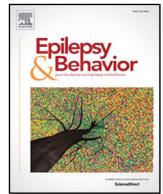




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Brief Communication

Initiating a new national epilepsy surgery program: Experiences gathered in Georgia



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ABSTRACT

Surgery is the most effective therapeutic approach for medically refractory epilepsies and a safe and cost-efficient treatment in terms of long-term expenses of direct, indirect, and intangible costs. Georgia is a Caucasian low- to middle-income country with a remarkable effort to deal with epileptic diseases, but without an appropriate epilepsy surgery program. To address the needs for such a service in this country, two joint German-Georgian projects were initiated in 2017 and 2019. In the framework of these projects, a productive exchange program involving German and Georgian experts was undertaken in the past two years. This program included training and mentoring for Georgian clinical colleagues, as well as joint case conferences and workshops with the aim of optimizing presurgical diagnostics and preparing for an epilepsy surgery program in Georgia. Finally, a post-surgical medium- and long-term follow-up scheme was organized as the third component of this comprehensive approach. As a result of our efforts, the first patients underwent anterior temporal lobectomy and all of them remain seizure-free up to the present day. Hence, epilepsy surgery is not only feasible, but also already available in Georgia. In this report, we aim to share our experiences in the initiation and implementation of surgical epilepsy intervention in Georgia and illustrate our recent endeavor and achievements.

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1. Introduction

Epilepsy is one of the most common neurological diseases worldwide, which affects people regardless of their social status, gender, or age [1]. Approximately 30% of patients with epilepsy exhibit drug-resistant epilepsy (DRE) [2] with little hope of achieving sufficient control of seizure activity by further medication [3]. In stark contrast, remission can be achieved by surgical intervention for many patients with DRE [4]. This is in particular the case for more than 80% of surgical patients

with DRE with mesial temporal-lobe epilepsy (MTLE) and hippocampal sclerosis [5,6], the prototype of a surgically remediable epileptic syndrome [4]. Epilepsy surgery is not only the most effective [7–9], but also a cost-efficient DRE treatment in terms of long-term expenses of direct, indirect, and intangible costs [10–12]. This also applies for low- and middle-income countries [13].

Despite the obvious benefits of neurosurgical intervention, there is a widely recognized surgical treatment gap [14], particularly in low- and middle-income countries lacking the appropriate specialization. Consequently, patients with MTLE with a clear-cut surgical recommendation and excellent outcome prognosis accumulate in these countries, even though those patients could be identified appropriately within a limited resource setting [15]. In addition, emerging economies like Argentina [16], Colombia [17], India [15,18], Lebanon [19], Panama [20], or Tunisia

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[21] report seizure freedom rates after surgical resection comparable to that of high-income countries [22]. Similar results can be achieved even in low-resource settings, as reported for Uganda [23].

Georgia with over 3.7 million population is a Caucasian low- to middle-income country with a remarkable effort to deal with patients with epilepsy, but without an appropriate neurosurgical program. In this country, the proportion of the patient group with medically refractory MTLE and hippocampal sclerosis is high (18% from over 8000 patients with DRE) [24]. To address the need for surgical epilepsy services in this country, two German–Georgian cooperative projects were initiated in 2017 and 2019 with the financial aid of the German Federal Ministry of Education and Research and the German Federal Ministry of Economic Cooperation and Development, respectively (projects' leader, T. Gloveli). The general feasibility of surgical epilepsy treatments in developing countries has been already outlined in several publications [25–28]. While each country has its specific conditions and has to find its own way in establishing surgical epilepsy services, the experiences gained might be nevertheless beneficial for other initiatives planning to initiate neurosurgical interventions. In this report, we aim to share our experiences in the initiation and implementation of neurosurgical epilepsy treatment in Georgia and illustrate our recent endeavor and achievements with reference to other published examples.

1.1. The basic outline of a new program

The launching event of the German–Georgian cooperation took place in 2017 in Tbilisi (Georgia), which brought together 25 European and Georgian physicians and researchers to explore and discuss the actual situation in Georgia, the potential to optimize diagnostic tools with a special focus on the presurgical evaluation, and the options for surgical interventions [29]. Key statements of this event can be summarized as follows: a) there is a noteworthy proportion of patients with intractable MTLE with clear-cut indication for surgical intervention based on seizure semiology, neurological examination, electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings [24]; b) epilepsy surgery is feasible to be established in Georgia with the potential for an impact not only for the country itself, but also for the whole South Caucasus region; and c) the German colleagues are happy to assist in the establishment of a surgical epilepsy program. Taking those key statements, we started to organize and initiate surgical epilepsy services in Georgia.

An epilepsy surgery program is based on the selection of eligible candidates by appropriate presurgical diagnostic procedures, the surgical intervention itself and postsurgical care including long-term follow-up. The diagnostic work-up to identify a surgically remediable syndrome comprise noninvasive video-EEG (VEEG) monitoring, brain MRI, and neuropsychological evaluation. With such a limited approach, already 50 to 60% of patients with medically refractory epilepsy could be identified as suitable candidates [26], emphasizing the pivotal role of well-trained specialists, in particular the reliance on epileptologist and neurosurgeon. Some publications highlight the possibility to recommend surgery without VEEG based on indications in a series of nonictal EEG recordings in a selected group of patients with unilateral MTLE [30–33]. However, the corresponding decision-making process relies on experienced epileptologists and is not recommended outside a well-established epilepsy center with a high level of expertise [33]. In order to acquire the best possible means to evaluate and treat the patients in a new surgical program, it is thus desirable, if affordable, to hedge the diagnosis and surgical recommendation by VEEG. Organizing the appropriate partnerships in the Georgian capital Tbilisi (Institute of Neurology and Neuropsychology – INN – and Caucasus Medical Centre), the project described here, is in the favorable situation that the technical requirements (VEEG, MRI, and a well-equipped neurosurgical facility), as well as specialized experts including epileptologists, clinical neurophysiologists, neurologists, neuropsychologists, and an experienced neurosurgeon are readily available. Based on the existing technical

prerequisites, the project was therefore focusing primarily on the exchange of experiences by means of profession-specific training; internships of Georgian epileptologists, neuropsychologists, and neurosurgeon in Berlin (Germany); supervision of surgical procedures; and institutional networking. It is also our aim to raise the public awareness and promote the acceptance of epilepsy surgery as a suitable therapeutic intervention in Georgia. Therefore, we launched a series of reports in national newspapers and major national TV channels to publicize our cooperation and the new option of surgical intervention in epilepsy (Fig. 1).

1.2. Presurgical evaluation and the selection of eligible candidates

In eligible surgical candidates, the epileptic focus should be unambiguously localized using available technology [26,28]. This goal relies on the availability of a comprehensive epilepsy care unit in which such patients could be subjected to a multidisciplinary evaluation. Especially in resource-poor countries, the success depends on the ability of the team to decide on surgical candidacy while ensuring that surgery does not lead to impairment of neurocognitive functions [27]. The initial evaluation process of patients by Georgian physicians was performed in close consultation with German colleagues. As a first step, in our program, a Georgian team was visiting the Epilepsy-Center Berlin-Brandenburg and the Charité – Universitätsmedizin Berlin to experience the standard procedures and discuss their applicability and practicability for the Georgian setting. This visit focused on profession-specific training including EEG monitoring and analysis, presurgical evaluation, case conferences, and the attendance of surgical interventions. Based on those experiences and in preparation to the first surgical intervention in Georgia, a follow-up case conference via internet was organized to evaluate Georgian patients. The INN outpatient clinic provided the medical history, seizure semiology, and current and former medication, as well as a summary of the neuropsychological examination for each putative surgical candidate, which were discussed together with VEEG and MRI findings. Additional case conferences were jointly performed in Tbilisi, during the visit of the German partners, with up-to-date case summaries of surgical candidates presented and discussed prior to each surgical intervention.

In this initial phase, we made the experience that the direct interaction and partnership between German and Georgian experts is highly productive and represents an essential aspect for the success of the program. Therefore, an additional visit at clinical facilities in Germany was organized for an extended team of Georgian colleagues. This meeting was complemented by follow-up internet conferences. Direct communication was also carried out by means of e-mail and messenger services on the basis of the contacts established during the visits. Taken together, basic components of the knowledge transfer and exchange of experiences included visiting experts in specialized German facilities, case conferences and workshops in Tbilisi and Berlin as well as mentoring during the selection process via different electronic communication channels.

As a major aspect, unclear lateralization of the epileptic focus emerged during this phase of the program, making additional presurgical diagnostic procedures such as intracranial EEG necessary. However, epilepsy surgery centers in developing countries often lack the full range of state-of-the-art technologies to perform presurgical evaluation that are usually available in the developed world [27,28]. This is also the case for Georgia, and one of our aims is to extend the spectrum of available technologies. One Georgian patient with MTLE and inconclusive noninvasive monitoring results with respect to lateralization required invasive diagnostics for clarification. Therefore, we decided to introduce foramen ovale electrode recordings in Georgia (Fig. 2). This technique is less demanding, minimally invasive, and cheaper compared to subdural or depth EEG recordings, but also offers an efficacious means to evaluate patients with temporal lobe epilepsy for lateralization [34]. Eventually, this current patient had seizure onset zones



Fig. 1. Knowledge dissemination through regular joint workshops, case conferences, and outcome assessment by Georgian and German colleagues in Tbilisi and Berlin (upper left and center). The aims and achievements of the collaborative epilepsy program and benefits of epilepsy surgery were communicated to Georgian population in TV programs (example below) and newspaper articles (example upper right).

in bilateral mesial temporal structures. Nevertheless, the technique proved to be not only feasible, but also productive and a valuable tool in clarifying such cases in a resource-limited country.

1.3. Surgical interventions

Surgical seizure outcome is correlated to pathological findings and disease causes [35], making patient selection a crucial factor for the final success rate. The best outcome prognosis and a well-established experience of appropriate resection technique are associated with unilateral MTL with hippocampal sclerosis, a condition that is still abundant in developing countries without surgical epilepsy services. Furthermore, right-sided surgery is associated with a better prognosis for a meaningful improvement for quality of life (QoL) [36]. Hence, there was a general agreement in our program to start with the standard anterior temporal lobectomy (corticoamygdalohippocampectomy) on the right, nondominant hemisphere, which is well in line with the literature [13,26,28,37,38].

Prior to performing the surgical interventions in Georgia, the Georgian neurosurgeon involved visited the partner clinics in Germany. The primary purposes of these visits was to introduce and discuss different types of surgical interventions and the work-up for neurosurgery in

surgically remediable epileptic syndromes including invasive recording options. Since the epilepsy surgical work-up is a teamwork [39], the visiting neurosurgeon was also involved in consultations and presurgical diagnostics.

The initial surgical interventions in Georgia were jointly performed in Caucasus Medical Centre in Tbilisi. First, a German expert acted as a primary surgeon in order to advise the local surgical team and care for the establishment of appropriate routines (2018). This was followed by the Georgian surgeon performing the operation under supervision of the German colleague (2019). The participants agreed that this tandem approach is a safe and effective way for the program implementation. As indicated above, the first operations were anterior temporal lobectomies on the nondominant side, but in a stepwise approach, the same procedures will be performed on the dominant hemisphere as a next step, and more complex cases will follow later on, as the expertise of the Georgian participants will increase [see 26]. We believe that the future introduction of more invasive techniques such as subdural or depth recording electrodes bears the potential to broaden the spectrum of surgically remediable epilepsy cases and thus could contribute to the prospective progress of the program at later stages.

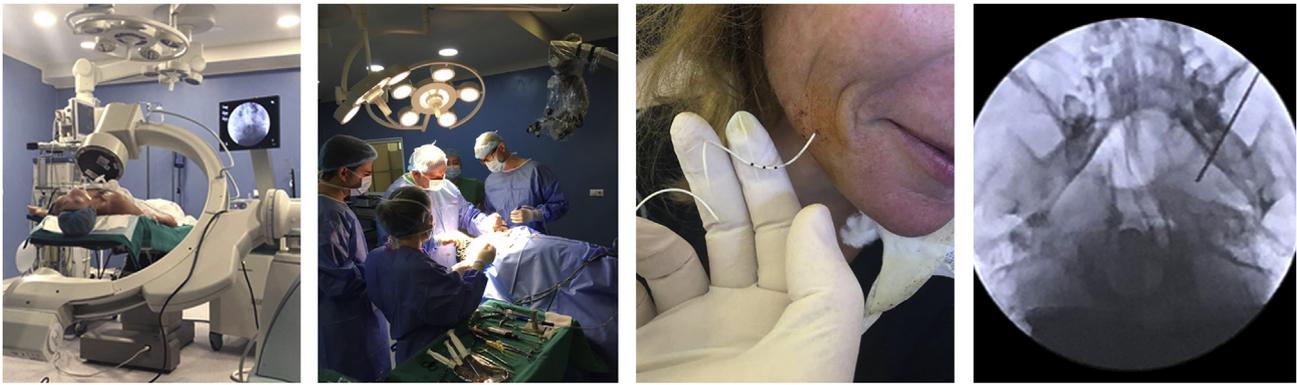


Fig. 2. The neurosurgery unit in the Caucasus Medical Centre have all necessary equipment and requirements to carry out the surgical interventions (on the left and middle). Patient with an implanted foramen ovale electrode and X-ray of electrode position (on the right).

Epilepsy surgery can also open up a new science perspective for Georgia such as to implement brain research of resected human tissue in order to provide direct insight in physiological and pathological mechanisms of this disorder [40]. Establishing such research in Georgia is of great benefit due to the high proportion of a rather uniform patient group with medically refractory MTLE and hippocampal sclerosis that is nowadays not more available in first world countries to this extent. To take advantage of this opportunity, we established an electrophysiology laboratory at the Caucasus Medical Centre in close proximity to the surgical unit, which is optimal for tissue viability [40]. Our goal here was to analyze the resected human tissue by the means of combined electrophysiological, morphological and immunohistological approaches [41,42].

1.4. Postsurgical outcome and care

All four patients who underwent epilepsy surgery in the Caucasus Medical Centre in Tbilisi are seizure-free up-to-date (one patient > 18 months, two patients > 12 months, and one patient > 7 months), which we believe is a great success of our program. It not only marks important cornerstones for the initial phase of the project, but also confirms the importance of commitment for everyone involved. High rates of seizure freedom are also reported by other studies in developing countries [e.g., 21], which might be partially related to the appropriate selection of best-suited patients. However, it should be noted that remission is also a function of time with a certain risk for later relapse [35]. The longer a patient stays seizure-free, the smaller is the likelihood for relapse. This is however not a simple linear relationship, because the risk of a relapse in surgery of MTLE with hippocampal sclerosis drops sharply within the first two years postsurgical with a further gradual decrease of around 1% annually [43].

Patients undergoing surgery report a significant and meaningful improvement in their QoL compared to a medical group without surgery [26,44–46], while meaningful and lasting improvements in the QoL are mainly achieved within the first two postsurgical years [44,46]. Seizure and aura freedom are the main factors for a positive assessment of QoL [36,44–46], while continued medication is unrelated to this dimension [46]. From this point of view, precaution should be taken in the reduction of medication, the patient should be fully aware of the steps taken and be well monitored and advised [47], which is also implemented in our projects. Yet, only 5% of patients undergoing epilepsy surgery do not consider this to be overall beneficial in the end [44], once again underpinning the power of surgical interventions as an important and effective treatment option in DRE.

Regarding the improvement in the QoL, the German and Georgian colleagues jointly examined the Georgian patients. All patients continued their medication and indicated obvious improvements in QoL.

Notably, all of them emphasized that in retrospect they would once again decide to undergo surgery, confirming the success of the initial phase of this new Georgian surgical epilepsy program from the patients' perspective. However, a period of at least two postsurgical years seems particularly significant, where antiepileptic drug (AED) treatment should be advised and patients be monitored accordingly. To ensure this postsurgical support and in order to further work on the sustainability of the project, a new follow-up German–Georgian cooperative project was launched in 2019 with the support of the German Society of International Cooperation (GIZ) and the financial aid of the German Federal Ministry of Economic Cooperation and Development (BMZ). This project focuses particularly on the postsurgical care and diagnostics but will also maintain support for the presurgical evaluation and the surgical cooperation.

1.5. Future perspectives

In this initial phase, we were focusing on the training of personnel in Georgia, in particular the neurosurgeon, who performed the initial operations and would function as a multiplier and disseminate his knowledge and experiences later on. Looking at the time scale, surgical interventions itself, although the essential central elements of our program, do not constitute significant costs in terms of time. In contrast, both the initial presurgical evaluation and the postsurgical care including AED management are more time intensive. For the establishment and consolidation of a comprehensive epilepsy care unit, it is essential that epilepsy surgeries are performed regularly, supported by a system of presurgical evaluation, with well-established criteria for patient selection, and follow-up care [28]. These elements have been implemented in our program. As the next step, we will not only systematically expand the screening activity for suitable candidates, but also focus on the postsurgical care in order to ensure sustainability of the work-up. The screening effort will be supplemented by the continuous use of minimally invasive foramen ovale electrode recordings in cases of inconclusive lateralization. As a future perspective, more invasive techniques such as subdural and depth electrodes might be introduced to expand presurgical diagnostic options.

The success of epilepsy surgery, and intimately related the acceptance of a new surgical program, depends critically on the selection of candidates, for whom postsurgical seizure freedom can be expected with high probability [27,28]. In the end, success is the best advocate [28]. For the initial phase, we selected patients with unilateral MTLE and right-sided hippocampal sclerosis for three reasons: firstly, MTLE with hippocampal sclerosis is associated with the best outcome prognosis in surgical remediable epileptic syndromes; secondly, better prognosis and a meaningful improvement in QoL is associated with unilateral MTLE of the nondominant hemisphere, and finally, MTLE with

hippocampal sclerosis is still common in Georgia, similar to other developing countries without surgical epilepsy services. We could take the initial steps successfully by performing the first epilepsy surgeries in Tbilisi, with all patients becoming seizure-free by surgery (Engel class I). In the future, we will expand the range of surgical interventions.

We believe that for the establishment of such a surgical program public relation is a valuable supplement, which can increase the general awareness, foster its acceptance, and thus finally support our efforts. This goal has been accomplished successfully, and we aim to launch further reports in the Georgian media for a continued cooperation in order to inform the public about epilepsy surgery as a suitable therapeutic approach in DRE (see also the project homepage <https://epilepcure.wordpress.com/>).

The establishment of an epilepsy surgery program requires appropriate equipment including VEEG, MRI as well as surgical facilities, practitioners with a specialized training, and a collaborative interdisciplinary team involving neurologists with specialization in epileptology, neuropsychologists, and neurosurgeons [48]. An epilepsy center with limited resources could already help many patients with a clear-cut indication for epilepsy surgery and might later on extend their service depending on a gradual build-up of available techniques and expertise, going from straightforward anterior temporal lobectomy to more complicated cases and challenging scenarios in epilepsy surgery [26]. The services offered should be well in-line with the technical state of the art and the experiences gained so far. In the long run, our goal is to further expand the networking of local institutions and clinics to create an interlinked central epilepsy care unit for the South Caucasus region with a broader base in Tbilisi. However, the future prospects of an expanded Caucasian surgical service, its specific layout and its speed of development ultimately depend on the progress to be achieved here. While this might be an ambitious future perspective, achievement of our program demonstrate that surgical epilepsy interventions in Georgia are feasible and already available as an effective treatment option for patients with DRE.

2. Conclusions

Experience gained in Georgia clearly show that an epilepsy center with limited resources could already help patients with a well-defined surgical indication. While only a few experts are needed to guide surgical epilepsy interventions, a close initial monitoring might be desirable. Our intention in the present program was to enroll the project with slow progress, seeking for the best outcome by evaluating each step carefully. In addition, we selected patients with unilateral MTLE and right-sided hippocampal sclerosis (nondominant hemisphere), which have the best outcome prognosis. All selected patients in Georgia who underwent anterior temporal lobectomy are seizure-free up to the present day, emphasizing the success of the initiation phase of our program. Hence, the project will continue to focus on this surgical intervention with an extended range of presurgical diagnostics and aims to expand its services step-by-step.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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