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Relationship between PON1 phenotype and headache duration in migraine patients

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Aim: The available data on the activity of paraoxonase-1 (PON1) in patients suffering from migraine without aura (MWoA) is scarce. The present study was conducted to fulfill the objective of investigating the probability of an association between PON1 phenotype distribution and headache duration in patients suffering from MWoA.

Materials and methods: Seventy-six patients who suffer from MWoA and were not experiencing attacks at the time and 65 healthy volunteers were enrolled for the purpose of evaluation in the present study.

Results: The levels of serum paraoxonase, arylesterase activities, and lipid hydroperoxide (LOOH) were determined for these subjects. The results obtained revealed that no statistical differences existed between the group suffering from MWoA and the control group with respect to the PON1 activity and the phenotype distribution (all values of $P > 0.05$), while the levels of serum LOOH were noted to be higher ($P < 0.05$) in the patient group. However, a significant relation was found between the $PON1_{192}QR$ phenotype distribution and headache duration in patients suffering from MWoA ($P < 0.001$). It was observed that patients with the $PON1_{192}RR$ (BB = homozygous high activity) polymorphism had headaches of shorter duration than patients with the $PON1_{192}QQ$ (AA = homozygous low activity) and $PON1_{192}QR$ (AB = heterozygous intermediate activity) polymorphisms. Along with these results, significant negative correlations were found between the ratio of salt-stimulated paraoxonase/arylesterase and headache duration (r: -0.40, $P < 0.001$) in patients suffering from MWoA in comparison to the control group. Finally, the activities of both paraoxonase and arylesterase were found to be inversely correlated with the levels of serum LOOH in the patient group [(r: -0.23, $P < 0.05$) and (r: -0.27, $P < 0.05$), respectively].

Conclusion: The results ascertained through the present study suggest that a significant correlation exists between PON1 phenotype distribution and headache duration in patients suffering from MWoA. Additionally, to the best of our knowledge, this is the first study to evaluate the association between PON1 polymorphism and headache duration in patients with migraine. PON1 phenotype distribution will play a key role in headache duration in patients with migraine.

Key words: Paraoxonase, arylesterase, phenotype, lipid hydroperoxide

Migrenli hastalarda PON1 fenotip ile başağrısı süresi arasındaki ilişki

Amaç: Aurasız Migrenli hastalar ile paraoksanaz-1 aktivitesi arasındaki bilgiler yok denecek kadar azdır. Bizler bu çalışmamızda aurasız migrenli hastalarda PON1 fenotipik dağılım ile baş ağrısı süresi arasındaki ilişkiyi ortaya koymaya çalıştık.

Yöntem ve gereç: Bu çalışmaya 76 tane aurasız migrenli hasta ile hayatlarının herhangi bir döneminde hiç migren atağı geçirmemiş 65 gönüllü sağlıklı hasta dahil edildi.

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Bulgular: Her iki gruptada serum paraoksonaz/arilesteraz aktivitesi ve lipid hidroperoksitleri ölçüldü. Elde edilen sonuçlar değerlendirildiğinde hasta grubunda lipid hidroperoksitlerinde belirgin bir artış gözlenirken ($P < 0,05$), PON1 fenotip dağılımı ve paraoksanaz/arilesteraz aktiviteleri her iki gurup arasında istatistiksel olarak herhangi bir fark yoktu ($P > 0,05$), Ancak, hasta grubunda PON1 fenotip dağılımı ile başağrısı süresi arasında anlamlı bir ilişki tespit edildi ($P < 0,001$). Böylece, $PON1_{192}RR$ (BB = homozigot yüksek aktivite) polimorfizimine sahip olan hastalarda başağrısı süresi $PON1_{192}QQ$ (AA = homozigot düşük aktivite) ve $PON1_{192}QR$ (AB = heterozigot orta düzey aktivite) polimorfizimine sahip hastalarda daha kısa süreli olarak gözlemlendi. Bu sonuçlarla ilişkili olarak salt stimulated paraoksanaz/arilesteraz oranı ile aurasız migrenli hastalardaki başağrısı süresi ile anlamlı derecede bir koreleasyon tespit edildi ($r : -0,40$; $P < 0,001$). Ayrıca hasta grubunda hem paraoksanaz hem de arilesteraz aktiviteleri, lipid hidroperoksitleri ile ters bir şekilde korele idi (sırasıyla, [($r : -0,23$; $P < 0,05$); ($r : -0,27$; $P < 0,05$)].

Sonuç: Bu çalışmada elde edilen sonuçlar değerlendirildiğinde; aurasız migrenli hastalarda başağrısı süresi ile PON1 fenotipik dağılım arasında anlamlı bir korelasyon tespit edildi. Buna ilaveten, Bizim bilgilerimize göre böyle bir çalışma ilk kez bizim tarafımızdan yapılmış olup, PON1 fenotipik dağılımın migren başağrısı süresinde önemli bir rol alabileceğini ortaya koymaktadır.

Anahtar sözcükler: Paraoksanaz, arilesteraz, fenotip, lipid hidroperoksit

Introduction

Migraine is a complex disorder that incorporates certain neuronal and vascular disturbances within itself. The exact mechanism that represents the pivotal step in the etiology of the headache and the reason women are 3 times more susceptible to migraine than men are still unknown (1). Several studies indicate that migraine is associated with the presence of adverse vascular risk factors including: an increased level of oxidative stress and thrombosis (2), an increase in body weight (3), high blood pressure (4), hyperlipidemia (5), impaired insulin sensitivity (6), high homocysteine levels, strokes, and coronary artery diseases (CAD) (7-9).

Serum paraoxonase-1 (PON1) is a glycoprotein synthesized mainly by the liver that circulates in serum in association with high-density lipoprotein (HDL) (10); moreover, it is a Ca^{2+}-dependent serum esterase that is widely distributed in liver, kidney, and intestine tissues, as well as serum (11). It is a protein comprising 354 amino acids with a molecular mass of 43 kDa, and plays a key role in the protection of low-density lipoprotein (LDL) and HDL from the oxidation process by hydrolyzing the activated phospholipids and lipid peroxide products (12). Previous studies have demonstrated that the activity of serum PON1 is associated with the modulation of endothelial functions (13), the regulation of coronary vasomotor tone, and the occurrence and extent of CAD (14).

Epidemiological studies have revealed wide variation among individuals in serum PON1 activity. It is known that PON1 has at least 5 polymorphic forms. Among these, 2 major polymorphic structures form at codon 192 [A/G: Gln (Q)/Arg (R)] and codon 55 [T/A: Leu(L)/Met (M)], and these were demonstrated to correlate with enzyme activity (15,16). The position of the 192 Q/R polymorphisms is the major determinant of the resultant PON1-activity polymorphisms. The occurrence and types of polymorphisms affect the hydrolytic activity of the PON1 isoenzymes with respect to certain substrates such as paraoxon and lipid peroxides (16,17). Further, it has been suggested that a low rate of PON1 activity is induced by CAD. In addition, this activity, usually measured by using paraoxon as a substrate, is under genetic and environmental regulation and appears to vary widely among individuals and between populations (15,16,18).

Many researchers have suggested that the occurrence of migraine is biologically linked to the occurrence of CAD (19). It is also thought that hyperlipidemia plays a significant role in the pathogenesis of migraine (5,7,8). Additionally, the presence of hyperlipidemia and a decreased rate of PON1 activity were suggested as risk factors for stroke and CAD (17). Data is not yet available, however, regarding the role it plays in inducing migraine. The purpose of the present study was to examine the role that phenotype distribution and PON1 activity play in influencing the duration of migraine incidents. To the best of the authors' knowledge there has only been one similar study, and it demonstrated that PON1 genotype polymorphisms and allelic variants were

not related to risk for migraine in Caucasian Spanish people (20). The results of this study supported the results of our study, which examined phenotype distribution of PON1 in patients suffering from migraine without aura (MWoA). However, there are no available reports investigating the relationship between phenotype distribution of PON1 and headache duration in patients suffering from MWoA.

Materials and methods

Subjects

The present study was conducted at the Neurology Outpatient Clinic of Kafkas University, located in Kars in northeastern Turkey. The evaluated group consisted of 76 patients diagnosed with MWoA during a headache-free period. The mean age of the 55 female and 21 male patients included in the study was 31 ± 10 years. Their diagnosis was based on clinical symptoms in accordance with those symptoms established by the International Headache Society (IHS) in 2004 (21). The IHS conducted experiments to evaluate the parameters of headache duration, frequency, localization, severity, and the entire duration of the migraine incident. In order to assess the severity of headache the Migraine Disability Assessment (MIDAS) and Visual Analog (VAS) scale were employed (21,22). The factors of pregnancy, lactation, clinically unstable medical illness, or the use of any medication 3 weeks prior to initiation of the study were excluded. Sixty-five healthy volunteers (with mean age 31 ± 9 years; including 41 women and 24 men) were enrolled to constitute the control group in the present study. A thorough history of headache was acquired for all the subjects evaluated in the control group, and none of them were found to suffer from a headache disorder. Further, none of the subjects included in the present study revealed a history of any medical illness, nor had they taken any analgesics, ergot alkaloids, or any other drugs at least 3 weeks prior to inclusion in the study. None of the evaluated patients were under prophylactic treatment for their migraine disorder. For both patient and control groups hematological and biochemical parameters were determined on a regular basis. Moreover, both these groups consisted of non-smokers. The characteristics of the evaluated patients are given in Table 1.

The protocol followed in the present study was in accordance with the Helsinki Declaration, revised in 1989. For conducting the evaluations in the present study, the approval of the ethics committees of the Medical Faculty of the Kafkas University and the informed consent of the patients and the healthy individuals were sought and attained.

Exclusion criteria

The exclusion criteria for conducting evaluations in the present study included the usage of supplemental vitamins, respiratory disorders, HIV positive status, the habit of smoking, a diagnosis of diabetes mellitus or CAD, rheumatoid arthritis, malignancy, hypertension, acute-chronic liver diseases, renal dysfunction, and headaches. In addition, the presence of any disease related to headache occurrence was considered part of the exclusion criteria (this includes diseases of intracranial neoplasm, sarcoidosis and inflammatory diseases, facial or cranial structure disorders, cranial neuralgias, nerve trunk pain, and temporal arthritis). In order to conduct the evaluations, blood samples were obtained from the subjects following an overnight fast. The samples were collected in empty test tubes and immediately stored on ice at 4 °C. The serum samples were then separated from the cells by centrifugation at 3000 rpm for 10 min. The resultant serum samples were stored at −81 °C until their use in the experimental analysis.

Measurement of the rate of paraoxonase and arylesterase activities

Paraoxonase and arylesterase activities were measured with the commercially available Rel Assay Diagnostics kits (23) that are equipped with an auto analyzer (Aeroset®, Abbott®, Illinois, USA). Measurements to determine the rate of paraoxonase activity were performed in the alternating absence (basal activity) and presence of sodium chloride (NaCl) (salt-stimulated activity) by using the paraoxon substrate. The rate of the paraoxon hydrolysis (diethyl-p-nitrophenyl phosphate) was measured by monitoring the increase in the rate of absorbance at 412 nm. The amount of generated p-nitrophenyl was calculated from the molar absorptivity coefficient at a pH value of 8, which was 17.000 M^{-1} cm^{-1}. The rate of activity was measured briefly at 37 °C by adding 20 µL of the stored serum to 200 µL of the Tris buffer

(0.1 M, pH: 8.0), which contained 2 mM of $CaCl_2$ and 7 mM of paraoxon. The rate of paraoxonase activity was expressed as the unit U/L serum (11,13,16,23). Next, in order to measure the rate of the arylesterase activity, phenylacetate was employed as a substrate. The required reaction was initiated by adding the stored serum to the substrate and then reading the increase in the degree of absorbance at 270 nm. The blank readings were included in the evaluations to correct the value obtained for the spontaneous process of phenylacetate hydrolysis. The rate of enzymatic activity was calculated from the molar absorptivity coefficient of the produced phenol, 1310 M^{-1} cm^{-1}. For the evaluations conducted here one unit of the degree of arylesterase activity was defined as 1 μmol of phenol generated/min under the above conditions and expressed by the unit U/L serum. The phenotype distribution of PON1 was determined in the presence of 1 mol/L of NaCl (salt-stimulated paraoxonase). The ratio of the salt-stimulated paraoxonase activity to the degree of arylesterase activity was used to allocate the subjects to one of 3 possible phenotypes (11,13,16,23). The subjects were assigned to 1 of the following 3 phenotypes: QQ (homozygous low activity), QR (heterozygous activity), or RR (homozygous high activity). These phenotypes are defined by the ratio of the degree of activity with the ranges 0.73 ± 0.23 for QQ (AA), 2.9 ± 0.49 for QR (AB), and 5.09 ± 0.18 for RR (BB) (Figure 2).

Measurement of the level of serum LOOH

The serum LOOH levels were measured with a ferrous ion oxidation–xylenol orange assay. This particular assay depends on the oxidation of ferrous ion to ferric ion through the effect of various oxidants. Consequently, the ferric ion produced is measured with xylenol orange. The level of LOOH is reduced by the application of triphenyl phosphine (TPP), which is a specific reductant for lipids. The LOOH levels can be estimated through the difference in values that appear due to the absence or presence of TPP (24).

Other parameters

The levels of HDL-C, LDL-C, total cholesterol (TC), and triglyceride (TG) were measured through the commercially available assay kits (Abbott®, Illinois, USA) that are equipped with an autoanalyzer (Aeroset®, Abbott®, Illinois, USA).

Statistical analysis

The collected data was expressed as the mean ± standard deviation (X ± SD). The student T test was employed to compare the parameters of both these groups. The chi-square test was used to test the distribution of the phenotype. In addition, the correlations existing between the parameters in both groups were determined through Pearson's correlation analysis. A linear regression analysis was used to determine the exact relationships that existed between the parameters of age and gender among the evaluated subjects; migraine duration; headache frequency; the mean value of VAS; the mean value of MIDAS; the serum TG, TC, HDL-C, and LDL-C levels; and the degree of PON1 activities, or the LOOH levels. P-values < 0.05 were accepted as significant. The data was analyzed by using a computer program.

Results

The demographic, clinical, and laboratory data of both groups are given in Table 1 and Table 2. No statistically significant differences were recorded between the groups with respect to the parameters of age and gender (both at a value of $P > 0.05$). The polymorphism data and the allele frequencies of the study groups are given in Table 3. Finally, the phenotype distribution of the patients is illustrated in Figure 1. No significant differences were found to exist between the patients suffering from MWoA and the control group ($P > 0.05$) on the basis of the rate of activity of serum PON1 and the phenotype distribution; a significant difference appeared in the levels of serum LOOH between the patients and the controls ($P < 0.05$). The activities of both paraoxonase and arylesterase were found to be inversely correlated with the levels of serum LOOH in patients diagnosed with MWoA (r: -0.23, $P < 005$; r: -0.27, $P < 0.05$, respectively). In addition, significant differences were noted between the PON1 phenotype distribution and headache duration in patients diagnosed with MWoA, as determined through the chi-square test ($P < 0.001$), in comparison to the control group. The ratio of salt-stimulated paraoxonase activity to arylesterase activity correlated with headache duration ($r = -0.40$, $P < 0.001$) (Figure 3). The concentrations of serum TC, TG, and LDL-C were found to be significantly higher in the patients diagnosed with MWoA in

Table 1. The demographic and clinical features of patients diagnosed with MWoA and control group.*

	MWoA patients	Controls	Value of P
Age (years)	31 ± 10	31 ± 9	> 0.5
Sex (F/M)	55/ 21	41/ 24	
Mean body mass index	26.4 ± 3.3	24.8 ± 3.9	> 0.5
Migraine duration (years)	6.2 ± 4.2		
Headache frequency (per month)	7.3 ± 5.2		
Headache duration (h)	30.41 ± 19.56		
Mean value of VAS	8.8 ± 1.1		
Mean value of MIDAS	12.6 ± 6.4		

*The data are presented as mean ± SD

Table 2. Comparison of PON1 activity and laboratory parameters in patients diagnosed with MWoA and the control group.*

Parameters	MWoA patients	Controls	Value of P
Paraoxonase (U/L)	166 ± 90	171 ± 83	Ns
Salt-stimulated paraoxonase (U/L)	391 ± 257	400 ± 290	Ns
Arylesterase (kU/L)	174 ± 32	177 ± 36	Ns
LOOH (μmol/L)	8.5 ± 2.0	7.1 ± 2.3	< 0.05
TG (mg/dL)	145 ± 80	129 ± 60	< 0.05
TC (mg/dL)	213 ± 24	194 ± 26	< 0.05
HDL-C (mg/dL)	37 ± 6.3	34 ± 4.2	Ns
LDL-C (mg/dL)	147 ± 4.6	134 ± 9.7	< 0.05

*The data are presented as mean ± SD; Ns: non-significant

Table 3. Phenotype distribution in patients diagnosed with MWoA and the control group.*

Phenotype distribution	Migraine patients n (%)	Controls n (%)	Value of P
BB	8 (11)	6 (9)	> 0.05
AB	28 (37)	27 (42)	> 0.05
AA	40 (53)	32 (49)	> 0.05
Total	76	65	

*The data are presented as n (%)

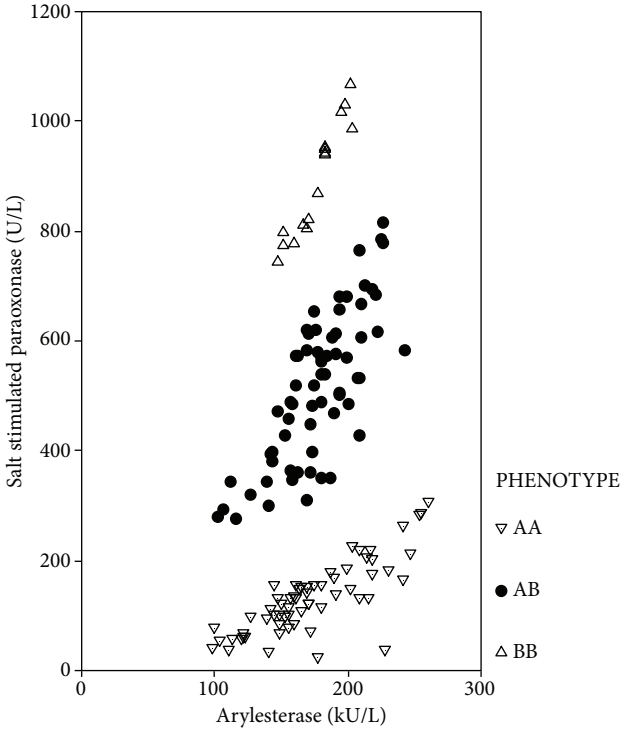

Figure 1. PON1 phenotype distribution in patients with MWoA.

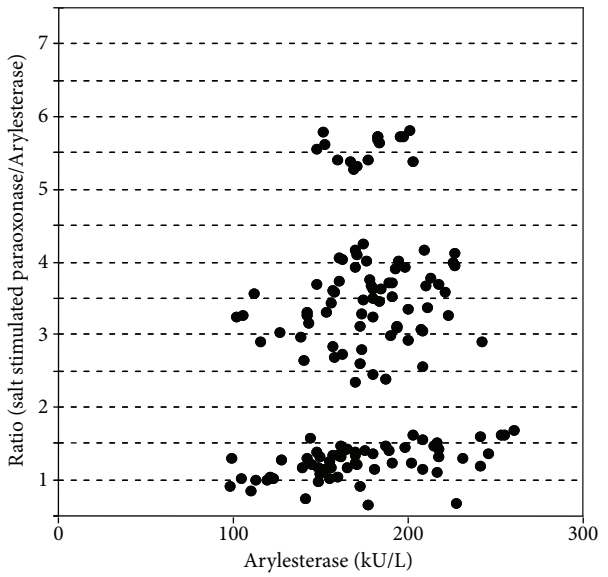

Figure 2. The ratio of salt-stimulated paraoxonase/arylesterase in MWoA patients.

comparison to the controls (for all parameters the value of $P < 0.05$); no differences were noted in the levels of HDL-C between the 2 groups ($P > 0.05$).

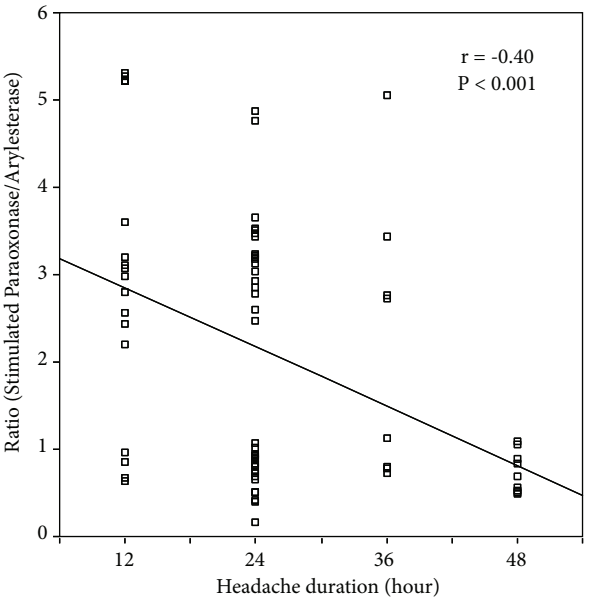

Figure 3. The ratio of salt-stimulated paraoxonase to arylesterase and headache duration.

It was also noted that PON1 activity and serum LOOH levels were not correlated with the age and gender of the subjects; migraine duration; headache frequency; the mean value of VAS; mean value of MIDAS; or the levels of serum TG, TC, HDL-C, or LDL-C ($P > 0.05$).

Discussion

The role of hyperlipidemia in influencing incidents of migraine is uncertain, since only a few studies have been conducted to evaluate the correlation between incidents of migraine and hyperlipidemia (5). The present study aimed to evaluate the association that exists between cardiovascular biomarker (PON1) activity and incidents of migraine. Further, this patient-control study was performed to investigate the role PON1 activity plays in influencing the occurrence and extent of migraine incidents, in order to provide additional information on this relationship.

The activity of the serum PON1 was noted to be reduced in a number of pathological conditions including CAD, hypercholesterolemia, type 2 diabetes, and renal failure (16,17). Previous studies indicate that PON1 can prevent the accumulation of lipid peroxide on LDL (10-12). In addition, numerous

epidemiological studies demonstrated that the rate of serum PON1 activity decreases in patients suffering from CAD (10-17). Knowledge about the influence of the rate of serum PON1 activity on patients diagnosed with MWoA, however, is limited.

In the present study no differences were observed in the rate of PON1 activity and phenotype distribution among the MWoA patients and the controls (Table 3). However, significant differences were noted between the levels of LOOH and hyperlipidemia among the 2 groups (Table 2). These results are consistent with those generated by similar previous reports (2,5). The molecular mechanisms of migraine have not yet been completely explained. Therefore, it is suggested that hyperlipidemia and oxidative stress may be associated with migraine attacks. Moreover, it is believed that hyperlipidemia and the consequent occurrence of LOOH and oxidative stress play a role in the pathogenesis of migraine (2,5,25,26).

No differences were noted in the rate of PON1 activity and the levels of HDL-C when comparing the patient group with the control group (Table 1). In contrast, the rate of PON1 activity was found to be inversely correlated with the levels of LOOH in the MWoA patients evaluated in the present study. Thus, there may be link between atherosclerosis and MWoA due to increased levels of LOOH which are produced by the oxidation of lipids (25,26).

Further, the rate of PON1 activity and phenotype were not correlated with migraine duration, headache frequency, mean value of VAS, or mean value of MIDAS in the present study; the rate of PON1 activity and phenotype as well as the ratio of salt-stimulated paraoxonase to arylesterase were correlated with headache duration (Figure 3). These results reveal that headaches were of shorter duration in patients with high homozygous activity ($PON1_{192}RR$ = BB phenotype) (Table 4). To the knowledge of the authors, there is no study other than the present one that reports on PON1 activity in MWoA patients. For this reason the results generated by the present study could not be compared with any other findings regarding PON1 activity.

The exact role played by the PON1 phenotype polymorphism in influencing headache duration in MWoA patients is uncertain. However, 3 possible mechanisms have been suggested: 1) The effects of PON1 on headache duration may be related to the peroxidase-like activity of PON1 and thus, PON1 may increase the anti-oxidant capacity that works against oxidative stress (27). 2) Some studies conducted on animals indicate that the rate of PON1 activity can be altered during the acute phase response, and the serum levels can be decreased. It was noted, however, that this decrease was transient since the rate of PON1 activity became equivalent to the values of the control group within 48 h (28). In the light of the findings of this study PON1 activity decreases oxidative stress; consequently, headache duration also lessens. 3) An incident of migraine is best understood as a neurovascular disturbance which leads to vasodilatation and the release of pro-algesic substances within the dura mater which in turn sensitizes peripheral and central neurons (1). Previous studies have shown that the activity of serum

Table 4. The parameters of PON1 phenotype and headache duration in patients diagnosed with MWoA.*

Phenotype	Headache duration (h)			
	0-12 (n)	12-24 (n)	24-36 (n)	36-48 (n)
BB (RR)	5	2	1	
AB(QR)	9	16	3	
AA (QQ)	4	23	4	9
Total (n)	18	41	8	9

*The data are presented as n, used x^2 test for all groups, and $P < 0.001$ was found

PON1 is closely associated with the modulation of endothelial functions (13). Thus, PON1 activity can modulate the neurovascular disturbances which increase headache duration in incidents of migraine.

In conclusion, the results generated by this study indicate that an increase in the rate of PON1 activity may play a significant role in headache duration during incidents of migraine by increasing degree of susceptibility to LOOH. In addition, the present study demonstrated that the distribution of PON1 phenotype may significantly contribute to decreased headache duration during incidents of migraine.

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