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Title: high density EEG and arterial spin labelling MRI perfusion in the diagnosis and follow-up of patients with Moyamoya vasculopathies

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Summary

Introduction

Paediatric central nervous system arteriopathies

Central nervous system (CNS) arteriopathies are considered the most common cause of stroke and stroke recurrence in children. Among CNS arteriopathies, Moyamoya (MM) vasculopathies defined as disease when idiopathic and Moyamoya syndromes when associate with systemic diseases, are important conditions characterized by progressive narrowing of the intracranial internal carotid arteries and their proximal branches associated with the development of fragile compensatory collateral small arteries, producing the characteristic “puff of smoke” angiographic appearance.[1,2] MM are extremely rare conditions with an estimated incidence of 1/1,100,000/year in Europe and a bit higher in East Asia with 0.35–1.13/100,000/year cases.[1]

The underlying cause remains elusive, but it is likely that many factors, both genetic and environmental, can contribute to the disorder.[3–6] Moyamoya syndrome has been found in children with a large spectrum of congenital malformations and genetic condition, the most frequent being Neurofibromatosis type 1, sickle cell disease, Down syndrome, PHACE syndrome and Alagille syndrome.[5,7]

The natural history of these conditions includes recurrent transient ischemic attacks, ischemic stroke or intracerebral bleeding. Intellectual disability and executive function deficit may also be present in MM patients, exacerbated by bilateral disease progression and clinical stroke occurrence.[8,9] Pharmacological treatment is not effective in preventing these clinical events and patients with significative neurological symptoms and compromised cerebral hemodynamic may benefit from surgical revascularization.[1,2,4] Timing of surgery is still controversial, especially at early stages of the disease. Although a radical surgical approach to restore the blood flow of the main cerebral arteries in patients with MM has not yet been found, revascularization surgery is usually performed to guarantee enough cerebral blood supply to prevent ischemic or haemorrhagic strokes.[3,7,10,11]

Several surgical procedures have been used for the treatment of MM, including direct anastomosis (i.e., superficial temporal artery - middle cerebral artery anastomosis), indirect anastomosis (such as encephalo-duro-arterio-synangiosis and encephalo-myo-synangiosis) and combinations of operations from these two categories. In adult patient direct anastomosis and/or combined direct-indirect revascularization surgery are the main and most effective treatment of Moyamoya vasculopathy. However, both these procedures are associated with higher rates of postoperative transient ischemic attacks or cerebral infarctions and may be technically challenging in young children. In recent years, indirect revascularization techniques (encephalo-duro-arterio-synangiosis and encephalo-myo-synangiosis) have proven to protect the brain against further cerebral ischemia in children with isolated or syndromic Moyamoya vasculopathies, lowering the risk of intellectual and executive problems.[5,8,9,12–14]

For the diagnostic assessment, although angiography is still the gold standard for evaluation of Moyamoya patients, it has several limitations because of its invasive nature and possible occurrence of complications.[9] MRI with perfusion imaging is often used to supplement information for surgical management, but conventional Perfusion Weighted Imaging (PWI) techniques require the intravenous injection of gadolinium-based contrast medium agents, an invasive procedure especially in neonates, infants and young children.[15,16] Finally, the evaluation of the cerebrovascular reserve, an important index to select surgical candidates, requires the use of acetazolamide that has several side effects and contraindications, especially in children.[17] Therefore, in recent years, several new non-contrast MR techniques have been developed to study intracranial arteries (3D angiographic sequences), and brain perfusion (Arterial Spin Labelling, ASL).[16,18,19] Moreover, new strategies are needed to estimate the cerebrovascular reserve, in adults performed with the injection of acetazolamide that is not used in children for the risk of adverse events.

Due to the rarity of the disease not only diagnosis, timing and type of surgical treatment choice remain controversial, but also clinical management after surgery, outcome evaluation and follow-up management are still unclear.

EEG in Moyamoya

EEG analysis could work as a significant complementary tool in the pre- and post-operative assessment of children with Moyamoya or other CNS vasculopathy. For instance, Moyamoya patients usually present a characteristic pattern few minutes after hyperventilation called "rebuild up phenomenon" that disappears after successful revascularization surgery, making EEG a simple and non-invasive instrumental method that can be easily compared with perfusion data in order to evaluate the results of surgery and to follow-up the patients.[20,21]

Sleep, synaptic plasticity studies through High-Density EEG

Sleep offers significant opportunities to study electrophysiological markers of potential therapeutic efficacy in neurological patients because during sleep confounding factors are minimized.

Sleep spindles are defined as bursts of 10–16 Hz oscillations during NREM sleep and they are linked to sleep dependent memory functions. Sleep spindles originate in the thalamic reticular nucleus and are propagated in thalamocortical feedback circuits. They correlate with general measures of intelligence and overnight memory performance improvement and have been shown to be causally linked to sleep dependent memory consolidation in animal work.[10,22–25]

Increasing evidences in healthy humans and animals suggests that NREM sleep specific slow cortical waves (0.5–4.5 Hz waves which appear and progressively increase through the NREM sleep, reaching maximum representation in stage N3), well known as sleep slow waves activity (SWA) is crucial in regulating synaptic plasticity and reorganization.[26,27] In particular, SWA may work as a homeostatic function promoting synaptic depression and leading to a general rescale.[28] An association was found between cortical areas strengthened with a repeated task during wakefulness and SWA locally increase in the same areas during subsequent sleep.[26,28,29] This effect is caused by the fact that stronger synapses led to stronger cortico-cortical connections and increased synchronization between neurons showed as slow waves of larger amplitude at the EEG recordings.[22,26,28,30]

Changes in EEG sleep spindles and SWA has been previously studied trough high-density EEG (Hd-EEG) technology. Hd-EEG is a dense array scalp recording system consisting in pre-cabled cuffs connected to a digital amplifier and to a computer. Number of used electrodes could vary from 32 up to 256. It provides a huge amount of quantitative data which require a post processing elaboration including source modelling analysis techniques. Due to these characteristics, it is a valid tool to explore subtle and extremely localized variations in EEG activity. Spindles and SWA changes have been previously linked to brain plastic processes not only in healthy brain during development but also in patients with epilepsy, epileptic encephalopathies and after stroke in two studies with adult patients and one with children and adolescent.[25,27,31–33] All of these studies observed sleep spindles and SWA local differences between healthy controls and patients and between subjects studied just after clinical events and during rehabilitation. EEG sleep graphoelements seem to be a sensitive parameter to assess neural activity. A reduction in sleep spindles was observed in patients with epileptic encephalopathies, making them a promising biomarker for cognitive dysfunction.[33] SWA amount was related to ischemic damages and also topography changes were detected and related to lesions localization and extension. During post-acute period SWA local increase, mainly in the perilesional and contralateral areas, was observed, suggesting that greater activity is possibly related to brain reorganization after stroke.[31,34]

Material and methods

We enrolled all pediatric patients with new onset Moyamoya between 1 to 18 years old candidates for revascularization surgery. Informed consent was obtained from the parents or legal guardians before each study.

For all patients a presurgical assessment and longitudinal clinical follow-up for 18 months length was performed, comprising:

-Clinical and neurological examination

-Digital EEG with 64 channels both pre- and post-operatively (before and 6 months after surgery) were performed both during wake and sleep (a

NREM/REM cycle will be recorded); hyperventilation activation procedure was performed whenever possible with a respiratory rate of 30/minute and duration over 3 minutes with at least 5 minutes of record after hyperventilation.

-Digital EEG with 19 channels performed both during wakefulness and sleep (a NREM/REM cycle will be recorded) for patients < 3 years old

-Signals were sampled at 128 Hz (19 channels EEG) and 256-512 Hz (64 channels EEG), filtered between 0,5 and 50 Hz and acquire referenced to Cz electrodes. Sleep EEG were scored according to standard criteria (AAMS 2015)

-MRI studies on a Philips Ingenia 3T unit both at presentation and on follow-up. Standard imaging protocols (including 3D T1, 3D FLAIR and T2-weighted images) were complemented by advanced MR imaging sequences such as SWI, MRA, black-blood vessel wall imaging, 3D pCASL and DSC-T2* PWI.

-Cognitive evaluation with Griffith's developmental scales in children till 7 years old, Weschler Scales in patients older than 7 years.

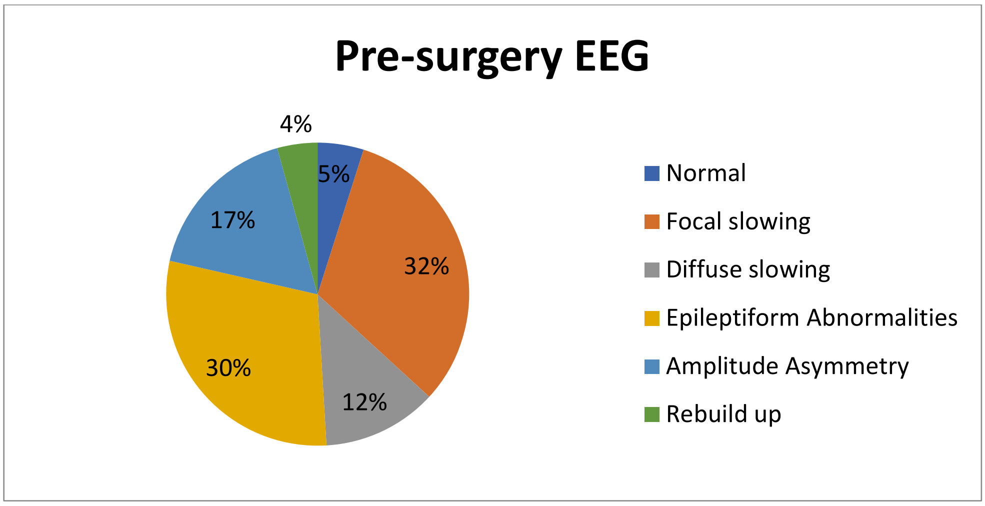
-Administration of specific questionnaire for migraine (Pediatric Migraine Disability Assessment-Ped MINAS).

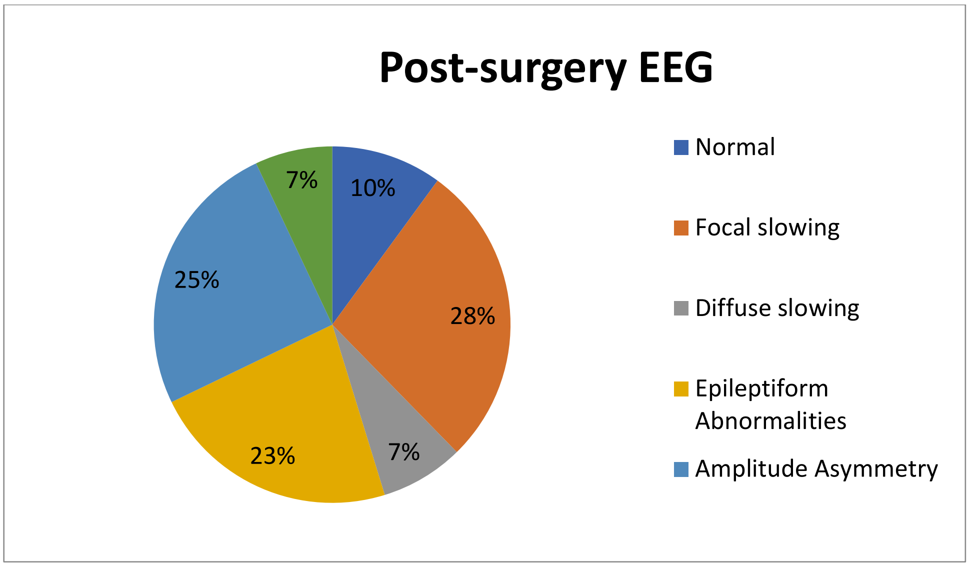
Results

Retrospective Moyamoya EEG study

Data of 21 patients who performed pre and postoperative EEG were retrospectively analysed (2009-2019). EEG characteristics were summarized in Table 2. In our series 6 patients presented seizures before surgery, 19/21 revealed some abnormalities in the preoperative EEG, the most frequent find was focal slowing in 13/21 patients, followed by epileptiform abnormalities observed in 12/21 patients. Before surgery hyperventilation activation procedure was performed in 12 cooperating patients, abnormalities were observed in 6/12 patients and rebuild-up phenomenon in one case,6 months after surgery hyperventilation was performed in 15 cooperating patients and 2/15 showed slowing during hyperventilation and rebuild-up phenomenon; in one case it persisted after 12 months. Postoperative EEG showed improvement in 13/21 cases, in particular 9/21 showed significant reduction of epileptiform abnormalities and 7/21 improvement of background activity organization with decrease of focal and diffuse slowing rate. 2/21 patients presented normal EEG before and after surgery. Six patients out of 21 remained stable and did not show any EEG improvement after surgery, 2 patients presented onset of epileptiform abnormalities in the first exam after surgery with subsequent improvement in the following ones.

EEG findings	Pre-op 21 patients (HP 12 patients)	Post-op 21 patients (HP 15 patients)
Normal	2/21	4/21
Focal slowing	13/21	11/21
Diffuse slowing	5/21	3/21
Epileptiform Abnormalities	12/21	9/21
Amplitude Asymmetry	7/21	10/21
Rebuild up	1/12	2/15





Data were recently used as a part of outcome evaluation, along with neurological and neuropsychological assessment, of Moyamoya patients who underwent surgical revascularization at Our Institute for the paper: "Tortora D.,Scavetta C., Rebella G., Bertamino M., Scala M., Giacomini T., Morana G., Pavanello M., Rossi A., Severino M. Spatial coefficient of variation applied to arterial spin labeling MRI may contribute to predict surgical revascularization outcomes in pediatric Moyamoya vasculopathy. Neuroradiology 62, 1003–1015 (2020). https://doi.org/10.1007/s00234-020-02446-4".

Prospective Moyamoya EEG study

Cohort description

Thirteen patients completed the presurgical EEG evaluation (9 patients > 3 years with 64 channels EEG and 4 patients < 3 years with 19 channels, 7 male and 6 female) and 11 completed the post-surgical assessment.

Unfortunately, due to the Sars-Cov2 outbreak one patient failed to attend the postoperative EEG control, the last one will be completed at the beginning of March 2022.

Cohort description data can be found in Table I.

Table I. Description of the study patients [N=13].

	n/N (%)
Sex: Male	7 (53.8 %)
Female	6 (46.2 %)
Moyamoya Disease, n (%):	6 (46.2 %)
NF1 related, n (%):	7 (53.8 %)
Age at surgery – ELDER (n=9) (years), *median*	10
Age at surgery – YOUNGER (n=4) (years), *median*	2
Symptom at onset: Headache – ELDER (n=9) , n (%):	7 (77.7%)
PEDMIDAS -ELDER (range: 0 -51):	
median at onset	11
median at follow-up	1
Symptom at onset: Seizures – YOUNGER (n=4), n (%):	4 (100%)

Six out of 13 patients presented with Moyamoya disease while 7/13 had Moyamoya syndrome associated with type 1 Neurofibromatosis (NF1). Based on the age of Moyamoya vasculopathy onset we could identify two group of patients, the elder one comprising 9 patients with a median age of onset 9 years old and the younger one comprising 4 patients with a median age of onset 5 months.

In the older group 7 patients presented with NF1-related Moyamoya syndrome and 2 with Moyamoya disease. The most frequent symptom at onset of Moyamoya vasculopathy was headache with migraine characteristics. In one case headache was associated with acute left hemiparesis (during a transient ischemic attack). One patient was asymptomatic at the time of Moyamoya syndrome diagnosis, cerebral vasculopathy was discovered during a routine MRI scan performed for NF1 scheduled follow-up. Another one with Moyamoya syndrome associated with NF1 presented with a cerebral ischemic left parietal lesion at the age of 6 years old and right hemiparesis.

Regarding the younger group, all patients were affected by Moyamoya disease. All of them presented at onset with focal seizures and ischemic strokes, in three cases involving the right middle cerebral artery (MCA) regions, while the remaining case showed bilateral MCA and posterior cerebral artery (PCA) involvement. Three out of 4 showed also motor impairment with hemiparesis.

All patients performed 3 Tesla brain angio-MRI before and after surgical treatment with TSE, SWI, 3DT1 and 3DFLAIR sequences, diffusion sequences with ADC, DWI and perfusion studies with 3D pCASL and DSC T2 with medium contrast agents and arterial TOF3D.

In the older cohort two patients presented with bilateral extended involvement of all the internal carotid arteries regions, while the others 7 had a unilateral less extended Moyamoya related picture.

In the younger cohort two patients presented with bilateral involvement.

MRI localization of Moyamoya-related alterations and side are summarized in Table II.

Table II. MRI localization.

Patient ID	**Arterial regions involved**	**Side**
Older		
1	ICA and MCA M1	Right
2	ICA and MCA	Right
3	ICA	Bilateral
4	M1	Left
5	ICA and MCA	Right
6	MCA	Right
7	ICA and MCA	Left
8	M1	Right
9	ICA	Bilateral
Younger		
10	ICA	Bilateral
11	MCA	Right
12	MCA, A1	Left
13	MCA, ACA	Bilateral

ICA = Internal Carotid Artery; MCA = Middle Cerebral Artery; ACA = Anterior Cerebral Artery.

All patients underwent to revascularization surgery both with direct (mostly used in severe affected older patients) or indirect revascularization techniques or a combination of different techniques. Patients with bilateral involvement received two-times surgery starting with the most affected hemisphere. Surgical data can be found in table III.

Table III. Surgery description.

Patient ID	**Type of surgical revascularization**	**Side**
Older		
1	STA-MCA (M4) bypass + EDMPS	Right
2	STA-MCA (M4) bypass + EMS	Right
3	1st STA-MCA (M4) bypass + EMS	Right
4	STA-MCA (M4) bypass + EDMPS	Left
5	STA-MCA +EMS	Right
6	EDAS + EMS destra	Right
7	STA-MCA bypass	Left
8	STA-MCA bypass	Right
9	1st STA-MCA (M4) bypass + EDMPS	Right
Younger		
10	1st EDAS	Rigth
11	EDAS + EDMPS	Right
12	EDAS + EDMPS	Left
13	1st EDAS + EDMPS	Left

STA-MCA = superficial temporal artery (STA) to middle cerebral artery (MCA) bypass surgery; EDMPS = Encephaloduromyoarteriopericraniosynangiosis; EMS = Encephalomyosynangiosis; EDAS = Encephaloduroarteriosynangiosis.

No major complications (cerebral haemorrhage, cerebral ischemia, exitus) and no post-operative mortality occurred. Mild surgical complications occurred in three patients (small self-resolving epidural blood layers in two cases and CSF fistula requiring two percutaneous evacuations in one patient). One patient presented a few episodes of acute postoperative focal seizures (APOS) and antiseizure treatment with levetiracetam was administered for 18 months after surgery and then gradually stopped.

None of the patients presented further cerebral ischemic events after revascularization surgeries during the follow-up period (median 24 months, range 10- 48 months).

Aspirin (dosage 3-5 mg/kg/day) was administered to the whole group of patients since Moyamoya diagnosis and through the follow-up period without relevant side effects.

All 5 patients presenting before surgery with neurological impairment experienced improvement of their symptoms.

One patient with acute left hemiparesis at onset experienced a normalization of the neurological picture after surgery, the other 4 patients showed a significant motor impairment reduction with a residual mild hemiparesis after surgery.

Regarding headache, a standardized questionnaire (PEDMIDAS made by three score: total, frequency and severity) was administered before and after surgery to the patients belonging to the older group. Seven out of 9 presented headache with migraine characteristics at onset. PEDMIDAS scores showed a significant improvement in all cases with decrease in frequency, severity, and in the total score. Three patients out of 7 resulted headache-free after revascularization surgery (See Figure 1,2,3). None of the patients required a headache prophylaxis treatment during the study period.

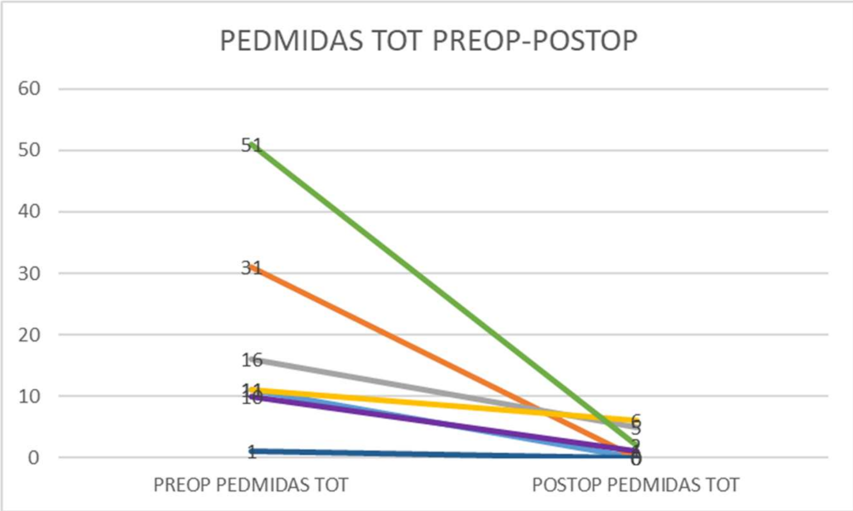


Figure 1*: preoperative and postoperative PEDMIDAS total score.*

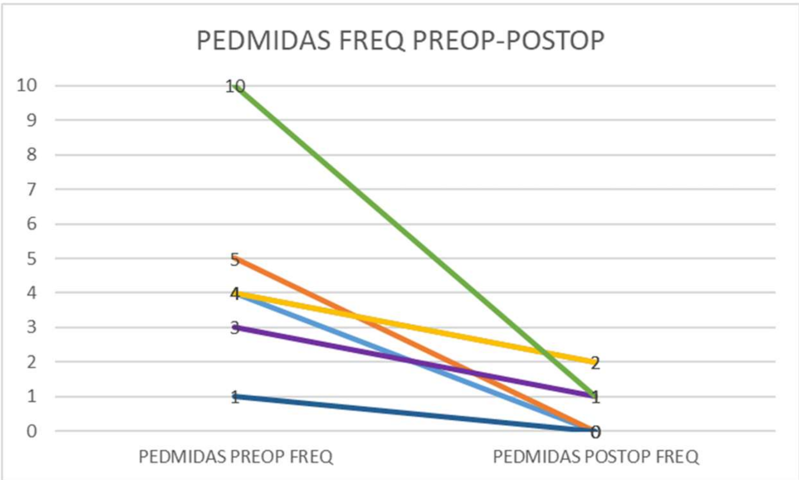


Figure 2*: preoperative and postoperative PEDMIDAS frequency score.*

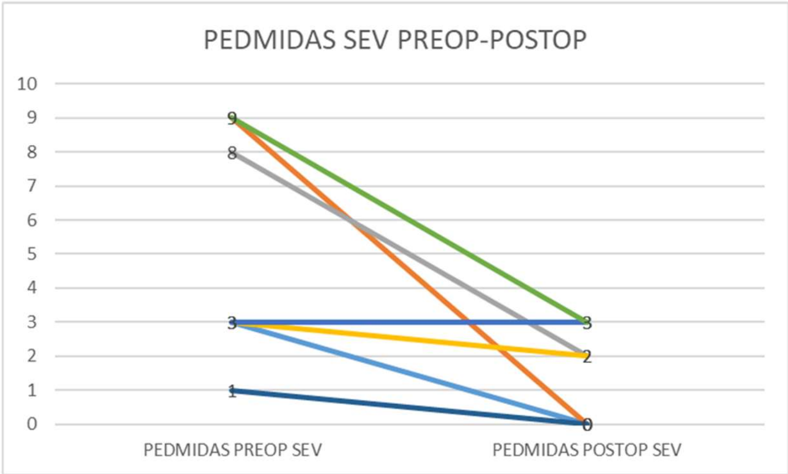


Figure 3: *preoperative and postoperative PEDMIDAS severity score.*

Regarding seizures, all the 4 patients in the younger group presented with epilepsy at onset. Two of them had frequent seizures before surgery, one experienced weekly focal motor seizures and another one developed epileptic encephalopathy with spasms. All patients experienced a reduction of both seizures' frequency and severity after surgery. At last follow-up, all of them presented with well-controlled epilepsy undertaking only one antiseizure medication (1 patient with carbamazepine, 1 levetiracetam, 1 phenobarbital and 1 vigabatrin).

EEGs description

Unfortunately, due to the Sars-Cov2 outbreak one patient failed to attend the postoperative EEG control and was excluded from the analysis, another one will be completed at the beginning of March 2022.

EEG of the remaining 11 patients were visually reviewed, epochs containing large movement artifacts or arousal were rejected and channels contaminated by continuous artefact were manually identified.

Patient 8 was excluded due to abundancy of slow hypersynchronous theta waves in the first phase of sleep, presence of several arousals and the impossibility to reach a sufficient time of phase 2 NREM both in the preoperative and postoperative EEG.

Patient 10, the one affected by epileptic encephalopathy with spasms, was excluded because of subcontinuous epileptiform abnormalities in both the preoperative and postoperative EEG making difficult to recognize physiological sleep graphoelements.

NREM sleep EEG data recorded before and after surgical revascularization treatment have been analysed by means of power spectral density (PSD) computed using Welch's method, looking in particular for sigma (10-16 Hz) and delta band (1-4 Hz) in order to identify differences in sleep spindles or delta waves distribution.

In three patients (ID 7,11,12) the power spectral density analysis did not show any peak in the sigma band (in the presurgical or in the postsurgical

EEG exam) probably due to diffuse technical artifacts, further analysis is ongoing to overcome the problem.

The setting of the study with a daytime nap sleep recording did not permit the registration of a sufficient time of N3 NREM sleep and even in the 6 patients selected for the power spectral density analysis N3 NREM phase was limited to a few minutes of the whole EEG. The power spectral density analysis of the delta component showed a small increase only in patients 4-5-6 (See Figures).

Sigma band power spectral density analysis instead showed an increase in the postsurgical NREM sleep in all the 6 analysed patients except one (Patient 5).

Further analysis of spectral power in NREM sleep before and after the revascularization surgery was performed using topographical maps in order to differentiate between the surgically treated hemispheres and the hemisphere not treated.

Topographical maps were realized presenting ratio between the postoperative – preoperative /postoperative + preoperative ratio.

Topographical maps showed that the difference between the preoperative and postoperative spectral distribution was more significant over the surgically treated hemispheres.

Power Spectral Density analysis and topographical maps of the patients can be found in Figures 4-10.

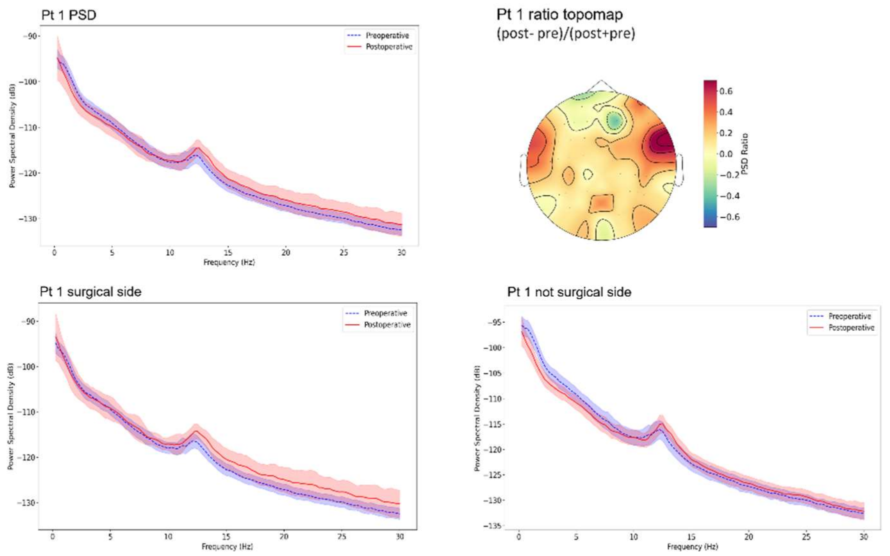


Figure 4: Patient 1 with NF1 related MM, right ICA and MCA-M1 involvement, treated with right STA-MCA (M4) bypass + EDMPS

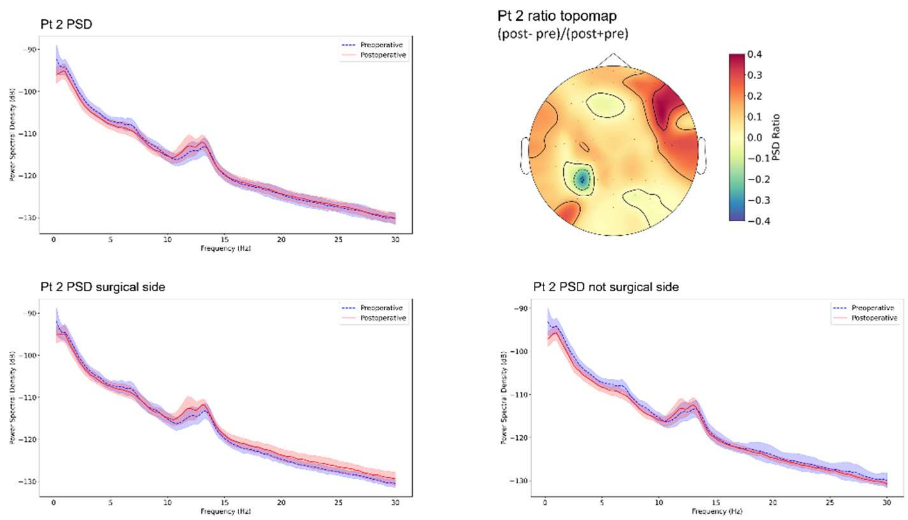


Figure 5: Patient 2 with MM disease, right ICA and MCA involvement, treated with right STA-MCA (M4) bypass + EMS

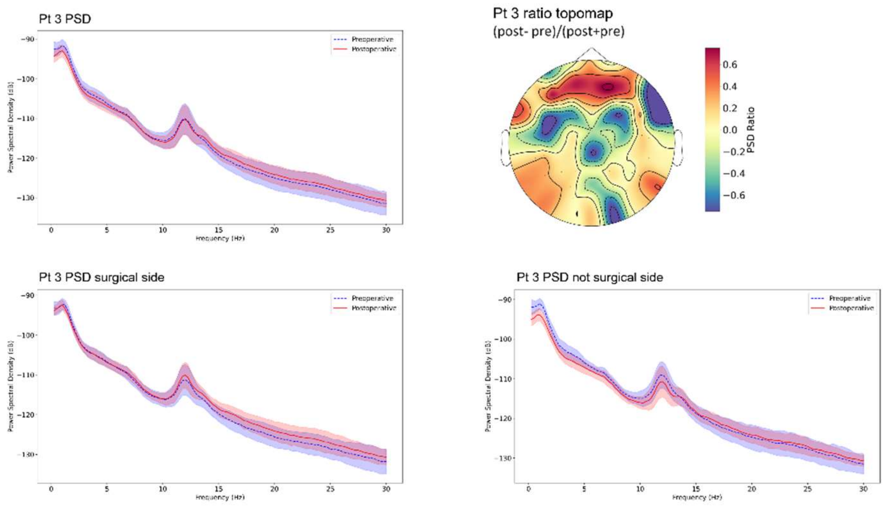


Figure 6: patient 3 with MM disease, bilateral diffuse ICA involvement, recorded after 1st surgery, right STA-MCA (M4) bypass + EMS

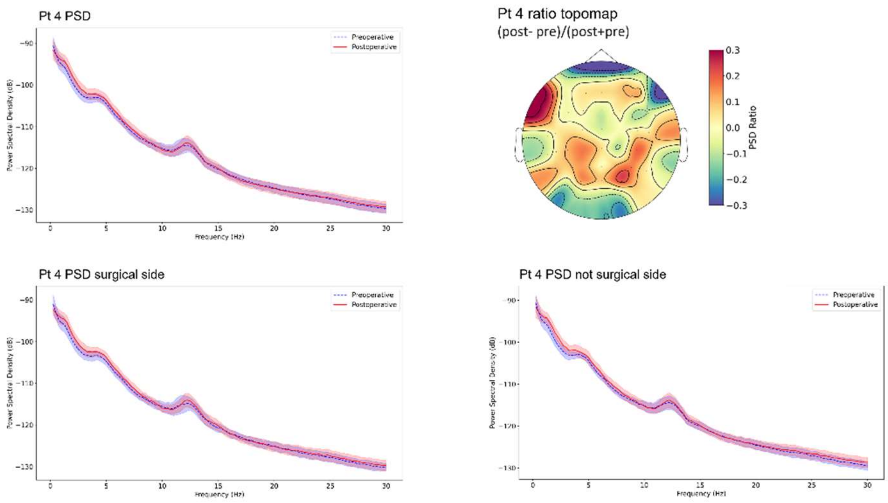


Figure 7: patient 4 with NF1 related MM, left M1 involvement, STA-MCA (M4) bypass + EDMPS

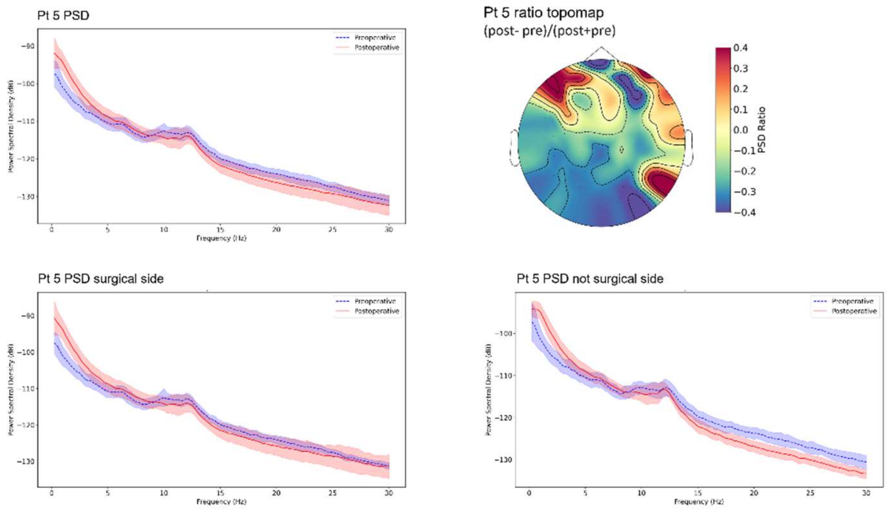


Figure 8: patient 5 with NF1 related MM, right ICA and MCA involvement, right STA-MCA +EMS

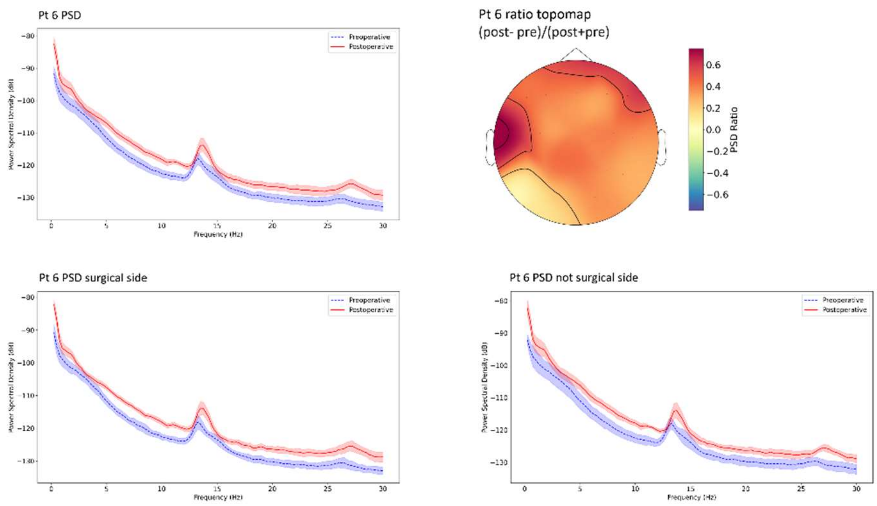


Figure 9: patient 13 with MM disease, bilateral diffuse MCA ACA involvement, recorded after 1st surgery left EDMPS

The differences between postsurgical and presurgical area of average Power Spectral Density were further measured through integral calculus and reported in Table IV.

Table IV. EEG Area Average Power Spectral Density postsurgical - presurgical.

Patient ID	**All**	**Surgical side**	**Not surgical side**
Older			
1	12.215	20.284	5.516
2	14.198	24.475	5.488
3	-9.038	9.14	-29.593
4	0.841	2.004	2.29
5	-18.417	-16.401	-18.38
Younger			
10	22.917	23.039	22.603

Discussion

The main object of our study was to explore EEG sleep studies role in Moyamoya vasculopathy in order to find new feasible tools for MM diagnosis, outcome evaluation after revascularization surgery and follow-up.

Preliminary data showed that EEG sleep studies can reveal significant differences before and after revascularization surgery in a subgroup of our patients with change in power spectral density within sigma and delta band, making EEG a non-invasive promising tool that could be used for outcome measure and follow-up, even when hyperventilation activation procedure is not available due to lack of patient cooperation.

Another object was to validate clinical use of PEDMIDAS score for the evaluation of headache in Moyamoya patients. Prospective use of a standardized questionnaire for headache evaluation permitted to measure the headache burden efficiently and easily before and after surgery in our paediatric cohort of patients.

In our prospective cohort of pediatric patients affected by Moyamoya vasculopathy revascularization surgery was well tolerated without any major complications observed.

Surgery was effective in reducing occurrence of new cerebral ischemic lesions; none of the patients experienced any stroke, cerebral haemorrhage or transient ischemic attacks after surgery during the follow-up period, confirming efficacy of direct and indirect revascularization surgical techniques in preventing ischemic events in paediatric Moyamoya vasculopathies.[3,10,35] Evidence in the literature about the natural history of Moyamoya without surgery report a 5-years risk of repeated stroke or haemorrhage up to 65% in symptomatic patients and 3.2% year stroke risk in asymptomatic ones.[36]

In our cohort, all patients experienced a clinical improvement after surgery with reduction of motor impairment and headache similarly to what reported in previous cohorts.[7] We also observed seizures frequency and severity reduction in epileptic patients as recently reported in another study by Alramadan et al.[37]

Headache is one of the most frequent symptoms of MM vasculopathies at onset, reported in 20 to 76.4 % of the patients, however studies addressing the description, burden as well as pharmacological management of this symptom in MM patients are still scarce.[38,39] Our results confirmed and supported previous findings reporting frequent headache improvement after revascularization surgery.[7,38,39]

EEG NREM sleep power spectral density analysis of 6 patients of our cohort with Moyamoya vasculopathy revealed significant differences before and after revascularization surgery. Five over 6 patients showed increase in the sleep spindles sigma band and 3/6 showed delta band increase.

With a further analysis we showed that our findings were more relevant in the surgically treated hemisphere. Topographical maps supported our results.

Sleep spindles reduction have been demonstrated in thalamic strokes as well as in schizophrenia and epileptic encephalopathies with a correlation with cognitive dysfunction.[25,33,40] In a recent report increase in sleep spindles with a coincident cognitive improvement has been reported after a successfull pharmacological treatment in a patient with epileptic encephalopathy.[25]

Our hypothesis is that an increase of the power density in sigma band could correlate with the clinical improvement after surgery in MM patients, making EEG sleep study a non-invasive innovative outcome biomarker of revascularization techniques.

Our study had some limitations due to the small sample size and due to the rarity of the disease, making necessary the implementation to large multicentre studies in order to validate EEG sleep studies utility in diagnosis and follow-up of MM patients.

Conclusion

EEG sleep studies showed significant differences before and after revascularization surgery in a subgroup of our cohort with change in Power Spectral Density of sigma and delta band, making EEG a non-invasive promising tool for Moyamoya patients' evaluation.

PEDMIDAS is a standardized questionnaire that can be easily used at diagnosis, as an outcome measure of revascularization surgery efficacy and during follow-up in Moyamoya patients presenting with headache.

Large multicentre studies are needed in order to validate EEG sleep studies utility in diagnosis and follow-up of MM patients and to identify proper and evidence-based clinical management guidelines.

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