Acta Neurochir (2012) 154:2003–2008
DOI 10.1007/s00701-012-1492-0

CASE REPORT

Plastic relocation of motor cortex in a patient with LGG (low grade glioma) confirmed by NBS (navigated brain stimulation)

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Received: 2 June 2012 / Accepted: 20 August 2012 / Published online: 4 September 2012

Abstract We report on a patient with LGG, in whom NBS mapping confirmed relocation of the primary motor cortex (M1) concurrent with multistage surgery. Comparing the NBS results at 18 months with the initial results revealed that the M1 representation had shifted from the precentral to the postcentral gyrus. The patient underwent a third surgical intervention. Intraoperative direct cortical stimulation (DCS) confirmed the shift of the M1. Plastic changes in M1 localization permitted complete tumour removal without neurological sequela. To our knowledge, this is the first report on a LGG patient where induced brain plasticity has been confirmed by NBS mapping.

Introduction

Low grade gliomas (LGG) represent 15 % of all primary brain tumours diagnosed in adults annually [20]. The extent of tumour resection is known to be a positive prognostic factor for these patients [20]. Therefore, the goal of LGG surgery should be to achieve maximal tumour resection while preserving neuropsychological function. Gliomas, especially LGGs, tend to be located within the functional regions in many cases [7], making extensive resection of the tumour difficult.

Navigated brain stimulation (NBS) is a novel method for non-invasive functional mapping which allows for risk-benefit balancing based on objective findings. NBS is the only non-invasive method analogous to intraoperative direct cortical stimulation (DCS), which is the gold standard for facilitating the preservation of functional regions during brain tumour surgery [6, 15, 16, 20].

In 2008, Robles, et al., presented two cases of patients in whom long-term brain plasticity allowed for a multistage surgical approach to LGGs in eloquent areas [17]. In these two cases, the dislocated eloquent areas were language areas and brain plasticity which was revealed by sequential fMRI in combination with DCS [17].

Here, we report on a patient with an LGG, in whom a change of motor cortex localization concurrent with multi-stage surgical procedures was confirmed by sequential NBS mapping.

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Case report

Onset

A 20-year-old male, with no prior history of neurological symptoms, was referred to hospital after suffering a general convulsion during exercise. On admission, a neurological examination revealed no apparent abnormal neurological findings except a heavy feeling in the right leg. MRI revealed a well-demarcated T1-hypointense and T2, FLAIR-hyperintense 5.0×3.2×4.0 cm mass in the left frontal lobe that was not enhanced by intravenous infusion of gadolinium (Fig. 1a, g). The lesion had invaded the left precentral gyrus (Fig. 1a).

Initial treatment

Preoperative cortical mapping was performed using an NBS System (Nexstim Oy, Helsinki, Finland), a noninvasive device comprising a stereotactic navigation system, a transcranial magnetic stimulator and coil, a 6-channel EMG

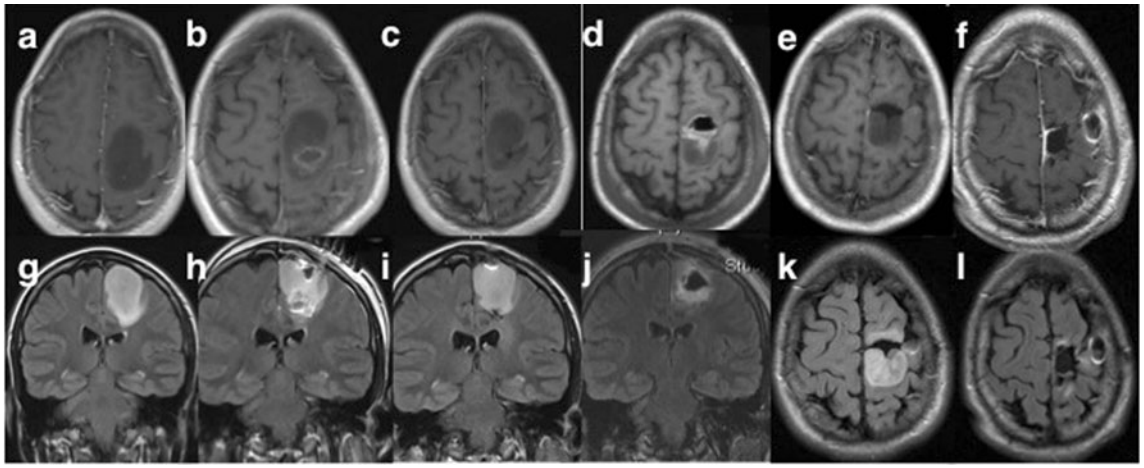

Fig. 1 Chronological change in MRI findings of the tumour **a**–**f**: T1-weighted MR image with intravenous injection of gadolinium (Gd) of the tumour, **g**–**l**: FLAIR MR-image of the tumour, **a** and **g**: at the time of initial presentation of the patient, **b** and **h**: immediately after the first operation, **c** and **i**: before the second operation, **d** and **j**: just after the second operation, **e** and **k**: before the third operation, **f** and **l**: 3 months after the third operation

recorder, a central processing unit, and dual display screens. Using anatomical landmarks, the patient's head was coregistered with the MR data set. Surface EMG electrodes were attached to the abductor pollicis brevis (APB), abductor digiti minimi (ADM), first dorsal interosseous (FDI), and tibialis anterior (TA) muscles. After the patient's motor threshold was determined on the tumourous hemisphere, NBS mapping was systematically performed at 110 % of the resting motor threshold, as previously described elsewhere [15, 16]. The coordinates of the motor representation area "hotspots" were stored in the NBS System's database. Preoperative mapping with NBS at stimulation intensities within the usual range elicited motor responses, recorded on EMG, mainly from the lateral region of the tumour, but also from directly above the tumour (Fig. 2b). This latter observation led the surgical team to aim primarily for preservation of function and tissue sampling, rather than complete tumour resection. Intraoperatively, the central sulcus and M1 were identified by somatosensory phase reversal with median nerve stimulation, as described elsewhere [10]. The infiltration of the precentral gyrus as predicted from preoperative NBS mapping was confirmed by intraoperative DCS (anodal monopolar stimulation, 400 Hz, pulse width 1 msec, train of 3). Responses from hand muscles were obtained at 7 mA stimulation intensity. Due to the highly eloquent location of the tumour, the surgeon performed only a small resection (Fig. 1b, h). Immediately after the operation the patient experienced right hemiplegia, which resolved by the time of discharge (10 days postoperatively) to mild paresis (British Medical Research Council grade 4/5) of the right lower extremity. Histopathology confirmed that the tumour was a grade 2 astrocytoma (LGG) with no sign of anaplasia or an oligodendroglioma component.

Malignant transformation of the tumour

The patient received no adjuvant treatment and was followed up in the outpatient clinic. A follow-up MRI showed local tumour progression at 6 months after the initial operation (Fig. 2 c, i), and the patient was readmitted for a second operation. No preoperative mapping was performed

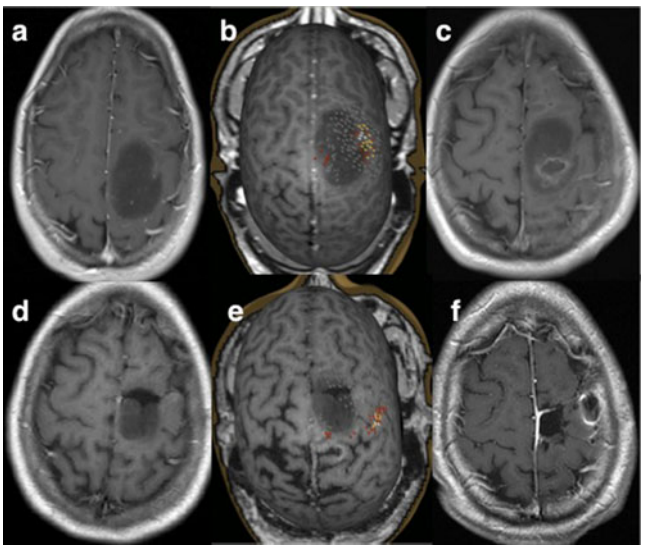

Fig. 2 **a**–**c**: Before the first surgery: preoperative T1-weighted MR image with intravenous injection of Gd of the tumour (**a**) low grade glioma spans the precentral gyrus which is outlined by the coloured TMS stimuli (**b**); this is confirmed intraoperatively and only a partial resection was performed (**c**) **d**–**f**: After 18 months: preoperative T1-weighted MR image with intravenous injection of Gd of the tumour (**d**) Repeated NBS mapping showed that the M1 has shifted to the postcentral gyrus (**e**) The tumour was resected completely (**f**). (* On the far right image, lower row (**f**), note that the area on the tumour side corresponding to the clearly visible hand knob on the healthy hemisphere has been resected)

at this time, but intraoperative DCS again confirmed the location of the dorsal part of the tumour to be within the precentral gyrus. A second partial resection was performed with the resection margin anterior to the precentral gyrus. Postoperative imaging showed 60 % resection of the FLAIR-signal abnormality (Fig. 1 d, j). As after the first operation, the patient experienced a worsening of motor function in the right lower extremity postoperatively. However, at 6 weeks function the patient recovered to the preoperative status, with only a mild impairment of coordination. Histopathology from the second operation confirmed that the tumour had evolved into a grade 3 astrocytoma and consequently the patient received adjunctive chemo- and radiotherapy, consisting of temozolomide in combination with radiation (60 Gy/ 30 fr).

Third operation for the tumour

After the second surgery, the patient continued to be followed-up in the outpatient clinic. Ten months after the second operation, following 10 cycles of chemotherapy, MRI revealed a 5×6×4 cm mass that suggested local tumour recurrence. The results of a FET-PET study suggested the presence of an active component to the tumour. Clinically, the patient experienced worsening of coordination in the right leg. Due to the clinical progression, supported by the results of the imaging studies, a third operation was planned. Although the patient reported increasing difficulties with coordination, on admission the patient was alert and had no recognizable sensory disturbance. Notably, the slight, permanent paresis that persisted after both the first and second operations had not worsened.

Preoperative mapping by NBS was performed and, to our surprise, the results revealed that the patient's M1 had shifted from the precentral gyrus to the postcentral gyrus. In the final NBS mapping session the same muscles were used for recording response as in the initial NBS mapping session. The NBS results showed the same mediolateral distribution of muscle responses with a lateral clustering of hand muscle responses and medial responses from the TA muscle. The motor threshold of the APB and FDI muscles was 18 % higher than in the initial mapping session and, in order to obtain responses from the TA muscle, stimulation intensity needed to be increased by an additional 25 %. Based on the findings from NBS mapping, a radical resection was proposed to the patient. The patient agreed to the potentially risky procedure, with full knowledge of the risk of permanently losing motor function.

The patient underwent surgical resection of the tumour mass, guided by the preoperative NBS mapping information in combination with intraoperative DCS and direct subcortical stimulation. During the operation, neurophysiological cortical mapping was performed. Stimulation of the precentral gyrus did not evoke any responses from hand or leg muscles despite using maximal stimulation intensities of 15 mA and 25 mA, respectively. The M1 area of the patient was identified in the postcentral gyrus with hand muscle responses being evoked at 11 mA stimulation intensity confirming the result of preoperative NBS. Interestingly, no response from leg muscles could be evoked despite using maximal stimulation intensity of 25 mA. Also, somatosensory phase reversal remained inconclusive with no phase reversal phenomena obtainable.

Considering the pre- and intraoperative findings we felt confident enough to start resecting towards the previous M1 in piecemeal fashion. To help ensure preservation of motor function in the hand we performed repeat stimulation and when approaching the pyramidal tract and the precentral gyrus, we also used subcortical mapping. We stopped resecting in the dorsal direction at the point where 3 mA stimulation caused responses from the arm muscles. Complete resection of the tumour was achieved under a surgical microscope. From postoperative MRI at day 1 there was no apparent sign of residual tumour. An MRI obtained at 3 months postoperatively showed no apparent tumour progression (Fig. 1f, l). Interestingly, although the postoperative MRI showed that the tumorous gyrus which clearly corresponded to the precentral gyrus on the contralateral healthy hemisphere had been partially resected, the patient had no new neurological sequelae after the operation (Fig. 1e, f, k, l). Histopathology confirmed that the tumour was a grade 3 astrocytoma. The patient was discharged from the hospital 7 days postoperatively without neurological worsening. The clinical course of the patient is summarized in Table 1.

Discussion

Low-grade gliomas (LGG) have a particular predilection for the functional regions such as insula and supplementary motor area [7, 20]. The median overall survival for patients with LGG is typically 5–15 years [20]. Nowadays, we can predict improved outcome among adult patients with hemispheric LGG in extensively resected tumours [21]. Histological upgrading of LGGs is a special consideration for these patients, as it carries a dramatically worse prognosis [20]. Based on these considerations, maximal tumour resection should be the surgical goal as long as patients are not burdened with neurological sequela. Agreeing to aggressive surgery may often be a difficult decision because patients often present with no neurological abnormal findings at the time of diagnosis [19, 20], seizures being the most common symptom at presentation (80 %) [19, 20].

Preoperative functional brain imaging has come to be used widely in the field of surgical treatment of low grade gliomas [6, 16, 20]. The most widely adopted method is

Table 1 Clinical course of the patient

Time course (months)	0		7		18	
	before first operation	after 1st operation	before 2nd operation	after 2nd operation	before 3rd operation	After 3rd operation
Tumor status	268 ml mass	33 % resection of flair signal abnormality	287 ml mass	60 % resection of flair signal abnormality	503 ml mass	No sign of residual tumor
Paresis in patient's Rt L/E [a]	5/5	plegia→4/5	5/5 (Mild impairment of coordination)	Transient worsening→5/5 (Mild impairment of coordination)	4/5 to 5/5, progressing coordination problems	4/5 to 5/5, same as preoperative status
RMT	34 %	N/A	N/A	N/A	40 % (118 % of previous RMT)	N/A
Somatotopy of motor cortex	Precentral (NBS)	N/A	Precentral localization was confirmed during the operation		Postcentral (NBS)	N/A

[a] Right Lower Extremity (British Medical Research Council grade)

functional magnetic resonance imaging (fMRI) [16]. Magnetoencephalography (MEG), positron emission tomography (PET) and electroencephalography (EEG) have also been used for preoperative mapping [16]. These methods are indirect. Further, fMRI and PET rely on metabolic changes due to cortical activity after voluntary action, e.g., muscle contraction [16].

NBS is an enhanced version of navigated transcranial magnetic stimulation (TMS), combining MRI data and computer analysis, to provide feedback on the exact 3-dimensional location of maximal stimulation [16]. Since NBS mapping is a direct method, mapping is also feasible in patients that cannot make voluntary movements or are cognitively incapable of task compliance and is the only preoperative brain mapping modality that allows for stimulation mapping like the gold standard direct cortical stimulation [16]. Previous studies have shown that preoperative NBS mapping of the motor cortex in brain tumour patients is superior to preoperative fMRI mapping [13] and consistent with intraoperative DCS [15]. The efficacy of NBS mapping for localization of the motor cortex in patients has been fully established [15, 16].

We believe that the greatest advantage of NBS, when compared to other preoperative functional brain mapping techniques like fMRI, is that NBS is the only currently available non-invasive and painless technique, which is methodologically comparable to DCS in such terms that it allows for direct stimulation of cortical neurons. On the other hand, fMRI has also an advantage over NBS of being able to obtain information from the sulcal depths that comprise as much as two-thirds of the cortical surface[5, 22]. Different types of preoperative brain mapping techniques should be used complementarily.

Relocation of M1 from its normal position in patients with intracranial lesions has been reported in patients with brain tumours (including gliomas) [17], stroke [4], and arteriovenous malformations [1]. In 2008, Robles et al., reported successful treatment of two patients with LGGs in language eloquent areas through multistage surgical procedures [17]. The clinicians used sequential fMRI before and during surgeries in combination with intraoperative DCS mapping in order to reveal brain plasticity, and took advantage of long-term brain plasticity in order to make the extensive resection of the LGGs possible [17]. In their paper, the authors discussed that their series was too small to represent the definitive statement on brain plasticity with tumour resection. Subsequently, Barcia et al., also reported a similar case of brain plasticity [2]. The present case used NBS instead of fMRI to reveal brain plasticity and demonstrated relocation of the motor cortex for the first time [2, 17].

The accuracy and validity of NBS for preoperative use has been described in a previous report [15]. Methodologically, NBS is better suited to more exactly delineate the

extent of the primary motor areas, i.e., the essential motor areas, than indirect non-invasive techniques since NBS allows for direct stimulation-effect observation. In this report, the relocation of the M1 from the pre- to the postcentral gyrus was demonstrated by NBS mapping and confirmed by intraoperative stimulation. The patient's clinical course, with no new neurological deficit after resection of the anatomical hand knob, gives further evidence of plastic changes in the brain.

In this patient's case, the M1 of the patient relocated posteriorly, adjacent to the brain tumour. Rouiller et al., inflicted lesions in the motor cortex of monkeys, and used intracortical microstimulation and reversible inactivation to clarify the responsible region for brain plasticity [18]. Of the three candidate regions (1: contralateral intact motor cortex, 2: supplementary motor area (both ipsilateral and contralateral), and 3: cortical region adjacent to the lesion) evaluated, they found that the cortical region adjacent to the lesion was the place where M1 dislocates as shown in the present case.[18] They discussed that both the stage of development and the extent of the lesion might affect the type of motor cortex relocation.[18] When lesions in the M1 were induced in the mature brain, a new motor cortex was expected to be found in the region adjacent to the lesion [18]. Therefore, a posterior relocation of the primary motor cortex in this case would be logical. Since no diffusion tensor imaging (DTI) tracking was performed in the patient, no conclusions with regard to compensation for the potential loss of important association fibres (pyramidal tracts) can be drawn. In this respect, it is interesting that the motor cortex dislocated to the postcentral gyrus. These neurons located in parietal lobe might be utilized for brain plasticity, since it is reported that approximately 25 % of contralateral corticospinal projections originate in the parietal lobe (mainly in Brodmann areas 2 and 5) [9].

Experimental findings suggested that the final motor outcome appears to be heavily influenced by the age at which a lesion occurs [3]. In previous case reports on brain plasticity, glioma patients have also been relatively young (38 years, 22 years [17], and 27 years[2]). The exact underlining cause of motor cortex relocation as described here remains unknown. In this case, the age of the patient, 20-years-old at the time of initial diagnosis, might have contributed to brain plasticity; however, myelination of the corticospinal tract is complete at approximately 24 months in humans [14].

The accuracy and validity of NBS for identifying motor cortex preoperatively has been recently established[12, 15]. For further evaluation of the motor system, NBS has been used to enhance diffusion tensor imaging by implementing NBS data as seed points for fiber tracking[8, 11]. This method may be especially effective in patients with brain tumours and obscured anatomy[8]. Currently, efforts are being undertaken to implement the topographical as well as neurophysiological data provided by NBS to further objectify preoperative risk-benefit balancing in respect to maximal extent of resection and risk for neurological sequela.

Conclusion

To our knowledge, this is the first report on a LGG patient where induced brain plasticity has been confirmed by NBS mapping. This case report together with recent findings [2, 17] suggests that eloquent area relocation concurrent with multistage glioma surgery may not be a rare event. For patients with LGG in an eloquent location it is therefore important to routinely perform follow-up non-invasive brain mapping in order to capture this kind of eloquent area relocation and offer the patients the possibility of complete tumour removal.

Acknowledgments This work was supported by a grant from the Berliner Krebsgesellschaft.

Conflicts of interest None

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Comment

The authors present an interesting case of brain plasticity in a patient who underwent repeated surgeries for a low grade glioma (LGG) located in the motor area. Brain plasticity in patients affected by neurological diseases has been already largely described. The phenomenon is of striking importance because it can provide new insights in neurophysiological mechanisms and also could entail some remarkable and tangible advantages for patients in the clinical setting. In fact, brain plasticity is a main issue in neuro-rehabilitation and now an emerging concept in neurosurgery. With regard to the specific field of neuro-oncology, a distinction has been made between preoperative, intra-operative, and postoperative brain plasticity. Finally, a multi-stage surgery based on brain plasticity has been suggested to achieve maximal safe removal of brain tumors. The appealing and original data reported by the Authors on NBS represent a noteworthy advance in this setting.

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The authors report the case of a 20-year-old male who underwent three surgeries for a glioma involving the left precentral gyrus. The patient benefited from navigated brain transcranial stimulation (NBS) before the first and the third operation. NBS showed a relocation of the primary motor cortex, which shifted from the precentral to the postcentral gyrus. This functional reorganization was confirmed using intraoperative direct cortical stimulation. It allowed total resection without neurological deficit.

This is a very exciting paper. It demonstrates the existence of mechanisms of brain plasticity, thanks to the use of NBS combined with intrasurgical direct stimulation. This original study enables a better understanding of the pathophysiology underlying cerebral remapping, that is, the recruitment of the retrocentral gyrus to compensate the invasion of the precentral gyrus by the glioma. In addition, such knowledge led the authors to re-operate the patient, with an improvement of the extent of resection within the precentral gyrus while preserving brain functions. This observation supports the fact that cerebral plastic potential have been underestimated by neurosurgeons during many decades, and that it should be used to increase surgical indications within areas for a long time considered as inoperable [1]. Combination of different mapping techniques (non-invasive NBS in addition to functional neuroimaging) serially performed over time in the same patient, and correlated to intraoperative stimulation could optimize the chances to investigate patterns of reorganization at the individual level, and thus to open the door to more aggressive surgical strategies based on multistage approach [2].

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