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Peripheral Arterial Tonometry (EndoPAT)-measured Endothelial Dysfunction in Migraine with Aura children

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Abstract. *Background*. The association between Migraine with Aura (MA) and vascular disease has been previously reported. We investigated whether pre-clinical vascular alterations, such as Endothelial Dysfunction, are already present in children and adolescents with Migraine with Aura. *Methods*. We retrospectively enrolled 27 patients having Migraine with Aura, aged9 -18 years, and 31 age matched healthy control subjects to evaluateEndothelial Function by Peripheral Arterial Tonometry. This technique measures finger pulse wave amplitude, before and during reactive hyperaemia, and calculates the Augmentation Index (AI) and the Reactive Hyperaemia Index (RHI). We also set-up an Aura Severity Scale to assess disease severity and its relationship with AI and RHI alterations. *Results*. Also if the case-control study resulted only partially as significant, we found there is an inversely proportional relationship between the severity of the migraine measured with Aura Severity Scale and the values of the endoscore (a significantly reduced levels of AI (p-value <0,03) and a marginal reduction of RHI levels (p-value <0,07). *Conclusion*. Further studies should explore the impact of pre-clinical vascular alterations in children and adolescents with Migraine with Aura.

Key words: Migraine with aura, endothelial dysfunction, EndoPAT, arterial stiffness

Introduction

Migraine is a common, complex and debilitating neurological disorder, characterized by attacks of moderate to severe headaches lasting from 4 to 72 hours, often unilateral and pulsating, associated with nausea, vomit, and/or photophobia and phonophobia (1). Approximately 30% of subjects with migraine experiences the aura, constituted by recurrent and reversible, transient, focal neurological symptoms, typically preceding the headache (2, 3). In the International Classification of Headache Disorders (ICHD-3, 2018) aura is defined as *"Fully reversible neurologic dysfunction that precedes or accompanies a headache, with gradual onset, progression of 5 minutes or more and duration for each aura symptoms of 5-60 minutes"* (4).

The lifetime prevalence of migraine with aura is found in about 5% compared to migraine without aura which is about 8%. Migraine is more prevalent in women than men with a ratio 3:1, though prior to puberty the prevalence is higher in boys than girls (5). Visual aura is the most common type of auras (99% of cases): scintillating scotoma, blurred vision, tunnel vision and zig-zag lines; sensory disorders are the next most frequent aura symptoms (about 54 % of patients) and language deficits are the least common symptoms (about 32% of patients) and in these cases the differential diagnosis with other form like eg ischemic stroke, PRES, and other neurovascular pathologies are mandatory (6-12).

The complex pathogenetic mechanism of MA was disputed throughout much of the 20th and still

needs full clarification. In particular vasogenic and neurogenic theories were proposed, and probably both vascular and neuronal factors contribute to MA.

The neurogenic theory, proposed by Karl Lashley in the 1940s, hypothesized that aura was due to a wave of hyper-excitation spreading across areas of contiguous cortex (this event was termed cortical spread depression, CSD) (13). The vasogenic theory, that was largely accepted until 1980, held that MA was caused by recurrent episodes of vasospasm within cerebral vessels causing transient drops in blood flow and resultant neurologic symptoms. Headaches occurred as a result of rebound vasodilation that caused mechanical activation of nociceptive neurons within and around cerebral vessels.

Numerous studies have reported the association between MA and vascular diseases, in particular in adult patients with MA general measures and cardiovascular preventive strategies are an important step of therapy to reduce the vascular risk but also to reduce headache frequency and pain. In the general population arterial dysfunction has been linked to an increased risk of vascular diseases through an atherothrombotic mechanism; furthermore, in migraineurs the evidence of an atherothrombotic mechanism leading to vascular events is not supported and other mechanisms are hypotesized, like structural and functional changes in the arterial wall.

Recently the hypothesis of "vascular disease" in the pathogenesis of MA is emerging in the literature (14, 15).

Several mechanisms are proposed to explain this association between vascular disease and MA: the most commonly suggested mechanism is the "Endothelial Dysfunction". The endothelium is today considered an active metabolic and endocrine organ that produces a wide variety of substances and expresses a multitude of receptors, maintaining a favourable balance between vasodilation and constriction, thrombolysis and thrombosis, proliferation and apoptosis. The Endothelial Dysfunction is characterized by:

1. impairment of endothelium-dependent vasodilation, due to a decrease in the vasodilating factors and an increase in vasoconstricting factors;
2. endothelial activation, which is characterized by proinflammatory and procoagulant state (platelet activation, aggregation and suppression of anticoagulant substances).

Furthermore Endothelial dysfunction represent an integrated index of both the overall cardiovascular risk-factor burden and the sum of all vasculoprotective factors (16, 17).

There is evidence that migraine is associated with endothelial dysfunction, both as a cause and as a consequence also in specific disease (7, 18).

Various genetic and plasmatic biomarkers of endothelial disfunction are been identified (19):

- MHTFR variant C677T: individuals with the homozygous variant C677T (TT) showed higher levels of plasma homocysteine an excitatory amino acid, related to thrombophilic state: high homocysteine levels may influence the threshold for migraine headache (20, 21); moreover studies have found a significant association between the TT genotype and migraine, especially MA (22-26);
- eNOS gene polymorphisms (endothelial nitric oxide synthase) and alteration of NO pathway: NO plays an important role in the cerebral blood flow regulation, in the activation of trigeminovascular system nociceptors and in the release of vasoactive neuropeptides during the neurogenic inflammatory response (27-29);
- ACE polymorphism: ACE I/D polymorphism is a risk factor for vascular diseases; recently the ACE D/D genotype has shown to correlate with an increased frequency of migraine attacks in patients with MA;
- EMPs, endothelial microparticles produced in response to endothelial exposure to inflammatory cytokines; these trigger endothelial release of chemokines, inhibit nitric oxide synthase and attract leukocytes to the endothelial surface, promoting inflammation and thrombosis;
- elevated levels of ADMA, endogenous inhibitor of nitric oxide synthase, associated with oxidative stress, atherosclerosis, and cardiovascular disease;
- ET-1, known primarily as a potent vasoconstrictor of smooth muscle cells, is a peptide produced by the endothelium that regulates vascular tone, binding type B receptors on the endothelium to effect NO-mediated vasodilation;
- CGRP (calcitonin gene-related peptide):vasodilator peptide that induces pain response; increased CGRP levels have been reported in migraine attacks (30);

- VEGF (vascular endothelium growth factor): his production is regulated by growth factors and inflammatory cytokines and VEGF haplotypes seem affect susceptibility to migraine.

However, in many cases the quality of evidence is scarce, and the clinical use is poor; better quality studies are needed to clarify the significance of these biomarkers and the link with MA.

In addition, also different instrumental techniques to assess endothelial function have been developed in the last years, but the results are controversial and different heterogeneous techniques were applied to small group of patients. Moreover, some reports indicate a major detection rate of endothelial dysfunction if the instrumental measurements are associated to endothelial biomarkers; however, there is the possibility that endothelial biomarkers are more sensitive to detect early changes of endothelial function.

The more known instrumental techniques to evaluate the endothelial function are flow-mediate dilation to pharmacological stimuli(ultrasound); venous occlusion plethysmography; laser doppler flowmetry; arterial tonometry; in particular "peripheral arterial tonometry" (EndoPAT) is resulted as a promising non-invasive indicator of the vascular health of subjects with migraine. EndoPAT records the plethys-

Table 1: MA patients data.

ID	Sex	Age	Weight (Kg)	Height (cm)	BMI	SBP (mmHg)	DBP (mmHg)	FM (Kg)	FM (%)	LM (Kg)	RHI (EndoPAT)	AI % (EndoPAT)
1	F	14	40	153	17,09	105	69	8,04	21	30	1,22	–11
2	F	13	61,7	163	23,2	124	59	19,05	31	42,2	1,65	–19
3	F	16	62	164	23,05	120	61	18,02	29	40	2,21	–36
4	M	15	44,6	157	17,98	115	54	2,5	5,07	41.6	2,49	–9
5	F	17	68,1	167	24,42	103	65	21,09	32.2	39,9	2,02	–26
6	M	14,2	55,9	164	20,8	121	59	6,01	11,00	47,3	1,19	–2
7	M	13	46,60	171	15,95	106	52	4,08	10,2	41,8	1,72	–9
8	F	14	52,7	163	19,8	106	61	12,3	22,3	39,6	1,95	–5
9	F	14	62,8	165	23	109	55	18	28,7	42,5	1,85	–16
10	F	15	50,4	164	20,2	103	53	11,5	22,8	36,9	2,35	–6
11	M	13	39,2	153	16,7	85	45	4,1	10,5	33,2	1,19	–3
12	F	14	46,5	164	17,3	96	55	8,6	18,5	36	1,54	0
13	F	9	43	146,5	20,17	94	55	12,1	28,2	29,3	1,05	–3
14	F	15	53,6	160	20,09	102	55	14	26.2	39,6	2,34	–2
15	F	14	44,9	163	16,9	104	59	8,04	18,6	37,6	2,24	–1
16	F	18	64,2	157	26	123	78	19	29,60	34,6	1,29	–7
17	F	13,5	63,8	163	24,07	111	53	19,05	30,5	42	1,38	–4
18	F	13	53	165	19,47	101	50	11,03	21,04	39,6	1,44	–11
19	F	14	52,5	164	19,5	115	55	11,4	21,8	39	1,58	–10
20	F	15	52,6	160	20,5	110	56	12,2	23,2	38,3	1,63	–10
21	F	15	56,4	159	22,3	114	62	16,4	29	38	2,1	–1
22	F	17	56,8	157	23	100	53	13,2	23,3	41,4	1,28	–4
23	M	12	87,1	167,5	31,2	140	66	25,3	29,1	58,7	1,6	–7
24	F	13	44,9	159,5	17,8	113	52	9,6	21,3	33,5	2,56	–8
25	F	14	47	154,5	19,8	107	57	11,7	24,8	33,5	3,11	–10
26	M	15	46,9	166	17,02	98	53	3,7	7,8	41	2,55	–20
27	F	15	62	160	24	125	55	18,09	30,4	41	2,47	1

mografic pressure changes caused by the arterial pulse and translates this to a peripheral arterial tone (PAT). This instrument provides two indexes: RHI (reactive hyperemia index) which indicates the peripheral endothelium-dependent vasodilator capacity (nv>1.67) and AI% (Augmentation Index) which measures the arterial stiffness, reporting the difference between first and second peaks of the arterial waveform (AI (%) = (P2-P1)/P1).

EndoPAT was applied in adult patients suffering from migraine: for the first time, in 2012, Liman et al. demonstrated the presence of higher value of AI in women with MA (29 cases, 30 controls); no differences were found in RHI. In 2013, Caballero et al. demonstrated that: AI is increased in patients with chronic migraine compared with controls. These results indicate the presence of an alteration of arterial function in migraineurs, in particular the presence of

Table 2: Control patients data.

ID	Sex	Age	Weight (Kg)	Height (cm)	BMI	SBP (mmHg)	DBP (mmHg)	FM (Kg)	FM (%)	LM (Kg)	RHI EndoPAT	AI EndoPAT (%)
1	M	15	74	174	24,44	130	67	15,5	21	58,5	1,67	–15
2	F	17	49,6	157	20,12	115	70	6,9	13,9	40,5	1,76	10
3	F	15	62,5	164	23,24	110	61	17,9	28,7	42,3	1,99	–19
4	M	16	68	174	22,5	119	57	7,9	11,6	57,1	2,3	–15
5	M	17	68	185	19,87	124	57	6,1	9	61,9	2,29	–26
6	F	8	24,3	127	15,06	96	56	3,8	15,7	19,4	2,14	17
7	F	10	29,2	135	16,02	101	63	6,2	21,4	21,8	1,17	–4
8	M	13	60,2	171	20,59	118	61	8,3	15,4	50,9	1,84	–18
9	M	17	65,2	173	21,8	110	60	7,6	11,6	54,7	1,68	–30
10	M	14	57,7	170	19,97	128	58	8,1	14,1	49,6	1,58	–4
11	F	15	47,2	154	19,9	104	60	10,2	21,7	35,1	1,22	–3
12	M	14	91,3	179	28,5	138	80	21,2	23,2	66,6	2,16	–6
13	M	15	73,7	175	24,1	128	61	19,4	26,3	51,6	1,29	–11
14	M	15	62,5	172	21,13	129	62	6,9	11,1	52,8	1,09	–3
15	M	17	61,8	169	21,64	124	61	7,2	11,6	51,8	2,16	–15
16	M	17	82,1	173	27,43	124	63	14,9	18,1	63,9	2,31	–17
17	F	15	66	170	23,2	121	53	18,5	27,8	45,8	2,76	–17
18	F	17	54,4	170	18,82	107	63	10,4	19,1	41,8	2	–9
19	F	14	56,4	169	19,75	110	70	12,4	21,9	41,8	2,33	–17
20	F	13	51,5	161	19,87	100	60	11,8	23	37,7	2,47	–2
21	F	12	51,9	163	19,53	98	56	12,5	24	37,4	1,99	0
22	M	16	63	176	20,34	116	59	6,5	10,3	53,7	2,27	–16
23	F	13	50	160	24,24	100	58	10,1	20,3	37,9	1,93	–12
24	M	12	42,8	148	19,5	120	65	7,8	18,3	33,1	1,01	–14
25	F	13	56,4	163	21,23	105	64	14,9	26,5	41,5	1,01	–17
26	M	15	90	175	29	135	55	19,8	21,4	72,9	2,03	–23
27	F	15	51	162	19,4	107	58	11,2	22	37,9	1,22	–9
28	M	17	73	178	23,04	133	60	9,9	13,9	58,3	2,04	9
29	M	15	63,8	183	19	130	66	6,6	10,4	57,2	1,18	–18
30	F	12	39,4	151	17,3	114	64	6,7	17	31	1,55	–5
31	F	13	50,3	160	19,65	107	57	12	23,9	36,3	1,81	0

higher arterial of arterial system in MA.

We propose the first study for evaluation of endothelial dysfunction through Endopat in a population of children suffering from migraine with aura.

In particular the aims of the present study were: 1. to verify the presence of pre-clinical vascular alteration such as Endothelial Dysfunction in children with MA; 2. to verify the eventual correlation between an alterated endothelial function and the MA severity.

Methods

We retrospectively enrolled 27 children (6 male, 21 female) with MA (9-18 years of age) referred as out-patients to the Neuropediatric Unit of a tertiary level centre, in central Italy, that performed analysis with EndoPAT for evaluation of Endothelial Function.

Thirty-one (16 male, 15 female), age- and sex-matched healthy subjects without migraine served as controls enrolled from another study.

We included only females, when fertile, during the follicular phase of menstrual cycle. Clinical data of all enrolled subjects are summarized in Tables 1 and 2. Diagnosis of migraines was performed according to the International Headhache Society Classification (2).

Family history was obtained from patients and controls, focusing on neurological and cardiovascular diseases.

Exclusion criteria were: comorbidity with other cronic diseases; evidence of other CV risk factors; patients in pharmacological treatment; in all the patients, the presence of concomitant disease (other than MA) or increased risk of cardiovascular disease, or cigarette smoking, alcohol, or food abuse excluded by medical history, standard medical examinations and clinical tests.

The Instruments we used were: 1. "EndoPAT" for evaluation of Endothelial Function. All patients were retrospectively evalueted with "Aura Severity Scale" for evaluation of MA severity.

BMI was calculated using the formula weight $[(kg)/height (m)^2]$.

We used the same National reference data to calculate BMI z-score and Height z-score. Body composition weres measured using the Tanita BC-418 Segmental Body Composition Analyser (Tanita Corporation, Tokyo, Japan) (31, 32).

Informed consent to study participation was obtained from all the enrolled subjects or from their parents, as appropriate.

1. Assessment of Endothelium-Dependent Vasodilation – EndoPAT

In both MA patients and controls, peripheral endothelium-dependent vasodilator capacity was estimated assessing the reactive hyperaemia index (RHI) by means of an EndoPAT system (Itamar Medical Ltd, Cesarea, Israel). As previously described (33), the subject sat in a reclining chair with the hands at heart level and was propped in a comfortable position so that the fingers were hanging freely. Fingertip probes were placed on both index fingers and pulse wave amplitudes were recorded for the duration of the entire study consisting of 5-minute baseline recording, 5-minute occlusion of non-dominant arm using a BP cuff inflated to 40 mmHg above systolic pressure, rapid deflation of BP cuff (followed by reactive, flow-mediated hyperaemia) and pulse wave amplitudes recording for at least further 5 minutes. An integrated software program compares the ratio of arterial pressure waves in the two fingers before the occlusion and after the deflation to calculate the reactive RHI score as the ratio of the average pulse wave amplitude, measured over 60 seconds starting one minute after cuff deflation, to the average pulse wave amplitude measured at baseline. This ratio is normalized to the concurrent signal from the controlateral finger to correct for changes in systemic vascular tone (34).

EndoPAT calculates also the Augmentation Index (AI), a measure of arterial stiffness, analysing the pulse waveform of the PAT signal recorded during the base-line period. Lower or negative AI values indicate better arterial elasticity.

This data were also compared with traditional CV risk factors to determine the real, indipendent importance of the test.

2. Assessment of MA severity

To investigate the possible presence of a relationship between endothelial dysfunction and MA severity, we set-up an Aura Severity Scale (Table 3) derived from a "Visual Aura Scale" (35). The Scale was adapted

to identiflty the severity of aura in a cohort of patients with visual and sensorimotor symptoms.

The maximum score is 10 points

According to the Scale we identified 3 grades of severity:
1. Mild: 0-3 points
2. Moderate: 4-6 points
3. Severe: 7-10 points

Taking into consideration the worst episode of MA experienced by our patients, we assigned scores as follows: 3 points for Duration (1 point: <10'; 2 points: 10-30'; 3 points: >30'); 2 points for Visual Symptoms (1 point: Scotoma, Zig-zag Lines; 2 points: blurred vision); 1 point for Location (0 points if symptoms are Bilateral; 1 point if symptoms are Unilateral); 2 point to Weakness (0 points if absent, 1 point to mild lack of strenght, 2 points to severe lack of strenght); 1 point to Paresthesia; 1 point to Dysarthria. The maximum score is 10 that represents the weighted sum of visual and somatosensorial symptoms.According to the Scale we identified 3 levels of severity: Mild: 0-3 points;mModerate: 4-6 points; Severe: 7-10 points.

Statistical analysis

Normality of distributions was assessed using the Shapiro-Wilk test, Gaussian variables were expressed as mean ± standard deviation, while the not normally

Table 3: MA: severity scale.

	Duration (minutes)	Visual Aura Symptoms	Unilateral	Weakness	Paresthesia	Dysarthria	Total
1	2	2	1	-	-	1	6
2	2	2	1	-	1	-	6
3	2	2	-	-	-	-	4
4	3	1	-	-	-	-	4
5	2	2	-	2	1	-	7
6	2	2	1	-	1	-	6
7	3	2	1	-	-	-	6
8	1	2	-	-	-	-	3
9	2	2	-	-	-	-	4
10	1	2	-	1	-	-	4
11	1	2	-	-	-	-	3
12	3	2	-	-	1	-	6
13	1	1	-	-	-	-	2
14	1	2	-	-	-	-	3
15	2	1	1	-	-	-	3
16	2	2	-	-	-	-	4
17	1	1	1	-	-	-	3
18	2	2	1	-	-	-	5
19	2	2	-	-	1	-	5
20	2	2	-	2	1	-	7
21	3	2	-	-	-	1	6
22	3	2	-	-	-	-	5
23	2	-	-	2	-	-	4
24	2	2	1	-	-	-	5
25	2	2	-	-	-	-	4
26	2	1	-	-	-	-	3
27	2	1	-	-	-	-	3

distributed ones were reported as median and inter-quartile range.

Mann-Whitney test and t-test were performed to analyse differences between continuous variables. Ordinal logistic regression was carried out to study the influence of endothelial dysfunction on illness severity. Post-hoc power tests were performed to estimate the sample size of the groups, 1-β values of the significant variables were > 0.8, assuring appropriate sample size. The statistical analysis was conducted using the IBM SPSS software package, version 17.0.1 (Table 4).

Results

Case-control study

Tables1 and 2 summarize clinical and instrumental findings we observed in both patients and controls.

As shown in Tables, among non-Gaussian-distributed data, Height, Diastolic Blood Pressure (DBP), Fat mass (FM) % and Free fat mass (FFM) kg were significantly different between patients and controls. Specifically, analysing each point we found that:
- Height and Diastolic Blood Pressure were nearly the same in the two groups.

- Fat mass was greater in Cases group than in the Control one (both FM% both FFM Kg)
Among normally distributed variables, only Systolic Blood Pressure (SBP) was significant, and resulted greater in Controls group.

Relationship between Disease Severity and entity of Endothelial Dysfunction

As regards the severity of the disease, using the proposed "Aura Severity Scale" we obtained that in 2% of cases the severity was severe, in 30% mild and in 68% moderate (Figure 1).

Scores of Aura Severity Scale resulted related to the entity of the EndoScore alteration. The influence of Endothelial Dysfunction on illness severity has been analyzed with an ordered logistic regression. The sample output test used for the significant variables gives a result of 0,08: the numerosity of the variables is sufficient. The statistical analysis demonstrate that exists a significant correlation, confirming our hypothesis: considering a signification level *alfa* of 0,05, p-value for Augmentation Index is 0,03 and p-value for Reactive hyperaemia index is 0,07.

Table 4: Statistical analysis

| Variable	Obs.	Obs. with missing data	Obs. without missing data	Minimum	Maximum	Mean	Standard Deviation
Age (cases)	27	0	27	9,000	18,000	14,248	1,728
Age (controls)	31	0	31	8,000	17,000	14,419	2,187
Height (cases)	27	0	27	146,500	171,000	161,111	5,312
Height(controls)	31	0	31	127,000	185,000	165,839	12,869
BMI (cases)	27	0	27	15,950	31,200	20,789	3,462
BMI (controls)	31	0	31	15,060	29,000	21,296	3,200
DBP (cases)	27	0	27	45,000	78,000	57,296	6,615
DBP (controls)	31	0	31	53,000	80,000	61,452	5,347
FM, Kg (cases)	27	0	27	2,500	25,300	12,522	5,901
FM, Kg (controls)	31	0	31	3,800	21,200	10,942	4,717
FM, % (cases)	27	0	27	5,070	32,200	22,486	7,714
FM, % (controls)	31	0	31	9,000	28,700	18,523	5,716
LM (cases)	27	0	27	29,300	58,700	39,244	5,700
LM controls)	31	0	31	19,400	72,900	46,542	12,679
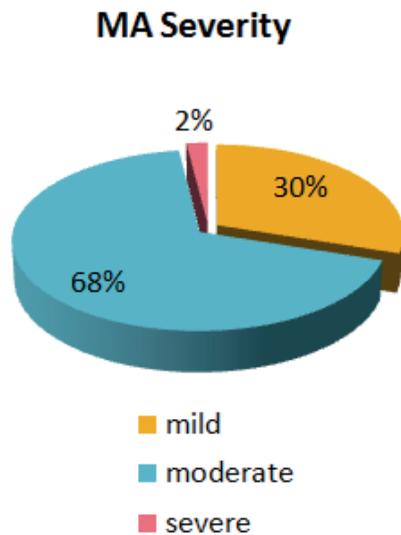
MA Severity

Figure 1. MA severity

Discussion

This is the first study which employ a PAT device in a pediatric cohort of migraineurs with aura to prove in these patients the presence of an altered endothelial response, presuming this as a determining factor in the development of migraine with aura.

This retrospective case-control study for evaluation of the traditional cardiovascular risk factors resulted only partially as significant, probably because the number of patients monitored (n=58) was insufficient.

Instead, the study for evaluation of the relationship between the MA severity and the vascular dysfunction, measured by the EndoPAT parameters (RHI and AI), resulted as significant: we obtained statistically significant results for RHI and in particular for AI: our results showed inversely proportional relationship between the severity of the disease and the values of the endoscore.

Children with MA may already have a subtle, preclinical endothelial dysfunction, and this endothelial dysfunction could represent a determining factor in the development of migraine with aura as well as in the predisposition to cardiovascular events.

This study can lead to extensive use of a safe and non-invasive diagnostic device to obtain early information about functional vascular health in risk groups, like migraineurs.

But what is the utility of these studies? Understanding the role of endothelial dysfunction in MA may lead also to develop preventive drugs for restore the endothelial dysfunction, preventing MA and cardiovascular events in these patients. To date it is uncertain whether cardiovascular events can be prevented by migraine prophylaxis and only one study showed an improvement of endothelial function during therapy with enalapril (36).

Future studies are required and need of a large number of selected subjects, rigorous inclusion and exclusion criteria, patient with a wide range of migraine condition in terms of frequency, duration and severity of attacks and standardized and reliable methods to measure the endothelial function.

We hope that endothelial function measurements may facilitate the prevention of cardiovascular events in migraineurs children, as well as improve the quality of life of pediatric patients suffering from MA.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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