

Stereotactic amygdalohippocampectomy for temporal lobe epilepsy: promising results in 16 patients

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ABSTRACT – Objectives. Minimally invasive procedures for treating temporal lobe epilepsy have been investigated recently, namely stereotactic and gamma knife amygdalohippocampectomy (AHE). However, the results are not fully satisfactory. Our aim was to evaluate efficacy and side-effects of stereotactic AHE mimicking the neurosurgical procedure in terms of extent of the lesion. **Methods.** 16 consecutive patients were assessed using VEEG, MRI, FDG-PET and WADA test. All had definite pharmacoresistant medial temporal lobe epilepsy. The stereotactic AHE was performed on the Leksell stereotactic system. All lesions exceeded 40 mm along the long axis of the hippocampus. **Results.** Seizure outcome was favourable on one year follow-up: 12 patients (75%) were seizure-free (Engel I), three (19%) were Engel II, and one (6%) was Engel III. Side-effects were mild, lasting up to 7 days: cephalgia, meningeal syndrome with sterile CSF in three subjects, and CSF leak lasting up to 3 days in seven subjects. **Conclusion.** Stereotactic AHE encompassing sufficient volume of the amygdalohippocampal complex appears to be safe, effective, and free from long-term side-effects.

Key words: stereotactic amygdalohippocampectomy, temporal lobe epilepsy, epilepsy surgery, seizure outcome

Attempts to perform epilepsy surgery less invasively than by classical open neurosurgical intervention have been made since the fifties. The pivotal contribution in this field was made by Talairach *et al.* (1974). The methodology, however, was limited both in the diagnostic pre-operative assessment (without ictal video-EEG) and the treatment procedure itself, based on reaching the target area by implementing stereotactic coordinates from anatomical atlas, skull x-ray, and ventriculography. Targeting the therapeutic

lesion was only partially based on individual anatomy. Modification of this method was also used by Vladyka (1978) until the late eighties when video-EEG (VEEG) and MRI made classical epilepsy surgery far more effective. We had an opportunity to reassess some of these previously stereotactically treated patients who were included in a space memory study (Bohbot *et al.* 1998; Stepankova *et al.* 2004), and their MRI examinations showed lesions varying substantially in location and size over the

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temporal lobe. Sometimes, the target structure – amygdalohippocampal complex – was partially missed, and this, apart from some misdiagnosed seizure types or side of seizure onset, was responsible for less satisfactory results. Stereotactic therapy of temporal lobe epilepsy (TLE) was re-introduced in a modern setup by the London – Ontario group (Parrent *et al.* 1999). Radiofrequency lesions encompassed the amygdala and anterior 13–21 mm (mean, 16.8 mm) of the hippocampus in the small-lesion group, and 15–34 mm (mean, 21.5 mm) in the large-lesion group. The outcomes, however, were clearly inferior to open anteromesial temporal resection (ATR) or amygdalohippocampectomy (AHE), only two of 22 treated patients were seizure-free.

Another novel approach has been thoroughly studied by Regis *et al.* (2004). In a prospective multicenter study, 23 patients were treated with gamma knife according to a standard protocol with promising results. However, at the time of maximum radiation effect, about one year following the treatment, 62% of patients needed corticosteroids for a mean of 73 days, and 3 required hospitalizations with intravenous treatment because of headache, nausea, or vomiting. All patients experienced a transient increase in their seizures. At the two-year follow-up, 13 of 20 patients reached Engel I, and 6 of 20 reached Engel II classification.

Considering the recent trends in medicine that strongly advocate minimally invasive procedures with immediate effect, and technology improvements that enables precise patient-tailored stereotactic amygdalohippocampectomy, we have decided to apply this procedure in a well defined series of patients with medial temporal lobe epilepsy and evaluate the outcomes. The primary objective was to evaluate the seizure outcome, the secondary objective was to evaluate procedure-related side-effects of the procedure. Neuropsychological outcomes will be a matter of a separate study.

Materials and methods

Sixteen consecutive epilepsy surgery candidates with pharmacoresistant partial complex seizures with or without secondary generalization were enrolled for stereotactic AHE based on consistent results suggesting definite medial temporal lobe epilepsy (MTLE) and the patient's preference for either classical AHE/ATR or stereotactic AHE. Respecting the subject's preference informed consent was obtained. All patients were assessed according to general standards. MRI, FDG-PET, WADA-test using methohexital, scalp ictal video-EEG analysis of at least two habitual seizures, visual field, and neuropsychological

Table 1. Summary of subject demographics, seizure history, pre-operative assessment, Engel classification one year after stereotactic amygdalohippocampectomy, and side-effects.

Patient n°	Age years	Sex	Epilepsy duration years	Seizures/month	VNS	MRI with MTS left/right	PET hypo left/right	WADA speech left/right	Engel class 12 months	Meningeal syndrome	CSF leak
1	48	m	48	6	y	L	L	L	I	0	0
2	58	m	18	5	n	L	R	bilat.	I	0	y
3	60	m	29	13	n	L	L	L	I	y	y
4	34	m	24	1	y	R	R	L	II	0	0
5	43	f	28	15	n	L	L	L	I	y	0
6	28	f	22	6	n	L	L	L	I	0	y
7	36	m	18	32	n	R	R	L	I	0	y
8	65	f	36	6	n	L	L	L	I	0	0
9	38	m	10	7	n	Normal	L	L	II	y	0
10	29	m	15	6	n	L	L	L	I	0	0
11	50	m	47	2	n	L	L	N/A	I	0	y
12	27	m	16	4	n	L	L	R	I	0	0
13	32	f	17	7	n	L	L	L	I	0	y
14	20	f	3	12	n	R	R	L	II	0	y
15	50	m	31	5	n	R	R	L	III	0	0
16	28	f	17	3	y	L	L	L	I	0	0
AV	40,4		23,3	8,3							

Mean age of our cohort was 40.4 years, 10 were males and 6 females. Mean epilepsy duration was 23.3, mean number of partial complex and secondary generalized seizures per month was 8.3. Three subjects were unsuccessfully treated with a vagus nerve stimulator. 11 subjects had mesial temporal sclerosis (MTS) on the left side, 4 on the right side, and one had normal MRI. Hypometabolism was found on positron emission tomography (PET) on the left side in 11 subjects, on the right side in 5. Speech dominance was in the left hemisphere in 13 subject, in one it was bilateral and in one on the right. Engel class I on one year follow-up was in 12 subjects, Engel II in three, and Engel III in one subject. Three subjects had meningeal syndrome up to 6 days, and 7 had minor cerebrospinal fluid (CSF) leak up to 3 days following the procedure.

assessment were performed (QOLIE-89, WAIS-R and WMS-R).

Patients were treated using stereotactic thermo-lesion of the amygdalohippocampal complex (4 right, 12 left). For the surgical procedure, the Leksell stereotactic system was used. The coordinate frame was attached to the patient's head under local anaesthesia. MRI with indicator box using Siemens Magnetom Expert 1T with a three-dimensional FLASH, T1- weighted sequence, and 1.3 mm slices with contrast enhancement to visualise cortical vessels were performed. Single trajectory along the long axis of the hippocampus was planned on SurgiPlan (Elekta Instruments). Entry point was placed in the occipital region to avoid cortical vessels being captured on MRI, and percutaneous drill-hole under local anaesthesia was performed. The trajectory of the probe avoided ependymal surface of the ventricles and the target point was placed in the amygdala. Thermocoagulation of the amygdalohippocampal complex and part of parahippocampal gyrus was planned according to individual anatomy of the patient. Stereotactic AHE was carried out by string electrode

with 10 mm bold active tip, and 17 to 30 (median 24) lesions were done using Neuro N 50 (Fischer-Leibinger) system in all patients along the 32-37 mm (median 35 mm) trajectory in the amygdalohippocampal complex. Local temperature was 75°C or 88°C depending on probe thickness. After the procedure, patients were hospitalized at a standard neurological ward.

Follow-up MRI scans were performed in all subjects 5-6 days, and then 6 and 12 months after the procedure. Neuropsychological parameters, enabling comparison to pre-operative results, were assessed one year following the stereotactic AHE.

Outcome data for one year post-operatively were classified using Engel's classification I = seizure free or auras only, II = rare seizures (not more than two per year), III = worthwhile improvement (reduction of seizures of 90% or more), IV = unchanged or worse (Engel, 1987). We adhered to the Engel classification in order to be able to compare our results with both older and recent literature, as the ILAE classification is still not generally used (Wieser *et al.* 2001).

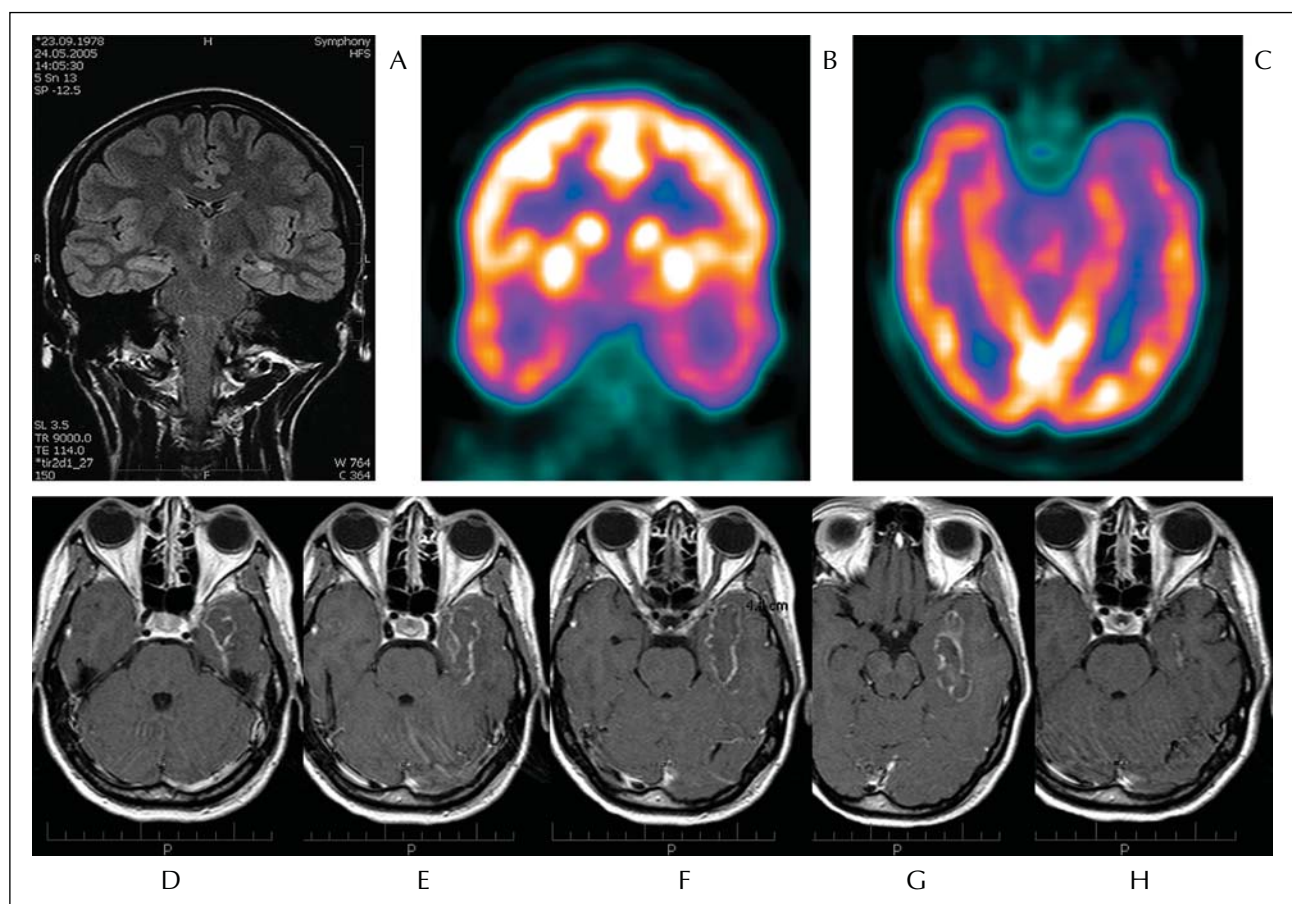


Figure 1. Results in patient 13. **A)** MRI showing mesial temporal sclerosis left; **B, C)** FDG-PET showing left temporal hypometabolism; **D, E, F, G)** MRI 3 days following stereotactic amygdalohippocampectomy; **H)** MRI 6 months following stereotactic AHE.

Results

Results are summarised in *table 1*. Of the 16 treated patients, 10 were males and 6 were females. The mean age was 40.4 years ranging from 27 to 65. The mean duration of epilepsy was 23.3 years (3-47 years). The total monthly number of seizures (partial complex and secondary generalized seizures) preceding the procedure ranged from 1 to 32, with the mean of 8.3. Vagus nerve stimulator had previously been implanted in 3 of the 16 patients with insufficient effect. All patients but one had mesial temporal sclerosis (MTS) on their MRI corresponding to the side of seizure semiology and seizure onset on the VEEG (*figures 1-4*). The one subject (BM) without MTS had clear-cut FDG-PET hypometabolism in his left temporal lobe and reached Engel II outcome. Fluoro-deoxy-glucose hypometabolism was present in the relevant temporal lobe in 15 of the 16 subjects. In one subject (ZJ) hypometabolism was opposite the MTS and VEEG seizure onset, and stereotactic AHE on the MTS side resulted in Engel I outcome. WADA tests were performed in 15 subjects, and showed speech dominance in the left hemisphere in 13, in the right hemisphere in one, and bilateral speech projection in one subject. The lesion was located in the dominant hemi-

sphere in 11 subjects. None of the 16 subjects developed permanent post-operative speech deficit. Complete neuropsychological outcome assessment will be presented in a separate report.

Lesions were clearly visualized on post-operative MRI examinations, they were quite uniform, and in all cases they encompassed the region of amygdala and hippocampus longer than 40 mm along their long axis (*figures 1-4*). The follow-up assessment confirmed that no subject developed long-lasting oedema detectable on other than post-operative scans. After a year, the lesion developed into oblong pseudocyst with collateral tissue atrophy encompassing a substantial portion of both amygdala and hippocampus (*figures 1-4*).

Seizure outcome was favourable: 12 patients (75%) were seizure-free (Engel I), three (19%) were Engel II, and one (6%) was Engel III.

Immediate mild post-procedure side-effects (cephalea and local pain in indicator box fixation points) lasting 1-2 days were present in all patients and were easily controlled by oral analgesics. Small cerebrospinal fluid leak was present in seven subjects and resolved under compressive bandage within 1-3 days. Three subjects developed definite meningeal syndrome requiring lumbar puncture that

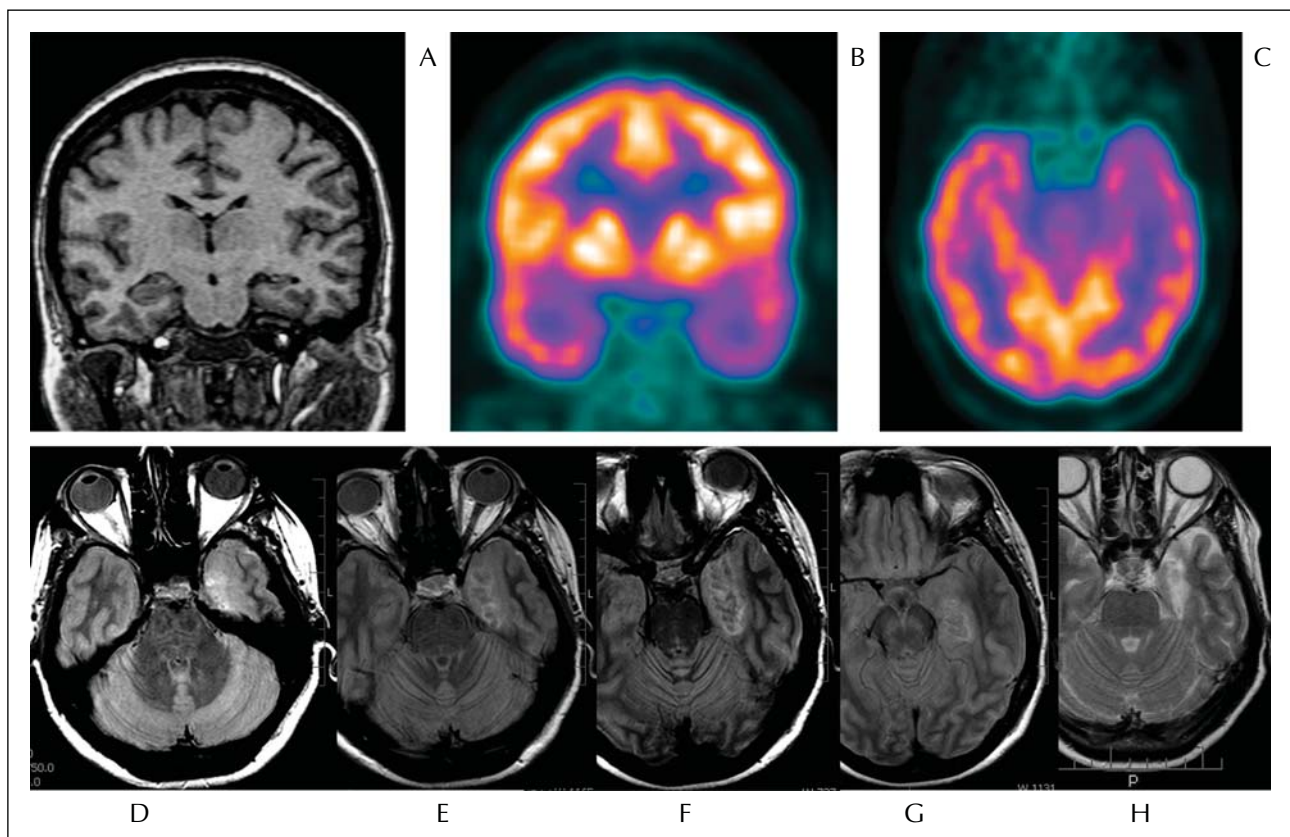


Figure 2. Results in patient 5. **A)** MRI showing mesial temporal sclerosis left; **B, C)** FDG-PET showing left temporal hypometabolism; **D, E, F, G)** MRI 3 days following stereotactic amygdalohippocampectomy; **H)** MRI 25 months following stereotactic AHE.

revealed hyperproteinorhachia and pleiocytosis. However, microscopic examination and cultivations were negative in all three cases. Meningeal syndrome resolved in 4-6 days on antibiotic therapy in two subjects, and the same course was observed in one subject without antibiotics. Long-term negative medical side-effects have not been observed.

Discussion

Outcome

The primary objective of the study – seizure outcome – is fairly optimistic with 75% of subjects falling within Engel class I, 19% within Engel class II, and one subject (6%) within class III. This outcome does not correspond to the results of the London – Ontario group (Parrent *et al.* 1999) in spite of the fact that the patient cohort has similar characteristics as far as seizure types, underlying pathology, and location of the epileptogenic zone are concerned. The substantial difference seems to be the larger longitudinal size of the lesion in our series (35 mm vs 21.5 mm) encompassing the amygdala and hippocampus

in a continuous manner. Another possible reason for different outcomes might be the homogeneity of our cohort with consistent subject's pre-operative assessment focusing convincingly on the one mesiotemporal structure, with 15 of the 16 subjects with MTS on the MRI and 15 of the 16 subjects with relevant FDG-PET hypometabolism.

Gamma knife epilepsy surgery for TLE was studied in detail by Jean Regis and collaborators (our centre contributed six subjects to this series). Gamma knife AHE appears promising. At the two-year follow-up, 13 of the 20 patients reached Engel I, and 6 of 20 reached Engel II class. However, the efficacy is not superior to open neurosurgery when compared to recent neurosurgery series, e.g. 71% Engel I patients in the Porto Alegre series (Paglioli *et al.* 2006), 54% (Bate *et al.* 2007), 62% (Hori *et al.* 2007), 77% (Erickson *et al.* 2005). Outcome in a comparable patient cohort in our study is at least similar to that of gamma knife surgery. The major difference compared to gamma knife intervention was the onset of treatment effect. With stereotactic AHE the effect is immediate while with gamma knife it has 12-18 months latency preceded by a period of increased seizure frequency and severity.

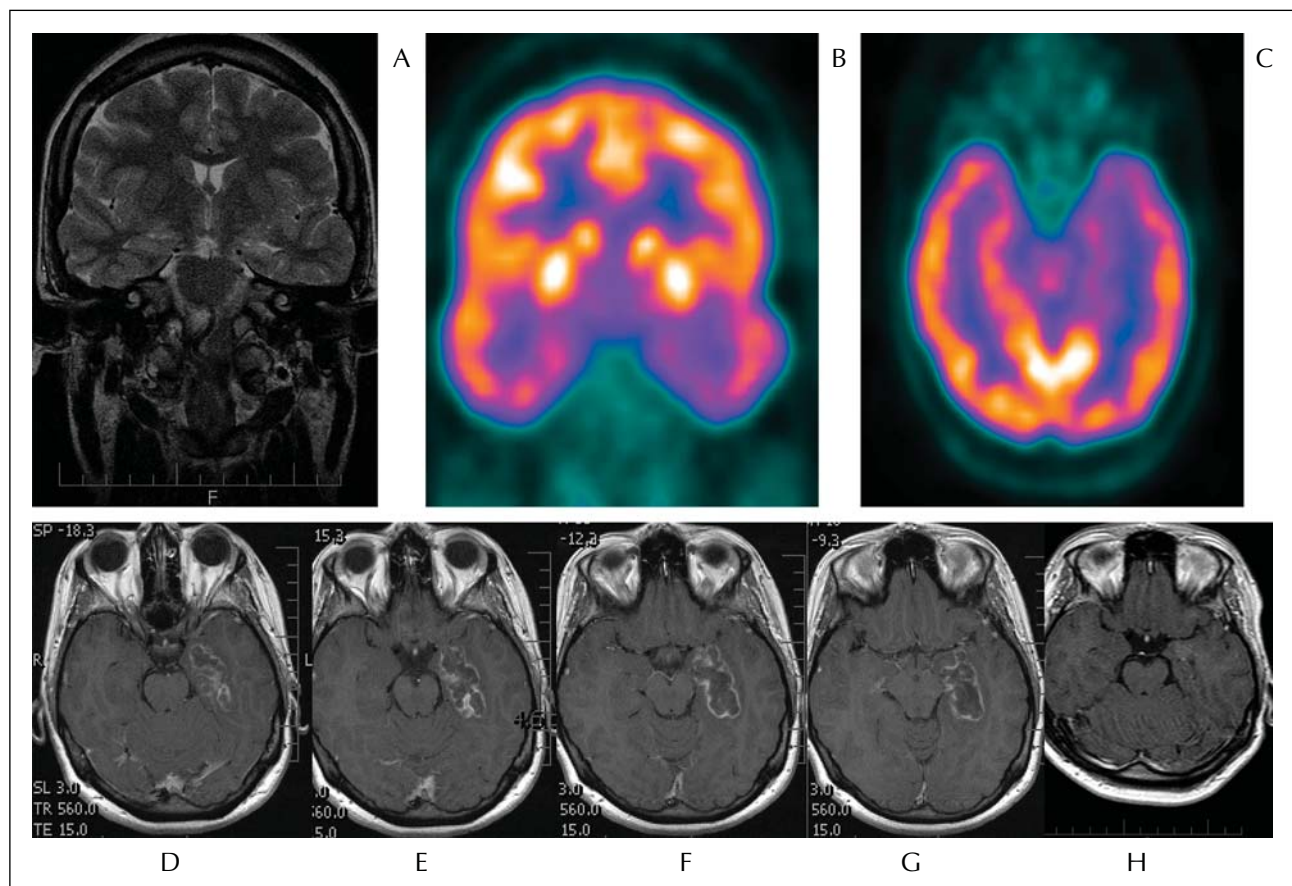


Figure 3. Results in patient 16. **A)** MRI showing mesial temporal sclerosis left; **B, C)** FDG-PET showing left temporal hypometabolism; **D, E, F, G)** MRI 2 days following stereotactic amygdalohippocampectomy; **H)** MRI 3 months following stereotactic AHE.

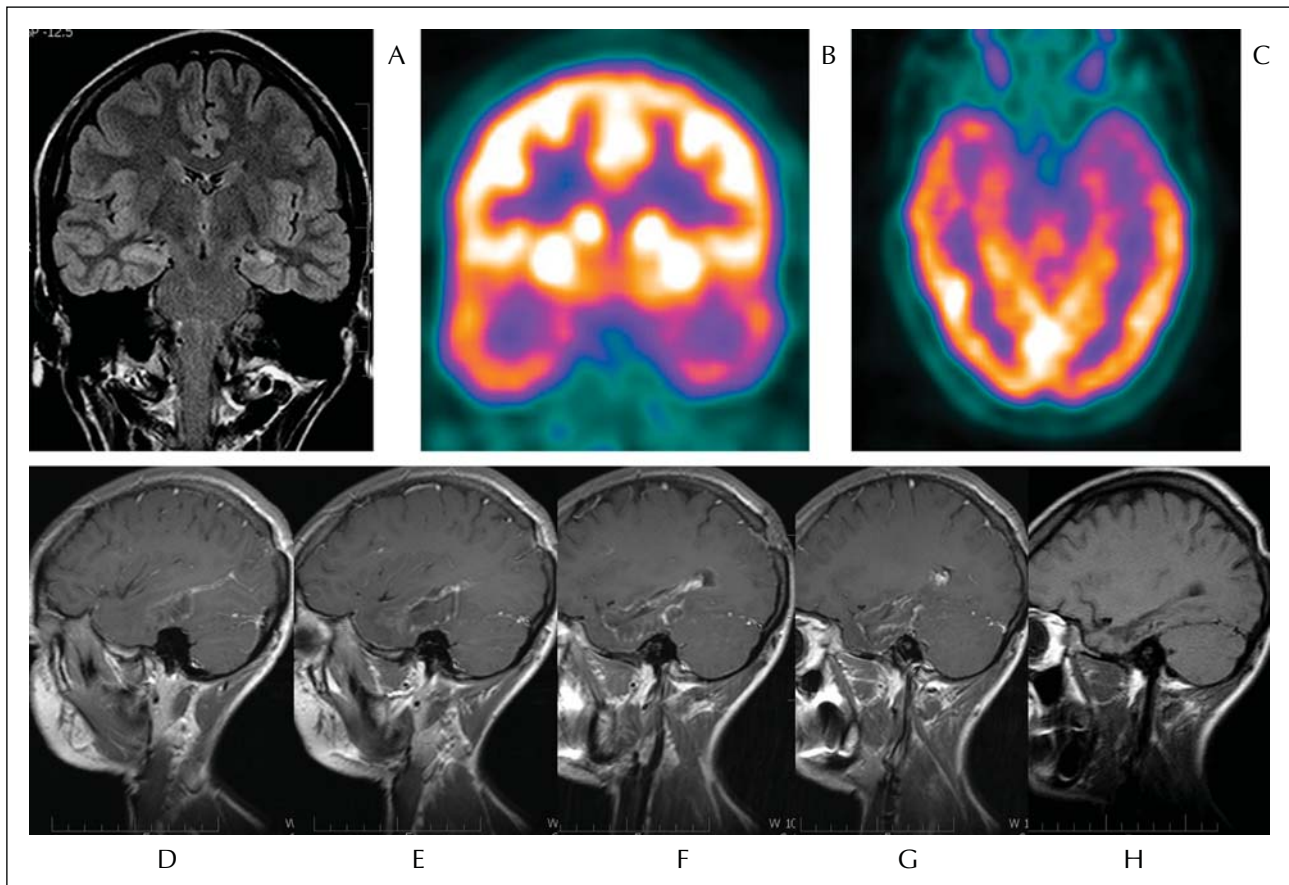


Figure 4. Results in patient IK. **A)** MRI showing mesial temporal sclerosis left; **B, C)** FDG-PET showing left temporal hypometabolism; **D, E, F, G)** MRI 3 days following stereotactic amygdalohippocampectomy; **H)** MRI 9 months following stereotactic AHE.

Epileptologic outcome of stereotactic AHE and neurosurgical AHE or ATR for temporal lobe epilepsy based on Engel classification after one or two years seems to be comparable: 75% Engel class I in our series of stereotactic AHE vs 71%, 54%, 62%, 77% (references above), and 66% in a comprehensive meta-analysis (Téllez-Zenteno *et al.* 2005). It is a matter of further follow-up of our subjects to assess the long-term seizure outcome. However, long- and short-term outcomes seem to be similar in controlled studies on temporal lobe resective surgery (Téllez-Zenteno *et al.* 2005).

Side-effects

Side-effects, apart from efficacy, are a major concern in every type of intervention no matter how minimally invasive it is. As for gamma knife epilepsy surgery, the procedure is extremely safe and non-invasive. However, the side effects of gamma knife are far from negligible (Regis *et al.* 2004). About one year after radiation, 62% of subjects developed substantial temporal lobe oedema which required corticosteroid treatment for an average of 73 days, and three subjects required hospitalization for

intravenous anti-oedema treatment because of intracranial hypertension syndrome. Another important issue is the temporary increase of seizure frequency and severity in some subjects.

Well known side-effects of neurosurgical AHE/ATL are either temporary (pain, early postoperative seizures, wound complications including CSF leak and inflammation, meningitis requiring antimicrobial therapy and others) or permanent (visual field deficit, major neurological deficit including hemiplegia in 1% of patients due to middle cerebral artery stroke). Side-effects in our cohort were only short-term, lasting up to seven days. Meningeal syndrome was most probably caused by stereotactic lesions reaching the CSF compartment as the CSF was sterile in all three cases.

Conclusion

Stereotactic AHE using the Leksell stereotactic system appears to be equally safe and effective as neurosurgical or gamma knife AHE at one year post-procedure. Long-term efficacy and neuropsychological outcomes are still to be assessed. □

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