Malformations of cortical development: New surgical advances

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Abstract

Epilepsy related to malformations of cortical development is frequently drug resistant or requires heavy medication, therefore surgery is key in their management. The role of stereotactic surgery has recently changed the diagnosis and treatment of focal cortical dysplasias (FCD), hypothalamic hamartomas (HH) and periventricular nodular heterotopias (PNH). In HH, radiosurgery using Gammaknife® leads to 60 % of seizure control and is associated with excellent neuropsychological results without significant endocrine function impairment. The seizure control rate is even higher (more than 80 %) with monopolar multiple stereotactic thermocoagulations and Laser interstitial Thermal Therapy (LiTT). While the first technique is associated with a 2 % complications rate (but with excellent neuropsychological outcomes), the latest has up to 22 % side effects in some series. All three of these techniques have encouraging results, but controlled studies are still lacking to provide evidence-based new therapeutic algorithms. With regard to the PNH, surgical management has long been limited by the depth of the lesions and their close anatomical relations with the functional brain connectome. Stereotactic approaches required to perform a SEEG, to locate the part of the PNH responsible for the seizure onset, are later followed by a stereotactic lesioning procedure, therefore doubling the bleeding risk. That is why SEEG-guided radiofrequency-thermocoagulation (SEEG guided-RF-TC), which makes it possible to perform these two steps in a single procedure, was considered as a promising option. A recent meta-analysis confirmed this intuition and reported 38 % of seizure-free patients and 81 % of responders with only 0.3 % of complications, making this approach the first treatment line, followed by LiTT. Among the multiple advances in the FCD identification by non-invasive investigations, a new modality of per-operative diagnostic procedure, the three-dimensional electrocorticography

may lead to simplify the preoperative investigation and enhance the accuracy of FCD delineation. Evidence is nevertheless still insufficient to validate this promising concept. Conventional surgical resection has also been concerned by significant conceptual advances during the past few years, in particular with the development of the hodotopic approach, initially in oncologic surgery. Associated with a better understanding of neuroplasticity in epilepsy and the setting up of functional mapping during SEEG or during awake surgery, the possibility of surgical resections grew up. A short-term perspective in this field, when surgical resection remains impossible, would be to target crucial nodes of the epileptic network, distinct from the core functional connectome.

Keywords: Epilepsy; Drug resistant; Dysplasia; Hamartoma; Heterotopia

1 Introduction

Epilepsy related to malformations of cortical development is frequently drug resistant and may require heavy medications, therefore, surgery is key in their management. Among the malformations of cortical development, three of them: hypothalamic hamartomas, periventricular nodular heterotopias and focal cortical dysplasias, recently underwent important changes of their respective surgical management. Hypothalamic hamartoma can be now considered as a well-limited lesion poorly integrated in a larger epileptic network, and in close relation with two non-compensable structures of the connectome, i.e. the mamillary bodies and the hypothalamus [1,2]. The surgical challenge is therefore to destroy a deep and hardly accessible lesion, as safely as possible. Periventricular nodular heterotopias are also well limited depth lesions but are usually integrated in a large epileptic network, and a large part of the lesion may not be involved in the seizure onset zone [3]. Consequently, the challenge is to provide a way to record a depth complex epileptic network and to damage it while being as less invasive as possible. Type II focal cortical dysplasia is a well-limited, usually accessible, malformation, whose epileptological prognosis is directly linked to the possibility of total removal. Its delineation is uneasy on imaging and is largely supported by electrophysiological data, including interictal abnormalities [4]. The challenge is therefore to perform an accurate electrophysiological mapping. The goal of this focused review is to determine how new surgical techniques can help to meet these challenges.

Additionally to these three specific pathologies, this work aims to expose some emerging surgical concepts, and strategies, related to either the superficial (cortical) or the deep-seated (in the white matter) feature of the malformations.

2 Hypothalamic hamartomas: emergence of alternatives to conventional surgery

Hypothalamic hamartomas are malformations of fetal brain development, considered to be part of the spectrum of the gray matter heterotopias, affecting the development of the hypothalamus. The clinical presentation of hamartoma is dependent on its site of attachment: seizures are related to posterior lesions, in close relation with mammillary bodies, whereas endocrine alterations (mainly precocious puberty) are essentially due to lesions attached anteriorly in the region of the tuber cinereum [2]. Since the first description of a surgical treatment of an hypothalamic hamartoma in 1969 [5], the discussion has been dominated by the opposition between two micro-neurosurgical techniques: one aiming to reach the lesion from below (pterional and transamygdala extension of transtemporal-transchoroidal approaches), versus another aiming to reach the lesion from above (transcallosal) [1,6]. Whatever the technique, the possibility of complete removal is correlated to the importance of the attachment to the mamillary bodies (neuropsychological risk) and to the tuber cinereum (endocrine risk) [7]. To overcome this obstacle, an endoscopic surgical procedure and three stereotactic approaches have been developed.

First, radiosurgery by Gammaknife® has been increasingly evaluated [8–13] since the first publication of a large multicentric series in 2000 [14]. The two level 2 evidence prospective studies reported respectively 60 % [12] and 66 % [11] of seizure control following radiosurgery and showed a progressive positive effect on behavior during the six following months, co-occurring with sleep patterns and EEG normalization [13]. No major adverse event was reported, especially concerning the endocrine function [8], except transient seizure control worsening and poikilothermia. This results when compared to equivalent studies related to surgical approaches [1], indicate comparable or better results for radiosurgery, with a reduced rate of adverse effects [15]. Secondly, multiple monopolar radiofrequency thermocoagulations have been proposed and a recent study, including 100 patients, reported 71 % of seizure freedom (and 86 % concerning specifically gelastic seizures) [16]. Permanent endocrine deficit concerned 2 % of patients and required replacement therapy for low levels of cortisol and thyroid stimulating hormone or desmopressin for diabetes insipidus. A specific study about neuropsychological outcome revealed a significant improvement after radiofrequency thermocoagulations [17]. SEEG-guided radiofrequency-thermocoagulation (SEEG-guided RF-TC), a procedure that couples SEEG to radiofrequency coagulations by means of the recording electrodes, has also recently been proposed for hypothalamic hamartoma treatment [18]. However, such an indication requires to be carefully justified, as phase II investigations are usually unnecessary in this specific clinical situation. Thirdly, Laser interstitial Thermal Therapy (LiTT) has been proposed as an alternative treatment of hypothalamic hamartomas. Only small series, with less than 15 patients, have been published [19–22]. The results are interesting and suggest a seizure freedom rate of 84 % [20] (from 55 % [21] to 86 % [22]) but with a rate of complications up to 22 % [21].

Lastly, an endoscopic surgical disconnection has been proposed as an alternative of transcallosal superior approaches, when complete and safe resection is not possible [1,23]. This approach can be technically challenging because the limits of such a disconnection are not always well defined. Nevertheless, the procedure can be repeated in a single patient when the results are not satisfactory. The largest reported series [24] of 212 procedures on 136 shows that 77.5 % of patients are Engel 1 + 2 and a complication rate of 12.5 %.

The absence of comparative studies makes it difficult to provide a new therapeutic algorithm, but these new encouraging techniques can legitimately be discussed at the patient level. Overall, radiosurgery seems to have the best safety, whereas multiple monopolar radiofrequency coagulations may have the best efficacy/safety ratio.

3 Periventricular nodular heterotopias: a new stereotactic algorithm

The surgical management of periventricular nodular heterotopias is very challenging. First, periventricular nodular heterotopias can be large lesions only a part of which might constitute the seizure onset zone (or a part of a larger epileptic network). Identification of this specific portion can be uneasy at the end of phase I presurgical investigation [3,25–27]. Secondly, the deep-seated feature of these lesions and their close anatomical relation with essential and non-compensable structures of the functional connectome such as the tapetum, the inferior longitudinal fasciculus or the vertical and posterior parts of the superior longitudinal fasciculus often make the surgery very risky [28]. Consequently, the possibility of a surgical treatment is limited in many cases, so that phase II investigations have been considered as necessary for decades. In this context, the development of SEEG-guided RF-TC [29] offered a possibility to go beyond these limits: within a single procedure the epileptic network is investigated (both the different parts of the heterotopia and the involved neocortex) and can be disabled, including in its deepest part. This particular indication of SEEG-guided RF-TC differs from those initially described [30], as in this case, SEEG is performed knowing that conventional surgery will not be an option [31]. This extended indication has been validated in the French national guidelines about SEEG [32,33].

First results of this approach was initially published as a sub-group of a larger study [34] which reported 7 % of seizure free patients and 48 % of responders but failed to draw conclusions about sub-groups. More recently, studies specifically focused on SEEG-guided RF-TC as a treatment of periventricular nodular heterotopias reported very exciting results suggesting that almost all patients can reach Engel 1 status [3,27,35]. A meta-analysis pooling the sub-groups of all available studies concluded that, in this specific indication, SEEG-guided RF-TC leads to a rate of 38 % of seizure free patients and 81 % of responders [36]. These data make SEEG-guided RF-TC the first line of treatment of periventricular nodular heterotopias. Based on the data about epileptic networks and functional cartography characterized during SEEG recording, additional stereotactic approaches can be used to produce larger lesions: either repeated SEEG-guided RF-TC to enlarge the targeted volume, or other techniques such as LiTT, or, more uncertainly, radiosurgery [37,38].

As a conclusion, SEEG-guided RF-TC is now the first therapeutic option for periventricular nodular heterotopias. In case of partial results, an additional procedure or a LiTT should be discussed.

4 Type II focal cortical dysplasias: evolution and perspective of the intracranial investigations

Type II focal cortical dysplasias are an exception in terms of EEG, since they have a specific electrophysiological interictal pattern, in opposition to other pathologies in which interictal EEG abnormalities are not considered as a signature of the epileptogenic parenchyma and in which long-lasting SEEG recordings are necessary [4,39]. Because complete removal of type II dysplasias is the essential prognostic factor in terms of seizure outcome, numerous approaches aim to enhance the accuracy of its delineation [40]. On the one hand, precise preoperative definition of the dysplasia is challenging and relies on complex and poorly accessible techniques, such as MEG, high-density EEG with tridimensional source reconstruction or high-field magnetic resonance imaging with heavy post-processing analysis. On the other hand, peroperative mapping is only performed by highly specialized teams, using surface brain electrodes.

In this context, a novel promising approach of ECoG, the 3D ECoG, has been proposed: usually, intraoperative electrocorticography (ECoG) is dedicated to functional mapping [41] because using this technique to delineate the seizure onset zone requires high-level signal analysis only mastered by a few teams, such as high-frequency oscillations detection [42,43]. Conversely, in 3D ECoG, source reconstructions are no longer necessary, and it allows a tridimensional sampling of the electrophysiological signal of the region identified by the pre-surgical investigation as a type II focal cortical dysplasia [44]. First results show that the technique is feasible, safe, and allows to enhance the definition of the resection limits defined by SEEG in 80 % of patients. If these promising preliminary results were confirmed in comparative studies, a new strategy might be to do without SEEG, and be able to perform a functional mapping during awake surgery. Moreover, because the preoperative investigation techniques that allow to draw more precise limits of type II focal cortical dysplasias are usually poorly accessible, 3D ECoG may provide a cost-effective and easier alternative, based on a two-step strategy: first, performing limited preoperative investigations, such as scalp EEG and high resolution magnetic resonance imaging with arterial spin labeling sequences [45], in order to have enough data to suspect the presence of a type II focal cortical dysplasia, then intraoperatively defining its surgical limits, based on the 3D ECoG [44].

5 Evolution of the resective surgical approach: cortex and functional brain connectome

Until recently, malformations of cortical development have been considered as non-functional structures whose surgical treatment was only limited by the surrounding so-called “eloquent areas”. Recent intracranial electrophysiological data nevertheless suggest that the border between functional cortex and malformative tissue is not so sharp [46], and how far it is possible to go with surgery is a topical issue. As low-grade gliomas surgery has faced very similar challenges which led to major improvements in the field, comparisons have been proposed with epilepsy surgery [47]. Even if both pathologies are long-term diseases, neuroplasticity does not seem to operate in the same way: in low-grade glioma, functions are usually largely reorganized among the connectome, whereas in epilepsy, cortical mapping shows that functions of cortical areas are usually very similar to the usual localisationist atlases,

suggesting that the pathology induces poor cortical neuroplasticity. In this case, the resection would thus have consequences close to those of an acute lesion, such as a stroke or a brain injury, leading to an immediate impairment [28]. Yet, in opposition to low-grade glioma surgery, the cortex only is targeted when removing the seizure onset zone and the white matter tracts, crucial for neuroplasticity within the connectome, are not altered [48]. A future approach for malformations of cortical development involving an “eloquent” cortical area could be to perform a resection, which could lead to transient post-operative neurological impairment. If the cortical resection is limited enough, and the underlying white matter tracts of the connectome preserved, this neurological impairment should recover within a few weeks or months due to a stimulation of the neuroplasticity, as usually seen after low-grade glioma surgery [49]. Left temporal anterior lobectomy, leading to a transitory alteration of verbal fluency which recovers in a few months if the inferior fronto-occipital fasciculus is preserved [50], or resection of the superior parietal lobule (SPL), leading to a optic ataxia recovering if white matter tract connecting the contralateral SPL are not damaged [48], are two examples, initially empirically developed, of this approach. Nevertheless, the benefit-risk ratio of such surgical strategy in epilepsy still has to be defined, and developing an exhaustive knowledge on the probability of recovery based on pre-lesional investigations, as it recently started to be done in neuro-oncology [51], would be very helpful.

6 Perspective for inaccessible malformations of cortical development: targeting network nodes rather than removing the seizure onset zone

Functional cortical areas are not the only limitation to surgery: preserving white matter tracts, can be particularly challenging, in particular in cases of deep or widely extended lesions. Consequently, the white matter pathological plasticity must also be taken into account, since epileptogenesis does not only induce modifications at a cortical level but also deeply modifies the white matter anatomy. The resulting epileptic networks are composed by both physiological pathways, that play a role in the connectome, and pathological aberrant pathways, which are not supposed to sustain any function [28]. These pathological organizations are well described at a local level [52] as well as on long distance tracks [53–56]. They consist of abnormal fiber tracts, distinct from the normal white matter anatomy: for instance, the fiber projections arising from periventricular nodular heterotopias and ending in the corresponding neocortical areas in front of them are obviously non-anatomical pathological pathways, that cross the physiological ones [57]. Data suggests that the organization of these networks evolves with time: the connectivity related to the epileptogenic zone being increasing while the connectivity in widespread distal networks being decreasing [58]. This organization may provide a benefit in terms of seizure spreading limitation, but may as well impair physiological networks of the connectome, impacting some functions negatively.

Even for patients in whom a cortical resection of the seizure onset zone is not an option after phase I investigation, SEEG could help to define the normal connectome by performing direct electric stimulations, and also to delineate the white matter tracks involved in the seizure spreading. The overlap of these two networks would possibly allow to define targets and zones whose lesions would damage crucial nodes of the epileptic network without impairing the connectome [28,33].

7 Conclusion

Technical advances, which mostly consist of stereotactic procedures, have already led to practical modifications of the surgical management of malformations of cortical development for both the diagnosis (focal cortical dysplasias) and the treatment (hypothalamic hamartomas and periventricular nodular heterotopias). It is likely that the recent conceptual advances in conventional resection surgery will lead to other developments and stretch the surgical limits in the management of malformations of cortical development.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

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