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What happens to temporal hypometabolism contralateral to side of surgery in patients with bilateral temporal hypometabolism?

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ABSTRACT

Objective: To see what happens on PET hypometabolism on the temporal lobe contralateral to the side of surgery in patients with bitemporal hypometabolism (BTH).

Patients and Methods: This retrospective study with prospectively defined data evaluated the pre- and post-surgical PET hypometabolism on the contralateral temporal lobe after resection of ipsilateral temporal lobe in 10 patients with BTH operated between January, 2010 and May, 2018. On PET we compared standard uptake values (SUV) and relative metabolic activities as compared to normal subjects by means of Z-scores of hypometabolism of unresected temporal lobes before and after surgery.

Results: Surgery did not lead to satisfactory seizure outcome and only 3 patients were seizure free. All but one were still using anti-epileptic drug. No significant change was noted on PET hypometabolism related to the contralateral temporal lobe at the last follow-up. Regarding the mean SUV, comparisons showed that the difference with respect to the mesial structures was significant ($p = 0.04$). But lateral cortex showed insignificant difference ($p = 0.21$) before and after surgery. Regarding the mean Z-score, no significant differences were found between both the mesial temporal structures ($p = 0.23$) and lateral temporal cortex ($p = 0.18$).

Conclusion: Surgery does not lead to improvements on PET hypometabolism of the temporal lobe contralateral to the side of surgery and hypometabolism on the contralateral side may be due to structural damage rather than functional deficits secondary to propagation of repetitive seizures. Seizure outcome is not satisfactory and before surgery patients or their next of kin should be informed in detail.

1. Introduction

Temporal lobe epilepsy associated with hippocampal sclerosis (TLE-HS) is the most common form of focal epilepsy and surgical treatment has been proven to be more successful compared to anti-epileptic drug (AED) therapy [1]. More importantly, surgery leads to higher rate of seizure freeness and increases quality of life in patients with TLE [2,3]. In patients with TLE-HS, architectural distortion and volume loss on the temporal lobe are the common findings on magnetic resonance imaging (MRI) and it may also associated with a variable degree of hypometabolism on ^{18}F-fluoro-deoxyglucose positron emission tomography (PET).

Preoperative work-up in TLE-HS generally demonstrates that epileptogenic zone is more extensive than appear on MRI, which may include the insula, other brain areas or contralateral temporal lobe. If preoperative findings from seizure semiology, electrophysiological and radiological studies including PET are compatible with each other, the treatment is straight forward; surgical resection becomes the first line of treatment. However, if one of preoperative findings shows discordant data such as bitemporal hypometabolism (BTH), the decision to have surgery is challenging and further work-up may be mandatory.

Patients with bitemporal epilepsy (BTE) have a variety degree of FDG-PET hypometabolism on both temporal lobes and in these cases decision to have surgery mainly depends on the findings from invasive electroencephalography (EEG) studies such as subdural grids or strips and/or depth electrodes [stereo-electro-encephalography (SEEG)] which have also been widely used for years in advanced epilepsy centers for invasive EEG monitoring, especially for temporal cases. The

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common notion and/or finding form the limited number of clinical studies is that seizure outcome in BTE is not satisfactory than unilateral temporal epilepsy (UTE) [4–6].

Whether hypometabolism is a cause or effects of continuous or repetitive seizures has not been clearly proven. Induced-seizure models in experimental studies showed that seizures can lead to architectural changes [7] and these changes then may cause seizures [8] or as demonstrated, seizure frequency and duration of epilepsy is associated with structural changes seen on MRI [9] and metabolic impairments seen on FDG-PET [10]. One of the reason having seizure after surgery in BTE may be due to that fact that hypometabolism on the contralateral temporal lobe is still epileptogenic zone.

In this retrospective study with prospectively defined data, we simply made a hypothesis: if contralateral temporal hypometabolism reflects a disturbance of function due to repetitive seizures, that hypometabolism is expected to improve (decrease) after surgery when patients are seizure free or have less seizure frequency compared to preoperative state. Thus our question is that what happens to temporal hypometabolism contralateral to the side of surgery in patients with bitemporal hypometabolism (BTH).

2. Patients and methods

2.1. Patients

Ten adult patients, who showed BTH on FDG-PET and were operated on temporal lobe epilepsy between January 2010 and May 2018, were included in this study. Seizure semiology, patients' medical and family history, use of AED and characters of seizures were noted. As in all epilepsy centers, all patients had high-resolution head MRI with epilepsy protocol and scalp EEG examinations. High-resolution MRI performed using a 1.5 T between 2010 and 2017 (Siemens Avanto, Erlangen, Germany) or 3.0 T after 2017 (Philips Inginia, Netherlands. The MRI protocol included Transverse spin-echo double-echo images of the entire brain, coronal fast spin echo T2-weighted, coronal FLAIR, coronal MPR TIR and 3-D FLAIR and T1-weigted images. The transverse and coronal sections were in parallel and perpendicular to the axis of the hippocampal formation. All patients underwent FDG-PET and invasive SEEG because of scalp EEG, head MRI and seizure semiology showed findings suggestive of BTE.

Depending on the findings from invasive SEEG and degree of hypometabolism, all patients underwent surgery in which temporal resection including the mesial temporal areas (hippocampal-parahippocampal complex, amygdala and uncus) were performed. Resection of the temporal cortex was tailored depending on the side of the temporal dominance. Surgical decision was made in these patients with BTH was solely depend on the findings from FDG-PET and SEEG. The side for resection was chosen if frequent ictal onsets from SEEG and more prominent hypometabolism are concordant. Since surgical technique has been extensively reported in the literature, we will not go into detail [2,3]. Briefly, our surgical technique included anterior temporal lobectomy with amygdalohippocampectomy (ATL + AH). In this surgical technique, the goal is to perform a temporal neocortical resection, extending habitually 5 cm along the sylvian fissure and 5 to 5.5 cm along the floor of the middle fossa on the non-dominant side and 4.5 to 5 cm in the dominant side, together with total or partial resection of the amygdala and uncus, and 2.5 to 3 cm removal of the hippocampus and parahippocampal gyrus.

2.2. FDG-PET studies and data analysis

All patients underwent FDG-PET scan before surgery and at the last follow-up. Briefly, after a minimum of 4–6 hours fasting, 290.4 MBq was injected intravenously and following 30 min rest, the patient's head was scanned using integrated PET-CT. A total of 20 FDG-PET scan was performed. Sixteen of the 20 was performed by using GE Discovery 710 PET/CT and the rest was performed by using Siemens Biograph LSO HI-REZ PET/CT. Average standard uptake values (SUV) and a Z-score metrics of metabolic activity as compared to normal subjects were calculated for each structure. Z-Scores reflect the number of Standard deviations from the database of control subjects; a negative value reflects hypometabolism as compared to the normal dataset, a positive score indicates hypermetabolism [10].

2.3. Statistical analysis

Statistical analysis was performed by using SPSS version 22.0.

Table 1
Summary of clinical characteristics of patients before and after surgery.

No	Age	Sex	Onset	Duration	Seizure frequency/ month		Number of AED	
	Yrs		Yrs	Yrs	*Before surg.*	*After surg.*	*Before surg.*	*After surg.*
1	39	F	20	19	60	None	3	2
2	18	F	6	12	4	4	3	3
3	37	F	1	36	24	8	3	3
4	33	F	12	21	3	1	3	3
5	30	M	12	18	26	None	4	None
6	32	F	1	31	3	2	4	3
7	43	M	1	42	10	10*	4	4
8	38	M	22	16	8	None	2	1
9	51	M	22	29	120	3	4	3
10	42	F	10	32	3	1	3	3

AED: Anti-epileptic drug; F: Female; M: Male; Yrs: Years.
* Number of seizures is the same after surgery but both duration and severity of seizures dramatically decreased.

Table 2
Components of seizures of patients before and after surgery.

No	Aura		Loss of consciousness		Automatism		Generalization	
	Before surgery	*After surgery.*	*Before surgery*	*After surgery*	*Before surgery*	*After surgery*	*Before surgery*	*After surgery*
1*	Present	Absent	Present	Absent	Present	Absent	Present	Absent
2	Absent	Absent	Present	Present	Present	Present	Present	Present
3	Present	Absent	Present	Absent	Present	Present	Present	Absent
4	Present	Present	Present	Present	Present	Present	Present	Present
5*	Absent	Absent	Absent	Absent	Present	Absent	Absent	Absent
6	Present	Absent	Present	Present	Present	Present	Present	Present
7	Absent	Absent	Present	Absent	Present	Present	Present	Absent
8*	Present	Absent	Present	Absent	Present	Absent	Present	Absent
9	Present	Absent	Present	Absent	Present	Present	Present	Absent
10	Absent	Absent	Absent	Absent	Present	Present	Present	Absent

* Indicates seizure free patients at the last follow-up period.

Table 3
Summary of surgical, histopathological diagnosis and follow-up.

No	Side of surgery	Pathological diagnosis		Follow-up
		Temporal neocortex	*Hippocampal complex*	Years
1	Right temporal	FCD type-Ia	Sclerosis	0.5
2	Left temporal	FCD type-Ib	Sclerosis	0.5
3	Right temporal	MCD	Sclerosis	1
4	Left temporal	FCD type-Ib	Sclerosis	2
5	Left temporal	FCD type-Ia	Gliosis	2
6	Right temporal	FCD type-Ib	Gliosis	5
7	Left temporal	FCD type-Ib	Gliosis	6
8	Right temporal	Gliosis	Gliosis	6
9	Right temporal	FCD type-IIa	Gliosis	8
10	Left temporal	FCD type-Ib	Sclerosis	8

FCD: Focal cortical dysplasia; MCD: Malformation of cortical development.

Table 4
Standard uptake values (SUV) on FDG-PET for the temporal lobes ipsilateral and contralateral to the side of resection.

No	Before Surgery				After Surgery			
	SUV on PET/**Right**		SUV on PET/**Left**		SUV on PET/**Right**		SUV on PET/**Left**	
	Lateral	*Medial*	*Lateral*	*Medial*	*Lateral*	*Medial*	*Lateral*	*Medial*
1	0.69	0.54	0.78	0.60	**Side of resection**		0.78	0.66
2	0.83	0.73	0.75	0.68	0.81	0.75	**Side of resection**	
3	0.77	0.63	0.65	0.58	**Side of resection**		0.69	0.60
4	0.86	0.68	0.74	0.65	0.81	0.70	**Side of resection**	
5	0.81	0.69	0.77	0.69	0.82	0.71	**Side of resection**	
6	0.78	0.55	0.84	0.62	**Side of resection**		0.82	0.67
7	0.90	0.75	0.49	0.50	0.94	0.81	**Side of resection**	
8	0.81	0.69	0.88	0.74	**Side of resection**		0.81	0.70
9	0.89	0.68	0.88	0.66	**Side of resection**		0.83	0.66
10	0.90	0.65	0.88	0.63	0.86	0.66	**Side of resection**	
	Mean ± SD (underlined numbers only)				**Mean ± SD (underlined numbers only)**			
	Lateral		Medial		Lateral		Medial	
	0.83 ± 0.07		0.67 ± 0.05		0.81 ± 0.06		0.69 ± 0.95	

PET: Positron emission tomography; SUV: Standard uptake value.

Table 5
Z-scores on FDG-PET for the temporal lobes ipsilateral and contralateral to the side of resection.

No	Before Surgery				After Surgery			
	Z-score on PET/**Rt.**		Z-score on PET/**Lt.**		Z-score on PET/**Rt.**		Z-score on PET/**Lt.**	
	Lateral	*Medial*	*Lateral*	*Medial*	*Lateral*	*Medial*	*Lateral*	*Medial*
1	−9.21	−4.71	−4.55	−2.93	**Side of resection**		−4.28	−0.86
2	−2.62	1.59	−5.57	0.03	−3.74	2.24	**Side of resection**	
3	−5.6	−1.76	−9.66	−3.68	**Side of resection**		−8.17	−2.91
4	−1.37	0.16	−5.87	−1.24	−3.66	0.54	**Side of resection**	
5	−3.69	0.41	−4.68	0.34	−3.41	1.08	**Side of resection**	
6	−4.84	−4.51	−2.22	−2.24	**Side of resection**		−2.96	−0.33
7	0.39	2.25	−15.79	−6.42	2.05	4.4	**Side of resection**	
8	−3.61	0.37	−0.56	2.05	**Side of resection**		−3.42	3.53
9	−0.25	0.14	−0.69	0.79	**Side of resection**		−2.66	−0.98
10	0.43	−0.93	−0.34	−1.88	−1.48	−0.81	**Side of resection**	
	Mean ± SD (underlined numbers only)				**Mean ± SD (underlined numbers only)**			
	Lateral		Medial		Lateral		Medial	
	−2.45 ± 3.0		−0.25 ± 2.10		−3.17 ± 2.52		0.29 ± 2.0	

Lt: Left; PET: Positron emission tomography; Rt: Right.
Z-score: Negative Z-score identifies decreased glucose metabolism (increased hypometabolism) compared to normal database.

Values are given as mean ± standard deviation. Comparisons before and after surgery was performed by using "student's *t* test". A probability value (p value) less than 0.05 was considered statistically significant.

3. Results

3.1. Patients

Our small sample of patients with BTH included 4 males (40%) and 6 females (60%) with a mean age of 36.3 ± 8.8 years at the time of surgery. The mean age of seizure onset was 10.7 ± 8.4 years and the seizure duration was 25.6 ± 9.7 years. All were on multiple AED therapy before surgery. The mean follow-up was found to be 3.9 ± 3 years; ranged from 6 months to 8 years. Tables 1 and 2 show a summary of clinical and seizure characteristics of 10 patients. Histopathological diagnosis showed focal cortical dysplasia (FCD) on the temporal cortex in 8 (80%) of patients, followed by 1 gliosis (10%) and 1 malformation of cortical development. Regarding the mesial temporal area, gliosis and sclerosis were found in half of the surgical specimens (50% gliosis and 50% sclerosis) (Table 3). Mean seizure frequency/month before surgery and at the last follow-up were 26.1 ± 37.4 (from 3 to 120) and 4.5 ± 3.7 (from 1 to 10), respectively. Although seizure frequency after surgery was decreased, the difference was not significant (p = 0.28). Only three patients (30%) were seizure free (Engel I). Severity of seizures such as number of aura (6 versus 1), loss of consciousness (8 versus 3), presence of automatism (10 versus 7) and secondary generalization (9 versus 3) decreased after surgery; however we were not be able to perform statistical analysis due to very small number of patients included. Regarding AED use after surgery, only one patient (10%) who was also seizure free was off AED. The number of AED decreased in 4 (40%) and was the same in 5 (50%) patients during follow-up. The mean number of AED before surgery was 3.3 ± 0.6 (2 to 4). At the last follow-up the mean number of AED was decreased to 2.7 ± 0.8 and the difference was significant (p = 0.03).

3.2. Metabolic changes on FDG-PET

Tables 4 and 5 summarize SUV and Z-scores obtained from the FDG-PET studies before and after surgery (at the last follow-up). Depending on the tables, nine patients (90%) showed decrease in hypometabolism on the mesial temporal structures (hippocampal-parahippocampal complex) whilst one (10%) showed increase on the contralateral temporal lobe. Regarding the contralateral lateral temporal cortex, decrease and increase hypometabolism were seen in 4 (40%) and 6 (60%) patients, respectively.

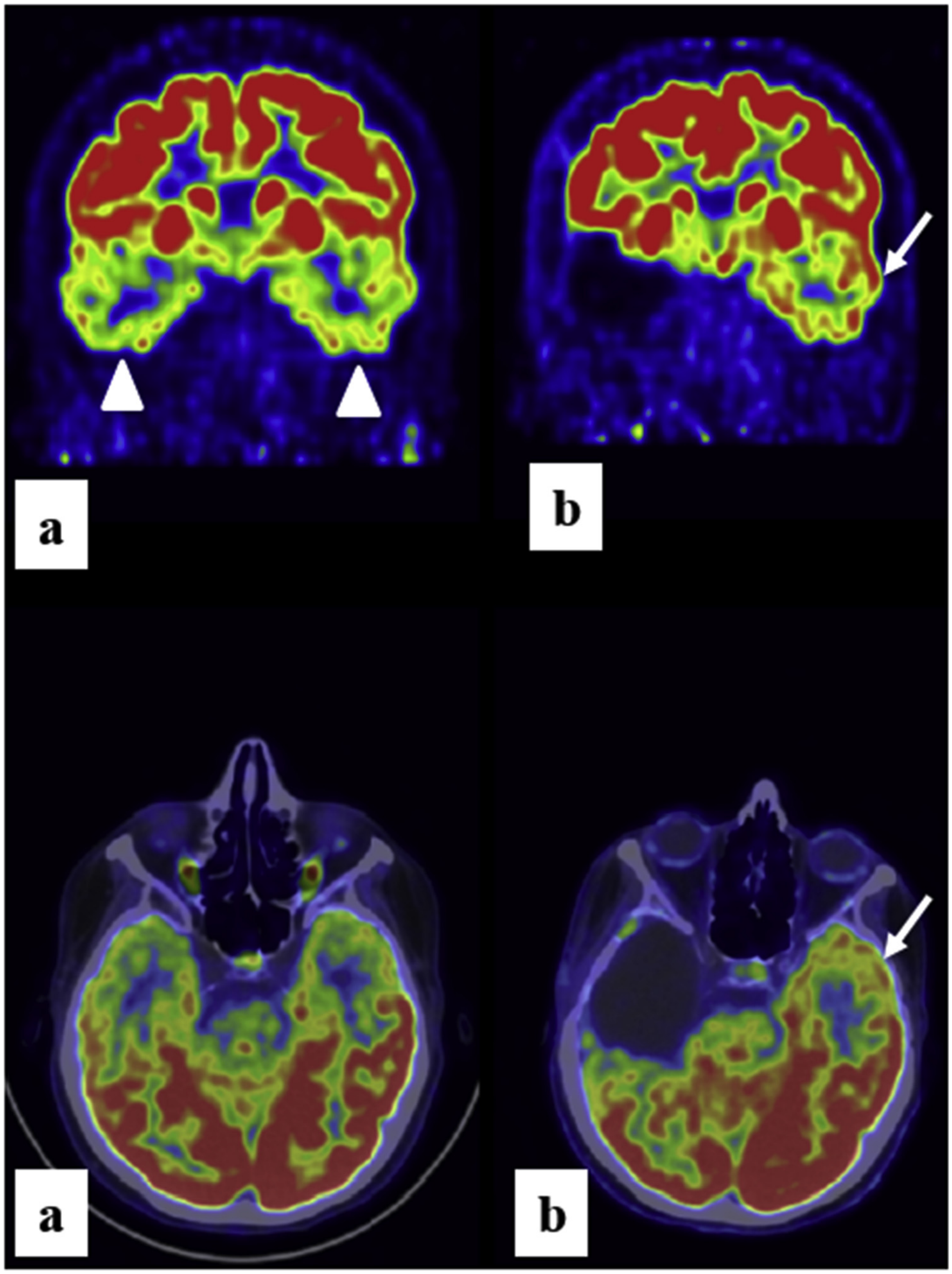

Fig. 1. This 32-year old female showed bitemporal hypometabolism (**a**; arrowheads) on FDG-PT before surgery. The patient underwent epilepsy surgery in which right anterior temporal resection including the mesial structures was performed. Five years after surgery, FDG-PET showed *improvement* (or decrease) in hypometabolism on the contralateral temporal lobe (**b**; arrows).

The mean SUV on the lateral temporal cortex and mesial temporal structures before surgery were 0.83 ± 0.07 and 0.67 ± 0.05, respectively. After surgery the SUV with respect to the same structures of unresected temporal lobe were 0.81 ± 0.06 and 0.69 ± 0.95, respectively. Statistical comparisons showed that the difference regarding the mesial structures was significant ($p = 0.04$). But lateral cortex showed insignificant difference ($p = 0.21$) before and after surgery.

The mean Z-score on the lateral temporal cortex and mesial temporal structures before surgery were -2.45 ± 3.0 and -0.25 ± 2.10, respectively. After surgery the Z-score with respect to the same structures of unresected temporal lobe were -3.17 ± 2.52 and 0.29 ± 2.0, respectively. Although lateral temporal cortex showed increased hypometabolism and the mesial temporal structures had decreased hypometabolism, the differences were not significant ($p = 0.18$ for lateral temporal cortex and 0.23 for mesial temporal structures). The results from the FDG-PET metrics suggest that there is no global improvement on temporal hypometabolism contralateral to the side of surgery in patients with BTH (Figs. 1 and 2).

Three patients (patient no: 1, 5, and 8 in the tables) in this paper were seizure free and deserve further mentioning. There were improvements on hypometabolism (decrease in hypometabolism) on FDG-PET in both lateral temporal cortex and mesial temporal structures of the contralateral temporal lobe after surgery in two patients (patient no: 1 and 5). Especially serious decrease on hypometabolism was noted on the mesial structures of the two patients. Furthermore patient no: 5 were off AED. Regarding the third patient (no: 8), there was no improvement on FDG-PET hypometabolism on both lateral temporal neocortex and mesial structures contralateral to the side of surgery but the patient was seizure free and was still on AED at the last follow-up.

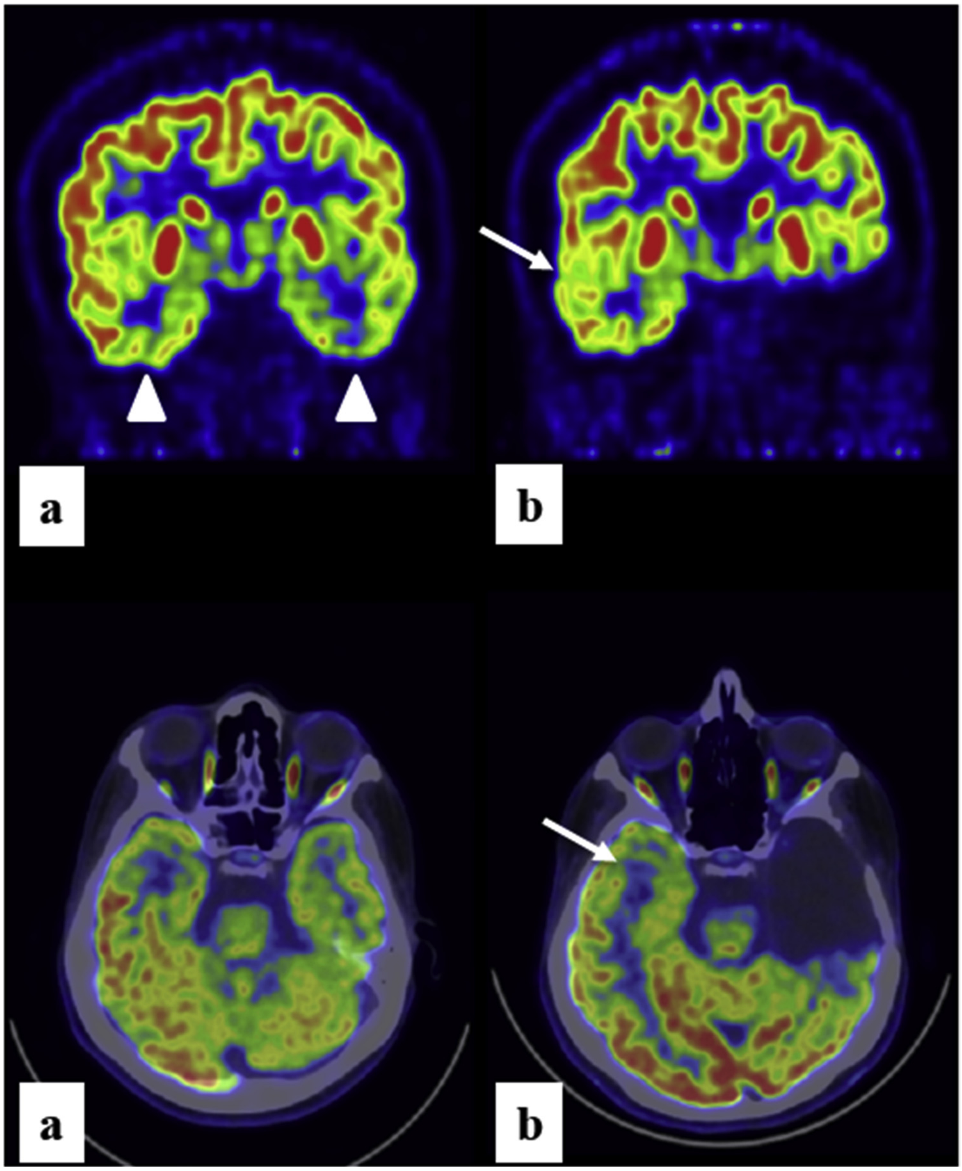

Fig. 2. This 33-year old female showed bitemporal hypometabolism sever on the left side (**a**; arrowheads) on FDG-PT before surgery. The patient underwent epilepsy surgery in which left anterior temporal resection including the mesial structures was performed. Two years after surgery, FDG-PET showed *worsening* (or increase) in hypometabolism on the contralateral temporal lobe (**b**; arrows).

4. Discussion

As far as we know, this is the first report to show whether there is any change on temporal hypometabolism on FDG-PET contralateral to the side of temporal lobe epilepsy surgery in patients who had BTH at long-term follow-up. The main findings from the limited number of patients with BTH are as follows: 1) seizure outcome is not satisfactory in these patients; 2) individually, hypometabolism on the contralateral mesial temporal structures shows improvements more common compared to the lateral temporal cortex; 3) however; surgery does not lead to overall improvements on hypometabolism in the contralateral temporal lobe; 4) seizure freeness may be related to decrease on hypometabolism on both mesial structures and lateral temporal neocortex in the contralateral temporal lobe; 5) patients with BTH who underwent surgery on one temporal lobe should be followed-up with FDG-PET after surgery; and 6) hypometabolism on the contralateral temporal lobe may be due to structural damage rather than functional impairments.

The body of evidence unfortunately showed contradictory results related to seizure outcome in patients with BTH. Some papers indicated good surgical outcome [11,12] and even rate of seizure free patients was reported as 47% [13]. On the other hand some others have found unfavorable seizure outcome [4,6] and even worsening after surgery [14]. It is interesting to note that some studies have found no significant difference between unilateral temporal hypometabolism (UTH) and BTH with respect to seizure outcome after surgery [11,12]. These results suggested that seizure onset zone in patients with BTH can also be unilateral. On the basis of our data related to limited number of patients we would like to underline that patients with BTH are not good candidate for surgery although seizure frequency decreased but the difference was insignificant compared to preoperative seizure frequency. Only three patients (3/10; 30%) were seizure free and two of them were still on AED. This result suggests that epileptogenic zone in these three patients with BTH might be unilateral and in order to get seizure freeness in these patients, improvements on contralateral hypometabolism should be noted on both mesial temporal structures and temporal neocortex. Patients with BTH in the present study benefited surgery in two ways: seizure frequency and/or severity and number of AED decreased. However; the majority of our patients were still using AED. We have to underline that the readers should be careful when interpreting the results from the clinical studies including ours that almost all studies had very limited number of patients with BTH and seizure outcome was not defined by using a common outcome scale. Thus, we believe that patients with BTH should be carefully evaluated before taking decision on resective surgery and agree with Didato, et al. [6] that therapeutic strategies other than resective surgery should be further sought in these patients. If surgery becomes mandatory for one temporal lobe due to, such as frequent daily or monthly seizures, the seizure outcome should be discussed with the patients or next of their kin extensively that the patients should know that seizure freeness may not be possible after surgery.

There have also been conflicting data regarding the source(s) of white matter changes (WMC). There is a notion that FDG-PET hypometabolism on the contralateral temporal lobe after the resection of ipsilateral temporal lobe may be related to the propagation of repetitive seizures since no significant differences of postoperative neuropsychological changes and seizure outcome between UTH and BTH is found [4,11,12]. Furthermore some studies suggested that WMC could be nonspecific reactive changes secondary to glial cell proliferation on unresected temporal lobe due to seizure activities [15]. However; others found that bilateral WMC could only be found in patients with BTH and that WMC was associated with FDG-PET hypometabolism in TLE-HS [16]. Regarding our results we found that seizure freedom and/or decreasing seizure frequency did not lead to global improvements on FDG-PET metrics on temporal hypometabolism contralateral to the side of surgery. Mesial temporal structures showed improvements more common than those of temporal neocortex. Inevitably, depending on our results we should ask the question: If FDG-PET hypometabolism on the contralateral temporal lobe has caused by propagation of repetitive seizures, why we did not see significant improvements on FDG-PET hypometabolism of contralateral temporal lobe in patients who were seizure free or have significantly decreased seizure frequency?. We think that there might be a structural change such as FCD on the contralateral temporal cortex as we found FCD in the majority of patients (8/10; 80%) on their temporal cortices of the resected temporal lobe. Similarly, contralateral mesial temporal structures might also have gliosis and/or sclerosis. Overall, depending on our sample we may claim that patients with BTH may in reality have structural changes on both temporal lobes and before proceeding surgery on one side, we have to be careful to decide whether surgery should be taken or not?.

Our results suggested that patients with BTH should be followed by FDG-PET since in our three patients who were seizure free; improvements on FDG-PET hypometabolism on both mesial and lateral temporal areas contralateral to the side of surgery were noted. We should note that these three patients with BTH may have unilateral TLE and contralateral hypometabolism might be caused by propagation of repetitive seizures. However; it is very difficult to maintain the same notion for the rest of our patients who were not seizure free and did not have improvements on the contralateral temporal hypometabolism globally.

5. Study limitations

The first limitation in this study is that we were able to include less number of patients with BTH. However, given that the current literature does have a very small number of patients with BTH, these limitations can be greeted with understanding. The second limitation is that our study had short-term follow-up. We suggest that larger cohort of patients with BTH and long-term follow-up with FDG-PET should be the study of the future in order to have more comprehensive results which may lead us to have optimal treatment protocol in patients with BTH.

6. Conclusion

Related to our small sample of patients with BTH, we conclude that surgery does not provide satisfactory seizure outcome and seizure free rate is very low. Global improvement on FDG-PET hypometabolism with respect to the temporal lobe contralateral to the side of surgery should not be expected because of hypometabolism on the contralateral temporal lobe may be caused by structural damage rather than functional impairments due to propagation of repetitive seizures.

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Declaration of interest

None.

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