pearson Chi Square: V 613.19068, DF 2, p< 0.000001

Father's sister daughter - Pearson Pearson Chi Square: V 656.76297, DF 2, p< 0.000001

Mother's sister - Pearson Chi Square: V 2543.35810, DF 2, p< 0.000001

Mother's sister son- Pearson Chi Square: V 259.00467, DF 2, p< 0.000001

Mother's sister daughter - Pearson Chi Square: V 1314.54910, DF 2, p< 0.000001

Father's father - Pearson Chi Square: V 62.78691, DF 2, p< 0.000001

Mother`s father - Pearson Chi Square: V 113.83140, DF 2, p< 0.000001

Father's mother - Pearson Chi Square: V 317.79623, DF 2, p< 0.000001

Mother`s mother - Pearson Chi Square: V 624.67300, DF 2, p< 0.000001

Based on the correlation between the discriminating variables, and standardized by canonical discrimination of the determined functions, the member of the family if suffers from headaches similar to a child's, the probability of a child to have the migraine headache, and not the non-migraine one, is 0,664 if mother suffers from headaches similar to a child's, 0,644 if father suffers from headaches similar to a child's, 0,411 if father`s mother suffers from headaches similar to a child's, 0,175 if mother`s mother suffers from headaches similar to a child's, 0,165 if mother`s father suffers from headaches similar to a child's, and 0,102 if father`s father suffers from headaches similar to a child's (Table 2).

Table 2. The factor structure matrix (canonical discriminative analysis) of the positivist of the family anamnesis for the migraine and non-migraine headaches.

Headaches	Migraine // other headaches
Mother	0,664
Father	0,644
Father's mother	0,411
Mother's mother	0,175
Father's father	-0,165
Mother's mother	-0,102

Based on the presence of recurrent headaches in the family of the children with headaches, and according to type of the child's headache, a correlative regressive analysis was done. 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. The correlation quotient of the migraine headache from the family as a whole to a child is 0,9653, and the determination quotient for the migraine headache from the family to a tested one, is 93,17%, which clearly shows that the family as a whole has the strongest influence on appearance of the migraine headache (Table 3).

When viewed individually, members of the first degree cousins and second degree cousins have the most significant influence: mother, brother, sister and grandparents from both parents side. The significant ones from the members of second degree cousins are mother`s brother daughter, father`s sister, and father`s sister daughter.

Table 3. Regressive correlation analysis of hereditability of the migraine headache from ancestors onto descendants

Family/ tested person	r_{12}	r^2_{12}
Family/ tested person	0,9653	93,17%
Father	0,3897	15,19%
Mother	0,9000	81,00%
Brother	0,9737	94,81%
Sister	0,7467	55,71%
Mother`s brother	0,1507	2,27%
Mother`s brother son	0,0653	0,43%
Mother`s brother daughter	0,8479	71,89%
Father`s brother	- 0,2266	5,13%
Father`s brother son	- 0,1504	2,26%
Father`s brother daughter	- 0,1820	3,31%
Father's sister	0,7041	49,58%
Father's sister son	- 0,0884	0,78%
Father's sister daughter	0,5771	33,30%
Mother's sister	- 0,1913	3,66%
Mother's sister son	0,1830	3,35%
Mother's sister daughter	0,0504	0,25%
Father's father	0,9800	96,04%

By analyzing the correlation and determination quotients, it has been managed to clearly separate those family members whose type of headache is more influent in appearance of the migraine headaches, from the ones whose influence is irrelevant. "Clearer" perceiving of these influences and surpassing the possible effects of multi co-linearity was enabled by application of non-parametric tests, above all, tests for the markers independence (Table 4).

Table 4. Non-parametric test of the independent markers for both nuclear and wider family (empirical frequencies)

Type of headache / family member	Mother	Father	Brother	Sister	father`s father	mother's father	father`s mother	mother`s mother	TOTAL
Without headache	1355	436	20	35	495	1013	2212	1945	7511
Migraine headaches	65	37	0	6	0	12	11	59	190
Non-migraine headaches	879	169	8	34	37	87	993	1140	3347
Total	3114	1449	37	100	592	1206	3377	3501	13776

Calculated value for X_0^2 is 3016,239 with 1% risk of error, and it confirms mutual dependence, i.e. the influence of the presence of recurrent headaches similar to those of the tested among the relatives, on the appearance of the migraine syndrome with children. The contingency quotient (C) of 0,429 confirms the direct existence of the influence of recurrent headaches similar to those of the tested within

the nuclear and wider family, on the migraine in children. The confirmation of presence of the influence of recurrent headaches similar to those of the tested on the appearance of the migraine in mother`s brother`s daughter, father`s sister and father`s sister`s daughter gives the contingency quotient 0,338.

Calculated value for F (F_{0A}=5.385) with 1% risk of error, confirms that the existence of the presence of recurrent headaches similar to those of the tested among the members of nuclear and wider family, statistically highly influences the appearance of the migraine with the tested children, i.e. that the migraine s is inheritable directly from the members of both nuclear and wider family (Table 5).
High correlation and determination quotients for certain relatives, required the evaluation of their actual place in heredity of the migraine, and excluding the errors due to multi co-linearity, by analyzing the variant (Table 6).

Table 5. Table for calculating the variants with one variability factor
Hereditability of the migraine syndrome with the members of both nuclear and wider family members

Sum total of the square of deviation	Number of degrees of freedom	Evaluated variants	Relation of the variants	Table value
S_A = 4371334.3	4	V_A=1092833.5	F_{0A}=5.385	F_{0A} (0.01;4;35)=3.925
S_R= 7103122.0	35	V_R=202946.34		
ST= 11474456.0	39			

Table 6. Table for calculating the variants with one variability factor. Hereditability of the migraine syndrome from the relatives who showed high correlation quotient

Sum total of the square of deviation	Number of degrees of freedom	Evaluated variants	Relation of the variants	Table value
S_A = 254818	4	V_A=637045	F_{0A}=5.578	F_{0A}
S_R= 799477	7	V_R=114211		(0.01;4;35)=7.85
S_T= 1054295	11			

Calculated value for F (F_{0A}=5.578) with 1% risk of error, confirms that the headaches of relatives who showed high correlation quotient due to excluding multi co-linearity which exists between the headaches of ancestors and descendants (and which was displayed through the correlation quotient), still does not significantly statistically influence the migraine headache of the tested group. Clear is the direct heredity of the migraine headache from the members of nuclear family (mother, father, brother, sister), members of wider family (grandparents from both sides), even some relatives (mother`s brother`s daughter, father`s sister, father`s sister`s daughter), but still, the relation among the members of nuclear and wider family (correlation quotient C= 0,429) is significantly stronger than the one with other relatives (correlation quotient C= 0,338).

DISCUSSION

It is very hard to study heredity of the recurrent headache. In the family anamnesis data, there are usually 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". Recurrent headaches of the children show significant but low heredity in general (heredity quotient 0.3882). The heredity of migraine headaches (with correlation quotient of 0.8598) is highly significant, while the influence of environmental factors on the appearance of non-migraine headaches is dominant (heredity quotient 0.2285) (KNEŽEVIĆ-POGANČEV, 2003; 2008).

By comparing the same age groups (aged 3 to 17 years), according to data obtained 2001, for the territory of Vojvodina, higher presence of the migraine among the twin pairs was detected (9,2%), (10,1% identical and 8,3% non-identical) in comparison to the rest of the observed population (8,63%), which speaks in favor of the genetic determination of the migraine (KNEŽEVIĆ-POGANČEV, 2003; KNEŽEVIĆ-POGANČEV *et al*., 2010). All recurrent headache, especially migraine in twins shows stronger ties between identical than non-identical twins. The correlation and determination quotient of the migraine headache of all the twins (r_{12}0.7498; r^2_{12}56.2%), identical (r_{12}0.8458; r^2_{12}1,54%) and non-identical (r_{12}0.6342; r^2_{12}40,22%), clearly show a very high degree of mutual dependence between the migraine headache of the twin siblings (KNEŽEVIĆ-POGANČEV .2003). They also show higher dependence and importance of the difference with identical twins, thus confirming the heredity of the migraine headache (LARSON *et al*., 1995; HONKASALO, 1999).

The heredity of liability to self-reported migraine and non-migrainous headaches was examined in two large cohorts from the Swedish Twin Registry consisting of 6448 (the older cohort) and 12 884 (the younger cohort) like-sexed twin pairs (SVENSSON *et al*., 2003). The results of structural equation model-fitting analyses showed that genetic effects for migraine headaches were stronger for the females (estimates ranging from 49% to 58%) than for the males (39% to 44%) in the two cohorts (LARSSON *et al.,* 2005). Unique non shared environmental effects were greatest for the "mixed" group in both sexes (estimates ranging from 60% to 69%)(LARSSON *et al.,* 2005). The results are discussed in view of similar large-scale twin studies examining the heredity of liability to migraine (LARSSON *et al.,* 2005; KNEŽEVIĆ-POGANČEV, 2003).

Recurrent headache and migraine is clearly a complex disease characterized by high population prevalence, an inconclusive mode of transmission, and a lack of clear evidence for phenotypic validity. Increasing knowledge from family and twin studies using contemporary diagnostic methods will help to clarify the factors contributing to the heterogeneity of this condition (SVENSSON *et al*., 2004).

CONCLUSIONS

Recurrent headaches in general and non-migraine headaches show no direct heredity from the members of nuclear and/or wider family. The migraine headache is directly heritable from the members of the nuclear family (mother, father, brother, sister), members of wider family (grandparents from both sides), even second degree relatives (mother`s brother`s daughter, father`s sister, father`s sister`s daughter), but still, the relation among the members of nuclear and wider family (second degree relatives) is significantly stronger than the one with other relatives.

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PORODIČNA POJAVA RECIDIVNIH GLAVOBOLJA I MIGRENE

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Cilj istraživanja je bio utvrđivanje prisutnosti i verovatnoće porodične pojave recidivnih glavobolja (nemigrenskih i migrenskih). Recidivne glavobolje mogu biti shvaćene kao heterogeno stanje sa nekim, još uvek neotkrivenim naslednim predisponirajućim faktorima, koji u interakciji sa faktorima okoline daju prepoznatljivu kliničku sliku. Današnji koncept nasleđivanja recidivnih glavobolja (migrenskih i ne-migrenskih) sugeriše multifaktorijelni način nasleđivanja.Nasleđivanje recidivnih glavobolja je ispitivano u Vojvodini, u kojoj živi populacija od oko 2 miliona ljudi različitog etičkog porekla (preko 20 različitih etičkih grupa). Ispitivanje je sprovedeno u periodu od 1988 do 2008 godine na uzorku od 30363 dece uzrasta 3-17 godina, prema mestu boravka, nezavisno od mesta rođenja. Komparirano je prisustvo glavobolja sličnih glavoboljama ispitanika kod svih članova porodice u tri generacije. Pozitivna porodična anamneza za recidivne glavobolje je prisutna kod 98,6% dece sa migrenskim glavoboljama, 64,7% dece sa nemigrenskim glavoboljama, ali i kod 32,4% dece koja nemaju recidivne glavobolje. Povezanost pojave recidivnih glavobolja je značajno snažnija kod članova uže porodice sa koeficijentom kontingencije 0,429 u odnosu na članove šire porodice sa koeficijentom kontingencije 0,338. Verovatnoća da će dete imati migrensku a ne nemigrenski glavobolju iznosti 0,664 ukoliko slične recidivne glavobolje ima majka, 0,644 ukoliko ih ima otac, 0,411 ukoliko ih ima baka po ocu, -0,175 ukoliko ih ima baka po majci, 0,165 ukoliko ih ima ded po majci i -0,102 ukoliko ih ima ded po ocu.

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