Epilepsy surgery in pediatric patients

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Abstract

Epilepsy surgery is a branch of functional neurosurgery, developed for treating patients with resistant epilepsy in pediatric and adult population. The etiology and clinical picture of pediatric epilepsy are very heterogeneous and patients who could benefit from surgery should be chosen very carefully. In this article we present preoperative preparation of epilepsy patients, as well as surgical techniques used in pediatric epilepsy surgery. Robotic stereoelectroencephalography (SEEG) is the most precise technique used for implanting intracranial electrodes. Epileptic foci can be excluded by resection or disconnection procedures. Hypothalamic hamartomas are most frequently treated endoscopically. The results of surgical treatment are good: about two thirds of children are seizure-free after surgery while in the rest of them we mostly achieve improvement.

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1 Introduction

Epilepsy surgery is a branch of functional surgery aimed at removing an epileptogenic region of the brain. In the narrow sense, epilepsy surgery does not include surgery of tumours causing epileptic seizures. The boundaries of the epileptogenic zone and the amount of brain tissue to be removed by the neurosurgeon are determined with the aid of surface and deep brain electroencephalography (EEG). Accurate magnetic resonance imaging (MRI) scans provide detailed images of possible structural abnormalities, the boundary between white and grey matter, and the cerebral vasculature. Also helpful in the search for epileptogenic regions are two functional imaging methods: positron emission tomography (PET) and single photon emission computed tomography (SPECT). The epileptogenic region must be surgically accessible, and its removal must not cause new neurologic deficits. The results of surgery strongly depend on patient selection. Therefore, surgical indications must be carefully evaluated in every patient. In appropriately selected patients, surgery gives very good results (1-5).

Epilepsy is one of the most frequent neurologic disorders both in adult life and in childhood. Its estimated prevalence in Slovenia being 1 % for the entire population, we expect to have about 20,000 patients with epilepsy, of whom 15,000 have active disease. Nearly half

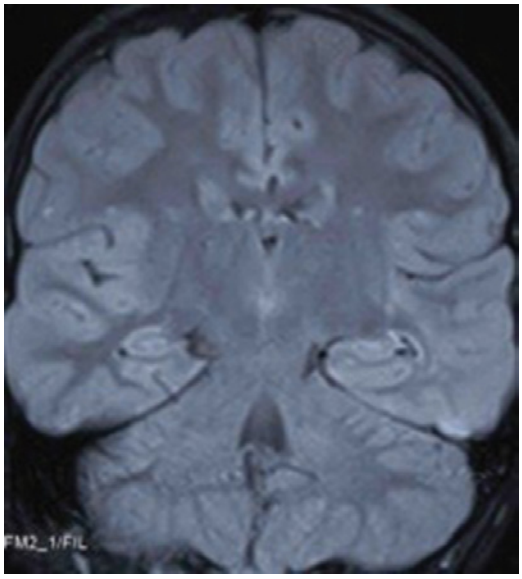

Figure 1: A 14-year-old boy with extensive type 2 cortical dysplasia in the left temporo-occipital region.

the patients develop epilepsy already in childhood. The prevalence in the population up to 19 years in Slovenia is 0.46 % (6). The primary treatment for epilepsy is medication, which is effective in about two thirds of patients, while 20 % to 30 % may be expected to have a refractory course. We speak of refractory (drug-resistant) epilepsy when the patient continues to have seizures despite treatment with at least two appropriately selected antiepileptic drugs given as monotherapy or in combination (7).

In the group of patients with refractory epilepsy, we must look for those who may benefit from other forms of treatment, above all from surgery. A paediatric neurologist (or neurologist treating adults) should possess adequate knowledge to identify at an early stage patients with active epilepsy and refer them to an epileptologist. The latter evaluates the possibility of surgical treatment and refers the patient as soon as possible for the necessary presurgical investigations. Prompt referral to the presurgical programme is important since active epilepsy causes numerous medical, social and cognitive deficits, especially in the early childhood period (8,9,10).

An important part of presurgical evaluation is accurate analysis of the patient's seizures (semiology) with seizure recording during long-term video-EEG monitoring. By neuroradiological investigations, we establish the presence of possible structural changes (lesions) associated with the seizures, or functional changes in patients without lesions. Neurological examination allows the detection of associated neurological abnormalities. A neuropsychologist and often a psychiatrist are vital members of the team. We evaluate the agreement among the findings of different investigations and possible drawbacks. We are guided by the rule that each patient with refractory epilepsy is a potential candidate for surgery until this treatment option has been ruled out by in-depth investigations. It may be reasonable for individual patients with an unfavourable course of epilepsy to undergo several repeated evaluations. Surgical treatment is carried out in an epilepsy surgical unit, where the patient is admitted after the completed investigations.

The principal indication for surgery is refractory focal epilepsy with a clear structural change or even without such a change. Less frequent indications are certain epileptic syndromes with primarily generalized seizures, where the main goal is to reduce the severity of seizures and their consequences (e.g. sudden falls). In the decision for surgical treatment, an important consideration, besides the frequency or form of seizures, is also the burden of epileptiform EEG abnormality during the seizure-free interval.

In certain childhood epileptic syndromes (infantile spasms, electrical status epilepticus in sleep, Landau–Kleffner

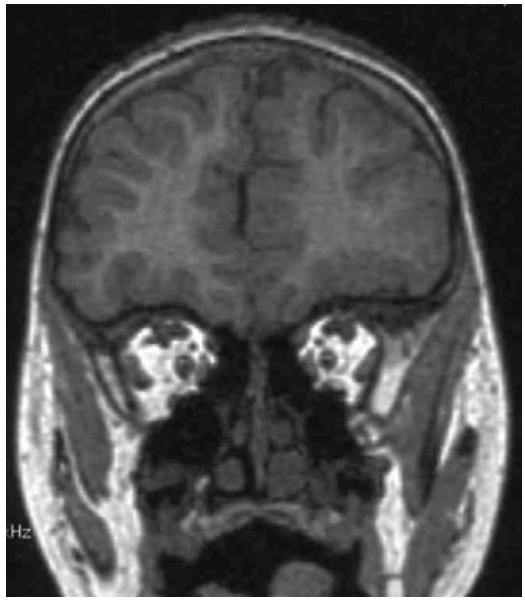

Figure 2: An 8-year-old boy with subtle type 1 cortical dysplasia in the left frontal region, and numerous daily seizures despite therapy. A blurred cortico-subcortical boundary is vaguely outlined. Invasive EEG recording was required.

syndrome etc.), the course of refractory epilepsy may be *encephalophatic*. Epileptic seizures may be causing little inconvenience to the patient and the environment, but the burden of abnormality is so pronounced as to produce encephalopathy. Since the associated developmental delay, or even decline, is sometimes very rapid, this alone (regardless of epilepsy activity) may constitute an indication for referral for surgical treatment.

The particularity of epilepsy surgery in children is connected with brain maturation. Early-onset epilepsy involving the language areas of the brain expectedly causes a deficit in the primary development of speech. When epilepsy in the language areas appears during a later period of development, we can observe a secondary decline in already acquired speech functions, such as occurs for instance in the Landau-Kleffner epileptic aphasia syndrome. If involvement of the language area occurs early on in the child's development, language can develop in symmetrical contralateral areas because of plasticity or equipotentiality of the brain (11,12). Similar remodelling occurs with other cognitive and even motor functions. The results of a study on a population of 70 children undergoing a hemispherotomy show that the ability for socialization and development of brain functions is inversely proportional to the child's age at the time of surgery (13).

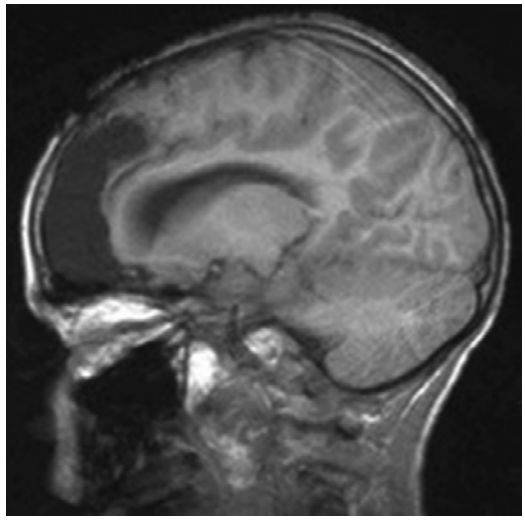

Figure 3: Patient from Figure 2; following cortical resection in the left frontal region, the boy has infrequent residual seizures and absence of neurologic deficits.

2 Preoperative investigations

Before planning possible surgical treatment, we must carry out all investigations designed to confirm the hypothesis on the location of the epileptogenic focus (or multiple foci) and aetiology of epilepsy.

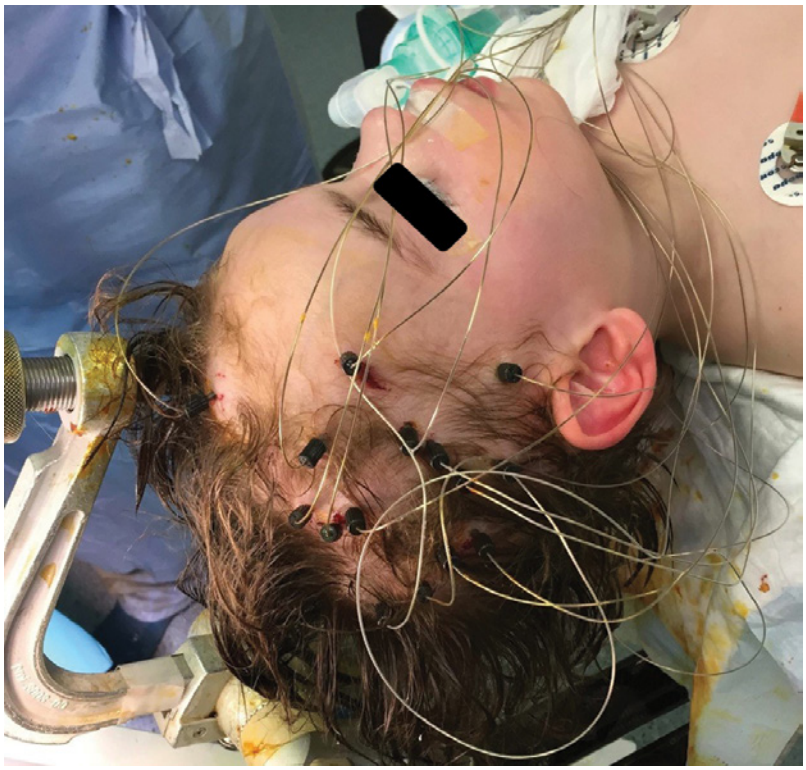

Figure 4: A 3-year-old girl with implanted intracerebral depth electrodes.

2.1 Localization of epileptogenic foci

An epileptogenic focus comprises the part of the cerebral cortex where abnormal impulses are triggered and the parts of the cortex where these impulses spread directly after seizure onset. Focus localization is based on long-term continuous surface video-EEG recording, usually lasting 2–14 days and nights, in the course of which we determine the electro-clinical and topographic correlations during the course of an epileptic seizure. The electrodes, usually 10–20, are placed on the scalp according to the international scheme. It is important to use an adequate number of electrodes (also in infants). Occasionally, it may be useful to place additional electrodes over certain regions. During a seizure, we perform targeted testing of the subject according to agreed protocols, adapted also for small children. We note the initial signs of the seizure and the neurologic deficits during and after the seizure (14,15).

In certain temporal lobe epilepsies, we can implant the electrodes into hippocampal structures through the foramen ovale. This increases the possibility of detecting abnormalities in deep-seated medial temporal structures, which, due to dipole orientation, may be missed by surface electrodes (16).

Video-EEG recording must take place also in sleep at least during one night, since sleep is a possible trigger of seizures or even the only period in which the epileptiform abnormality is expressed. Nocturnal recording also allows us to assess the physiological structure of sleep and possible subtle attacks occurring in sleep, which often pass unnoticed by the environment. It may be helpful to use programmes for automatic seizure registration, which allow the evaluation of possible subclinical seizures. In patients with less frequent seizures, we can increase the likelihood of seizure occurrence by activation procedures, such as sleep deprivation, hyperventilation, photic stimulation, or withdrawal of antiepileptic therapy. The presence of a parent or companion who is thoroughly familiar with the child's usual (habitual) seizures allows the personnel prompt recognition of seizure onset, good testing and realistic analysis of events. When different forms of seizures occur in the same patient, we must record and classify all seizure types.

2.2 Determining the aetiology

Aetiology determination is based on a detailed history and clinical examination with emphasis on neurologic examination, which includes a search for possible skin changes. Analysis of the neuroradiological investigations is impor-

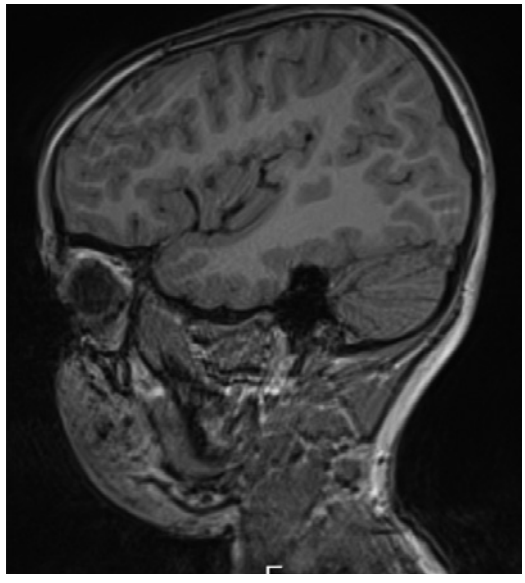

Figure 5: A 4-year-old girl with subtle cortical dysplasia in the right parietal area, the primary motor region for the non-dominant hand. Intracerebral depth electrodes are in place (black dots in the cerebral cortex). Because of frequent seizures, the girl had persistent paresis of the distal left hand.

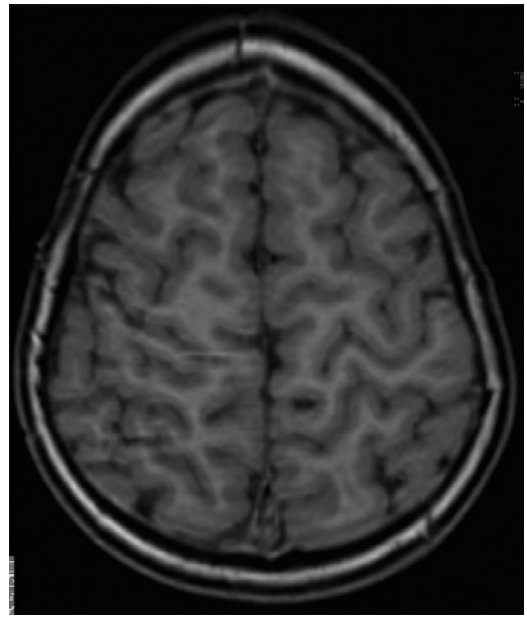

Figure 6: Patient from Figure 5, a few days after electrode removal. Coagulation was performed in the right primary motor region. A year after surgery, the girl is seizure-free and the function of her left hand has improved.

tant (17). If a child is unable to cooperate during an imaging study, we perform it under general anaesthesia. Structural abnormalities may be clearly pronounced (hemimegalencephaly, circumscribed malformations of cortical development, certain developmental tumours), or they can be discreet (thickened gyrus, blurring of the grey-white matter boundary, volume reduction in a certain region) (Figure 1 and Figure 2). Computed tomography (CT), though used less often than MRI, is helpful in looking for calcifications, like in the Sturge-Weber syndrome or in tuberous sclerosis.

In recent years, functional magnetic resonance imaging (fMRI) has been used increasingly for the assessment of cerebral cortex functions. This investigation requires a cooperative subject, who must be prepared in advance for undergoing the test protocol.

3 Surgical techniques

We distinguish between curative and palliative techniques. The choice of technique depends on the position and size of the epileptogenic focus. Among curative techniques, the most frequently used are resections of the epileptogenic focus and disconnection procedures, which in their extreme form may comprise an entire hemisphere.

3.1 Brain resection

A brain resection involves the excision of an epileptogenic focus. We distinguish between simple resections and resections associated with intracranial exploration.

Simple resections are possible if there is a clear anatomical and electro-clinical correlation of seizures, i.e. agreement between neuroradiological findings and

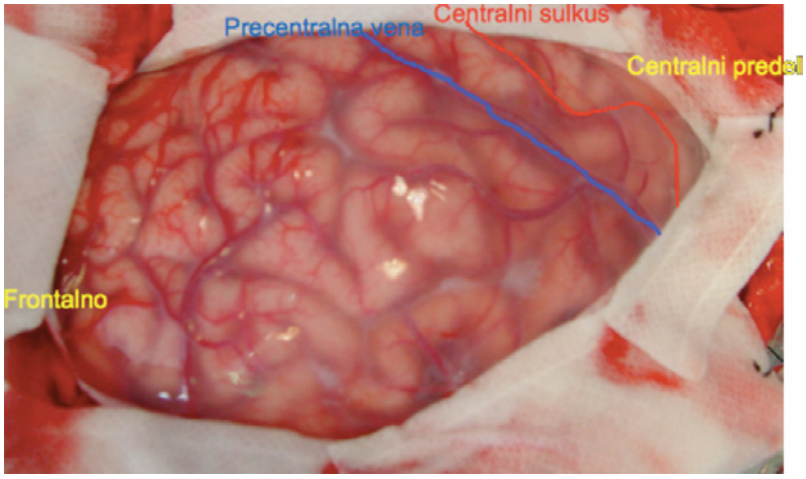

Figure 7: Surface of the cerebral cortex in a 6-year-old boy with type 2 cortical dysplasia in the right frontal area.

data acquired on seizure recording. The focus must not be located in a functional (eloquent) area of the brain, and the structural change must be anatomically well circumscribed (Figure 3). Simple resections are performed most often for mesial and polar temporal lobe epilepsies of the dominant hemisphere, but also for more widespread temporal lobe epilepsies of the non-dominant hemisphere. They are also carried out in Sturge-Weber angiomatosis, where the anatomical boundaries of the structural lesion usually coincide with the boundaries of the epileptogenic focus.

Resections associated with intracranial EEG exploration are carried out as a rule when there is a disagreement among the findings of preoperative investigations, or when the focus is close to functional areas and there is a greater risk of a neurologic deficit after the procedure. Intracranial exploration is often necessary in *extratemporal epilepsies* and in *non-lesional or cryptogenic epilepsies* where no radiological abnormalities are detected. Invasive recording of epileptic seizures is performed with the use of intracerebral electrodes. These enable, besides accurate topographic localization of the epileptogenic focus, also functional mapping of the cerebral cortex, whereby the location of functional regions is determined and their preservation is made possible.

We can implant either *intracerebral depth electrodes* (by stereotaxis or a robotic device, very rarely by craniotomy) or *subdural plate electrodes* (direct insertion with a major craniotomy).

3.1.1 Stereo electroencephalography (SEEG)

Intracerebral depth electrodes are implanted into anatomical structures, identified by presurgical investigations as the most probable epileptogenic regions. In the older SEEG technique developed by Bancaud and Talairach for adult patients, a stereotaxic frame and an arteriographic examination were used for determining the target anatomical structures (18). Nowadays, MRI and robots have made it possible to avoid both the arteriographic examination and the unpleasant stereotaxic frame. During the procedure, 10 to 20 thin wire electrodes are implanted according to a previously prepared scheme (Figure 4). For each electrode, a small burr hole is made, through which the electrode is inserted and attached to the skull with special threading. The electrodes may remain in place for up to two weeks (Figure 5). Resection of the epileptogenic zone is usually performed two to three months after electrode removal.

In the so-called thermocoagulation method developed recently, thermocoagulation of a small amount of brain tissue surrounding a previously implanted depth electrode is performed using currents that are higher than those used for stimulation in cortical mapping. In some cases, thermocoagulation alone can reduce the epileptogenicity of a certain region, whereby subsequent re-

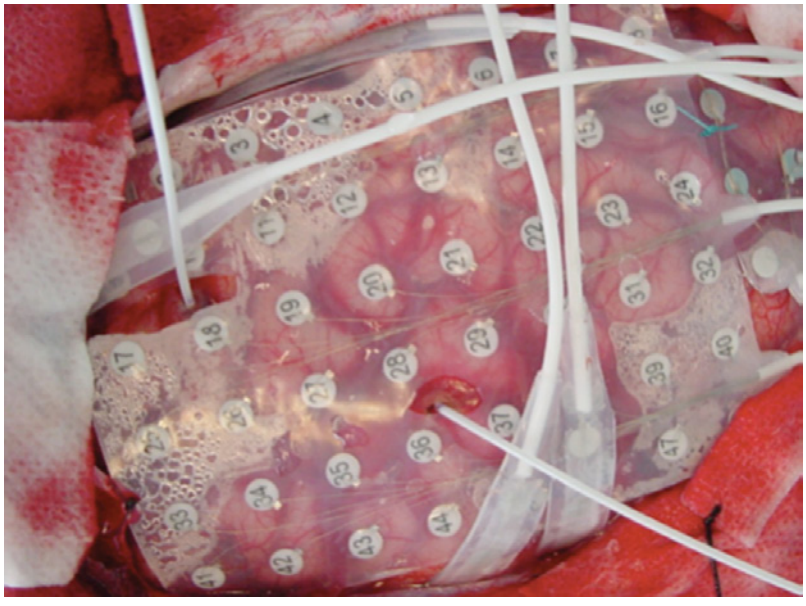

Figure 8: Patient from Figure 7; operating field following implantation of plate electrodes.

section of epileptogenic tissue is avoided (Figure 6). With depth electrodes, unlike with surface plate electrodes, we can very well explore also the temporal lobe and medial brain structures. This technique is not used in children under two years of age, since the skull thickness does not permit reliable electrode fixation.

3.1.2 Implantation of intracranial electrodes by craniotomy

This method is feasible also in the youngest patients. Usually we implant subdural plate electrodes, which allow exploration of the surface of the brain cortex (Figure 7 and Figure 8). Very rarely, intracerebral depth electrodes are implanted in this way. Plate electrodes allow rather accurate mapping of the sensory, motor and language areas of the cerebral cortex (19). Cortex is stimulated with trains of stimuli or with single stimuli at a high frequency (50 HZ) and increasing intensity. For localizing the language areas, 5-second stimulus trains are usually used while the patient is counting aloud. Single stimuli or 3-second stimulus trains are used for localizing sensory and motor areas. The response is observed on the side contralateral to stimulation as a contraction of specific muscle groups or as paraesthesias. The distance between two stimulation electrodes must be about 1 cm. Plate electrodes are left in place for 5–10 days. On their removal, the epileptogenic area is excised as well.

The decision for one or the other method depends on the surgical school, but also on the patient's age and the topography of the epileptogenic focus. By intracranial recording of epileptic seizures and mapping of functional areas of the cerebral cortex, we are able to accurately define the edges of an epileptogenic region and at the same time avoid postoperative neurologic deficits.

3.2 Disconnection procedures

Hemispherotomy is the interruption of the afferent pathways of a hemisphere with preservation of its vasculature (20,21). The connection between the hemispheres is completely interrupted, only a few efferent fibres are preserved. This technique is used instead of hemispherectomy (removal of a hemisphere), where a necrotic space is left intradurally, remaining a common site of complications due to excessive cerebrospinal fluid accumulation. Hemispherotomy is indicated when the epilepsy affects an entire hemisphere, which is no longer functional. The preoperative deficit (hemiplegia, hemianopsia) grows only slightly worse or remains unchanged after the procedure, but gait capacity is preserved. It is important to preserve the unilateral nature of any residual seizures and the functional integrity of the contralateral hemisphere. Smaller, more limited disconnection procedures are also possible, which aim to preserve the functionality of the cen-

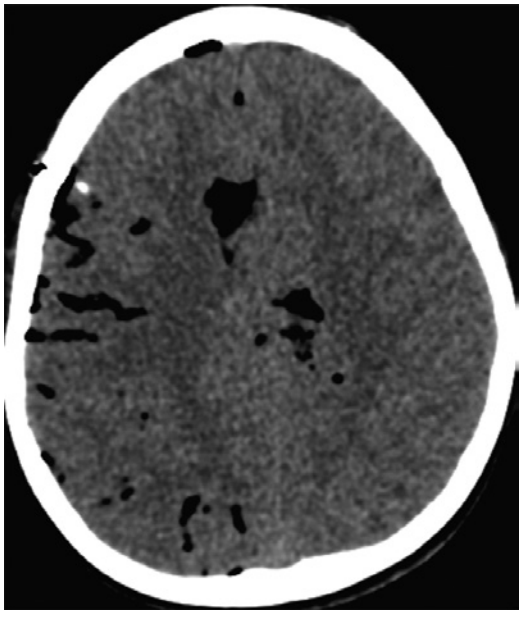

Figure 9: CT scan of a 9-year-old boy with pneumocephalus after removal of intracerebral depth electrodes.

tral region. In extensive yet incomplete involvement of a hemisphere, it is possible to interrupt both afferent and efferent fibres of the greater part of the hemisphere, while preserving the smaller, unaffected part.

3.3 Surgery of hypothalamic hamartomas

Hypothalamic hamartomas are congenital neuronal malformations located in the diencephalon region of the brain (hypothalamus and the mammillary bodies). They often cause refractory epilepsy with different forms of seizures characterized by gelastic components, and with an encephalopathic course (22,23). They may be associated with premature puberty. Surgical treatment of hamartomas is very demanding because of their proximity to the brain stem. They are mostly treated endoscopically, and less frequently by the classical microsurgical technique (24). Radiosurgical ablation is also possible (25).

3.4 Palliative surgical procedures

Their aim is to limit the spread of epileptic seizures by severing connections.

Callosotomy (26). The anterior two thirds of the corpus callosum are divided along the longitudinal axis. In this way, the main pathways by which impulses spread between the two hemispheres are interrupted. The indications for this procedure are multifocal and generalized epilepsies, such as the Lennox-Gastaut syndrome and infantile spasms (27). In drop attacks, posterior callosotomy can be performed (28). If carried out before the age of 10 years, callosotomy does not cause additional neuropsychological deterioration or language disorders (29).

Subpial transection (30) is a procedure in which the short cortico-cortical fibres involved in epileptogenesis are divided at the level of the cerebral cortex, while the vascularity of the pia as well as the long cortico-subcortical fibres essential for maintaining the function of the cerebral cortex are preserved. Thus, the functional areas of the cortex are fully preserved but the epileptogenic connections are severed. Subpial transection can be performed as an isolated procedure or in conjunction with limited resection of the epileptogenic region. It is usually ineffective in areas of dysplastic cortex.

3.5 Vagus nerve stimulation (VNS)

VNS was initially approved as an adjunctive method for the treatment of refractory focal seizures in adults and children over 12 years of age. Later it began to be used also in younger children (31). Although double blind trials were never conducted, VNS is reported to result in reduction of seizure frequency in about

half of patients (32,33). Its mechanism of action is unclear. In the short term, VNS probably affects the synchronization of cerebral electrical activity via the nucleus of the solitary tract. Its long-term action alters the concentration of neurotransmitters. Increased activity of the noradrenaline and serotonin pathways is thought to elevate the seizure threshold (33).

3.6 Deep brain stimulation

Although stimulation of deep brain nuclei is a well-established method in the treatment of movement disorders, numerous trials are underway to assess its efficacy also in patients with epilepsy. The targets used are amygdala, hippocampus, subthalamic nucleus, anterior centromedian nucleus of the thalamus, cerebellum, and head of caudate nucleus. In a randomized double-blind multicentric study of 110 patients, 56 % experienced a decrease in seizure frequency following stimulation of the anterior thalamic nucleus (34). It is worth mentioning that in Slovenia, the first attempts to treat (young adult) patients with epilepsy by cerebellar stimulation were made already 30 years ago (35).

4 Indications and contraindications in different age groups

When deciding about surgical treatment, we distinguish the following age groups: infants (up to 1 year), toddlers (up to 3 years), children (3–10 years), and adolescents (up to 16 years). The aetiology of epilepsy varies with age.

In infants, the most frequent causes of seizures are cerebral malformations (dysplasia, hemimegalencephaly). Ganglioneuronal tumours are rare. Most infants with epilepsy have severe and very frequent seizures, which may start already before the age of one month and occur several times a day. The most frequent procedure in this age group is hemispherotomy, focus resection being only second in frequency. The reason for the radical approach is a high and early epileptogenicity of hemispheric cerebral malformations.

In the age group up to 3 years, the predominant causes of epilepsy are cortical lesions (cortical dysplasia), followed by neuronal and glial tumours. The most frequent procedure is focus resection. Since the goal of these procedures is complete excision of the epileptogenic focus, intracranial exploration is often necessary. Exceptions are certain temporal lobe epilepsies and localized forms of the Sturge-Weber syndrome. Hemispherotomies in toddlers are performed in cases of extensive cortical dysplasia.

In older children, the most frequent procedure is focus resection. The exception is Rasmussen encephalitis affecting only one cerebral hemisphere, which is a good indication for hemispherotomy. Rasmussen encephalitis appears mostly after the age of three years, the patients' mean age being six years.

Caution is needed in non-lesional epilepsies, where invasive presurgical evaluation is usually necessary to clearly define the agreement between the result of MRI and EEG studies (36). Resections are generally not performed in non-lesional epilepsies, although in certain cases (tuberous sclerosis), resection of the most active focus may improve the condition (1).

5 Results of surgical treatment

On average about two thirds of patients are seizure-free after surgery. In a group of 75 patients under 12 years of age reported by Paolicchi and Jayakar, 59 % of operated patients were still seizure-free 5 years after the procedure (2). Wyllie and Comair reported on 62 children under 12 years of age, of whom 68 % were seizure-free 3.6 years after surgery (3). In 33 children under 15 years of age, Maehara and Shimizu found good results after temporal lobe resections (67 % seizure--free), and slightly poorer results after callosotomies (42 % seizure-free) and extratemporal procedures (33 % seizure--free) (4). Results in a group of 19 children with cortical dysplasia under 5 years of age undergoing SEEG surgery show absence of seizures after the procedure in 84 % and a motor deficit in 20 % - in 10 % as a transient disorder and in 10 % as a permanent sequela (5). In one child, electrode insertion was followed by the development of a subdural haematoma requiring surgical treatment. Other rare but possible complications of SEEG are infections (meningitis, bone flap infection), minor intraparenchymal bleeding after the insertion of electrodes, and pneumocephalus after their removal (Figure 9). These data allow the conclusion that epilepsy surgery is feasible with acceptable morbidity and with complete cessation of seizures in the majority of patients.

6 Status in Slovenia

In Slovenia, patients receive presurgical diagnostic evaluation, but epilepsy surgery is not performed. Both children and adults with epilepsy who are candidates for surgical treatment are referred to specialized centres abroad following evaluation by an experienced epilepsy team. Numerous patients who until recently were considered unsuitable surgical candidates now undergo successful operations (37-40). Since epilepsy surgery is a branch of neurosurgery that is developing rapidly as a result of new diagnostic and surgical methods, a further increase in indications may be expected in the future.

7 Conclusion

Surgical treatment of refractory epilepsy in children is feasible with acceptable morbidity and cessation of seizures in about two thirds of patients; most other patients experience a decrease in seizure frequency or a change in the form of seizures. Surgical complications are rare and mostly transient. The quality of life and the development in children improve significantly after the cessation of seizures and epileptiform activity.

Literatura

1. Koh S, Jayakar P, Dunoyer C, Whiting SE, Resnick TJ, Alvarez LA et al. Epilepsy surgery in children with tuberous sclerosis complex: presurgical evaluation and outcome. Epilepsia. 2000 Sep;41(9):1206–13.
2. Paolicchi JM, Jayakar P, Dean P, Yaylali I, Morrison G, Prats A et al. Predictors of outcome in pediatric epilepsy surgery. Neurology. 2000 Feb;54(3):642–7.
3. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P. Seizure outcome after epilepsy surgery in children and adolescents. Ann Neurol. 1998 Nov;44(5):740–8.
4. Maehara T, Shimizu H, Oda M, Arai N. Surgical treatment of children with medically intractable epilepsy—outcome of various surgical procedures. Neurol Med Chir (Tokyo). 1996 May;36(5):305–9.
5. Dorfmüller G, Ferrand-Sorbets S, Fohlen M, Bulteau C, Archambaud F, Delalande O et al. Outcome of surgery in children with focal cortical dysplasia younger than 5 years explored by stereo-electroencephalography. Childs Nerv Syst. 2014 Nov;30(11):1875–83.

6. Ravnik IM, Paro D, Tivadar I, Panjan B. Epidemiologie descriptive des épilepsies dans la région sanitaire de Ljubljana. In: Jallon P, editor. Epidemiologie des épilepsies. Paris: John Libbey; 1988. pp. 71–81.
7. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069–77.
8. Holthausen H, Pieper T, Kudernatsch M. Towards early diagnosis and treatment to save children from catastrophic epilepsy— focus on epilepsy surgery. Brain Dev. 2013 Sep;35(8):730–41.
9. Titus JB, Lee A, Kasasbeh A, Thio LL, Stephenson J, Steger-May K et al. Health-related quality of life before and after pediatric epilepsy surgery: the influence of seizure outcome on changes in physical functioning and social functioning. Epilepsy Behav. 2013 Jun;27(3):477–83.
10. Baca CB, Vickrey BG, Vassar S, Hauptman JS, Dadour A, Oh T et al. Time to pediatric epilepsy surgery is related to disease severity and nonclinical factors. Neurology. 2013 Mar;80(13):1231–9.
11. Vicari S, Albertoni A, Chilosi AM, Cipriani P, Cioni G, Bates E. Plasticity and reorganization during language development in children with early brain injury. Cortex. 2000 Feb;36(1):31–46.
12. Hertz-Pannier L, Chiron C, Jambaqué I, Renaux-Kieffer V, Van de Moortele PF, Delalande O et al. Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. Brain. 2002 Feb;125(Pt 2):361–72.
13. Bulteau C, Delalande O, Fohlen M, Jalin C, Pinard JM, Castelli N et al. Comportement et cognition chez l'enfant traité par hémisphérotomie. Approch Neuropsychol Apprentiss Enfant. 2002;68:204–6.
14. André-Obadia N, Sauleauc P, Cheliout-Heraute F, Convers P et al. Recommandations françaises sur l'électroencéphalogramme. French Guidelines on electroencephalogram. Neurophysiologie Clinique. Clin Neurophysiol. 2014;44:515–612.
15. Beniczky S, Neufeld M, Diehl B, Dobesberger J, Trinka E, Mameniskiene R et al. Testing patients during seizures: A European consensus procedure developed by a joint taskforce of the ILAE - Commission on European Affairs and the European Epilepsy Monitoring Unit Association. Epilepsia. 2016 Sep;57(9):1363–8.
16. Wieser HG, Siegel AM. Analysis of foramen ovale electrode-recorded seizures and correlation with outcome following amygdalohippocampectomy. Epilepsia. 1991 Nov-Dec;32(6):838–50.
17. Adamsbaum C, Robain O, Cohen PA, Delalande O, Fohlen M, Kalifa G. Focal cortical dysplasia and hemimegalencephaly: histological and neuroimaging correlations. Pediatr Radiol. 1998 Aug;28(8):583–90.
18. Talairach J, Bancaud J, Szikla G, Bonis A, Geier S, Vedrenne C. Approche nouvelle de la neurochirurgie de l'épilepsie. Méthode stéréotaxique et résultats thérapeutiques. Neurochirurgie. 1974;20(1):183–213.
19. Jayakar P, Alvarez LA, Duchowny MS, Resnick TJ. A safe and effective paradigm to functionally map the cortex in childhood. J Clin Neurophysiol. 1992 Apr;9(2):288–93.
20. Villemure JG, Vernet O, Delalande O. Hemispheric disconnection: callosotomy and hemispherotomy. In: Cohadon F, editor. Advances and Technical Standards in Neurosurgery. Volume 26. Vienna: Springer-Verlag; 2000. pp. 25–78.
21. Fohlen M, Jalin C, Pinard JM, Delalande O. De l'hémisphérectomie à l'hémisphérotomie. In: Bureau M, Kahane P, Munari C, editors. Epilepsies partielles graves pharmaco-résistantes de l'enfant : stratégies diagnostiques et traitements chirurgicaux. Paris: John Libbey; 1998. pp. 231–5.
22. Munari C, Kahane P, Francione S, Hoffmann D, Tassi L, Cusmai R et al. Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study). Electroencephalogr Clin Neurophysiol. 1995 Sep;95(3):154–60.
23. Kuzniecky R, Guthrie B, Mountz J, Bebin M, Faught E, Gilliam F et al. Intrinsic epileptogenesis of hypothalamic hamartomas in gelastic epilepsy. Ann Neurol. 1997 Jul;42(1):60–7.
24. Delalande O, Fohlen M. Disconnecting surgical treatment of hypothalamic hamartoma in children and adults with refractory epilepsy and proposal of a new classification. Neurol Med Chir (Tokyo). 2003 Feb;43(2):61–8.
25. Kameyama S, Shirozu H, Masuda H, Ito Y, Sonoda M, Akazawa K. MRI-guided stereotactic radiofrequency thermocoagulation for 100 hypothalamic hamartomas. J Neurosurg. 2016 May;124(5):1503–12.
26. Delalande O, Pinard JM, Jalin C, Fohlen M. Chirurgie et épilepsie. Neurochirurgie. 1998 May;44(1 Suppl):127–32.
27. Pinard JM, Delalande O, Soufflet C, Plouin P, Kim Y, Dulac O. Callosotomy in epilepsies following infantile spasms. Epilepsia. 1999;40:1727–34.
28. Paglioli E, Martins WA, Azambuja N, Portuguez M, Frigeri TM, Pinos L et al. Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity. Neurology. 2016 Nov;87(19):1968–74.
29. Lassonde M, Sauerwein H, Chicoine AJ, Geoffroy G. Absence of disconnexion syndrome in callosal agenesis and early callosotomy: brain reorganization or lack of structural specificity during ontogeny? Neuropsychologia. 1991;29(6):481–95.
30. Morrell F, Whisler WW, Bleck TP. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. J Neurosurg. 1989 Feb;70(2):231–9.
31. Healy S, Lang J, Te Water Naude J, Gibbon F, Leach P. Vagal nerve stimulation in children under 12 years old with medically intractable epilepsy. Childs Nerv Syst. 2013 Nov;29(11):2095–9.
32. Jayalakshmi S, Vooturi S, Gupta S, Panigrahi M. Epilepsy surgery in children. Neurol India. 2017 May-Jun;65(3):485–92.
33. Rutecki P. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia. 1990;31(s2 Suppl 2):S1–6.

34. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R et al.; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010 May;51(5):899–908.
35. Klun B, Stojanović V, Strojnik P, Stanič U, Vodovnik L, Žirovnik S. Chronic cerebellar stimulation in the treatment of epilepsy. Advances in neurosurgery. 1987;15:205-9.
36. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P. Seizure outcome after epilepsy surgery in children and adolescents. Ann Neurol. 1998 Nov;44(5):740–8.
37. Ravnik IM, Krajnc N, Tretnjak V, Kržan M, Gosar D, Župančič N et al. Collaborative cross border management of drug resistant paediatric epilepsy - example of a small Mediterranean country. Med Razgl. 2011;50 Suppl 3:59.
38. Krajnc N, Ravnik IM, Gosar D, Tretnjak V, Župančič N, Kržan M et al. Surgical management of patients with pediatric onset epilepsies from Slovenia. V: Pediatric epilepsy surgery: final program. Lyon: IDEE - Institute for Children and Adolescents with Epilepsy; 2009. p. 33.
39. Tretnjak V, Ravnik IM, Krajnc N, Gosar D. Referrals abroad for epilepsy surgery : experience in neuropsychological assessment gathered by the Center for Child & Adolescent Epilepsy at the Children's University Hospital in Ljubljana. V: 7th European congress on epileptology, Helsinki, July 02-06, 2006, (Epilepsia, vol. 47, suppl. 3). Copenhagen: Blackwell Publishing; 2006, p. 200-1
40. Ravnik IM, Krajnc N, Benedik Perković M, Gosar D, Vranič A. Comprehensive management of severe epilepsies in small countries with limited resources. Paediatr Croat. 2014;58(4):301–2.