Biopsy of Brain Stem Glioma Using Motor-Evoked Potential Mapping by Direct Peduncular Stimulation and Individual Adjuvant Therapy

—Case Report—

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Abstract

A 23-year-old man presented with a brain stem glioma manifesting as a 6-month history of right hemiparesis and diplopia. Serial magnetic resonance imaging showed an intrinsic diffuse brain stem glioma that gradually localized to the left cerebral peduncle after initial adjuvant therapy. Surgery was performed through a left subtemporal transtentorial approach under motor-evoked potential (MEP) mapping by direct peduncular stimulation. The lateral aspect of the midbrain was exposed, a train of five bipolar 25 mA pulses was applied, and MEPs recorded from the extremities. MEPs were only recorded from the left extremities even with left cerebral peduncular stimulation. Partial resection of the tumor was safely performed, with slight temporary neurological worsening. The histological diagnosis was anaplastic astrocytoma. Individual adjuvant therapy based on the results of real-time reverse transcription-polymerase chain reaction of $O^6$-methylguanine-deoxyribonucleic acid methyltransferase achieved an almost complete tumor response. Surgery under pyramidal tract mapping and intensive postoperative adjuvant therapy resulted in a good outcome despite the presence of a generally intractable intrinsic brain stem glioma.

Key words: brain stem glioma, motor-evoked potential, individual adjuvant therapy, $O^6$-methylguanine-deoxyribonucleic acid methyltransferase

Introduction

Brain stem gliomas can be classified into three stages: intrinsic, exophytic, and disseminated. Intrinsic brain stem gliomas can be further classified into three types: diffuse, focal, and cervicomedullary. Intrinsic diffuse tumors may be the most malignant, whereas most intrinsic focal tumors are astrocytomas. Brain stem gliomas have recently been aggressively treated by surgery under various mapping and monitoring systems. Almost all surgically treated brain stem gliomas were exophytic, and rarely peduncular, cervicomedullary, or diffuse. Diffuse and intrinsic brain stem gliomas without histological or molecular biological characterization are usually treated by radiation and chemotherapy.

We describe a case of diffuse brain stem glioma which developed into intrinsic brain stem glioma which was treated by surgery using motor-evoked potential (MEP) mapping by direct peduncular stimulation, and then by individual adjuvant therapy (IAT) based on the results of real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis of the surgical specimen.

Case Report

A 23-year-old man was admitted to The Kitasato Institute Medical Center Hospital on May 23, 2000, with a 6-month history of progressive right hemiparesis and diplopia. He noticed that he could not play his guitar as well as before in December 1999. He then began to drop his chopsticks, and found it difficult to walk both up and down stairs. Neurologi-
physical examination at the first admission showed bilateral abducens palsies, mild hypesthesia of the left side of the face and right extremities (8/10), mild right hemiparesis (muscle strength 4+/5), and hyper-reflexes in the bilateral upper extremities and the left lower extremity. T1-weighted magnetic resonance (MR) imaging showed a diffuse isointense area without enhancement by gadolinium in the left pyramis of the medulla oblongata to the whole pons (Fig. 1 upper row). T2-weighted MR imaging showed a hyperintense area (Fig. 1 lower row). Adjuvant therapy was given under a diagnosis of diffuse-type brain stem glioma, consisting of 175 mg of 1-(4-amino-2-methyl-5-pyrimidynyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) and 1.5 $\times$ 10^6 IU of interferon (IFN)-$\beta$ three times a week for 6 weeks, and local 60 Gy of radiation. He was discharged on July 13, 2000, with stable neurological signs and MR imaging findings despite the therapy. Maintenance therapy with $6 \times 10^6$ IU of IFN-$\beta$ weekly was continued for 2 years. His neurological deficits, including right hemihypesthesia and right hemiparesis, gradually worsened despite the continuous daily administration of 4 mg of dexamethasone. The MR imaging findings also gradually changed, with localization of the ring-like enhanced lesion in the left cerebral peduncle and reduction in the area of diffuse hyperintensity (Fig. 2). Administration of 195 mg of ACNU in the outpatient clinic on May 24, 2002 had no effect on the tumor regression. He was re-admitted to the Department of Neurosurgery on July 5, 2002, with severe right hemiparesis (muscle strength 3/5).

Tumor biopsy was performed through a left subtemporal transtentorial approach on July 16, 2002 to determine the subsequent adjuvant therapy, under general anesthesia with propofol, fentanyl, and muscle relaxant only at the beginning of the operation. MEP mapping was performed in two ways. A set of screw electrodes, with the anode on the left and the cathode on the right, were placed to monitor the transcranial MEPs as the control stimulation for direct peduncular stimulation with a made-to-order bipolar stimulator. Surface electrodes for electromyographic responses were placed on the bilateral abductor pollicis brevis (APB) and bilateral abductor hallucis (AH) muscles. A horseshoe-shaped scalp incision was made around the left ear and a temporal bone flap 6 cm $\times$ 4 cm was formed for craniotomy in the supine-lateral position. The left temporal lobe was gently retracted, preserving the vein of Labbé, to expose the left cranial nerves III and IV, and the basilar artery (Fig. 3). The thickened tentorium was cut and the interpeduncular cistern was opened.

MEPs were recorded for pyramidal tract mapping to select the entry point of the tumor biopsy by direct peduncular stimulation on the longitudinal axis with a bipolar electrical stimulator at intervals of 5 mm as shown in Fig. 4. Trains of five bipolar pulses of 25
Fig. 3 Photograph showing the subtemporal approach. The left temporal lobe was gently retracted, preserving the vein of Labbé, to expose the left cranial nerves III (arrow) and IV (arrowhead), and the basilar artery.

Fig. 4 Intraoperative photograph showing locations of direct peduncular stimulation on the longitudinal axis with a bipolar electrical stimulator at intervals of 5 mm (sites A–D). Stimulation of the right cerebral peduncle (site C) produced responses in the left abductor pollicis brevis and abductor hallucis muscles. Paradoxically, only the left extremities responded upon stimulation of the left cerebral peduncle (sites B and D). The tumor was removed through a small 4-mm incision at site A, at which no response was evoked in any extremity.

mA amplitude were used. The duration of each pulse was 0.2 msec and the interpulse interval was 2 msec. Stimulation of the right cerebral peduncle (site C in Fig. 4) produced responses in the left APB and AH muscles (Fig. 5). Paradoxically, only the left extremities responded to stimulation of the left cerebral peduncle (sites B and D in Fig. 4). No response occurred in the right extremities to either direct stimulation of an exposed site or transcranial high-voltage (600 V) stimulation using an interpulse interval of 2 msec, five pulse train, and duration of 0.2 msec via the screw electrodes. The soft tumor was removed piecemeal through a small 4-mm incision at site A in Fig. 4, at which no MEP response was elicited in any extremity. Although he complained of worsening diplopia for 2 weeks postoperatively, no definitive neurological worsening was observed after 1 month.

Histological examination of the tumor specimens found heterogenic astrocytic tumor cells, including gemistocyte-like cells, located relatively close together, and vascular endothelial proliferation (Fig. 6 upper left). Necrosis was also detected, probably due to the preoperative radiation and chemotherapy (Fig. 6 lower left). No pseudo-palisading was seen. The mean MIB-1 index was 5% (Fig. 6 right column). The histological diagnosis was anaplastic astrocytoma (grade III).

Total ribonucleic acid (RNA) was extracted from a specimen frozen at −70°C, and real-time RT-PCR...
Fig. 6 Photomicrographs of the surgical specimens showing heterogenic astrocytic tumor cells, including gemistocyte-like cells, located relatively close together, and vascular endothelial proliferation (upper left), as well as necrosis probably due to the preoperative radiation and chemotherapy (lower left). The mean MIB-1 index was 5% (right column). The histological diagnosis was anaplastic astrocytoma. Hematoxylin and eosin (left column) and MIB-1 (right column) stains, ×400 (upper row) and ×200 (lower row).
diagnosis of the ring-enhanced lesion was anaplastic astrocytoma, but the changes in MR imaging findings in the 1 year after the first adjuvant therapy may be partially attributable to the therapeutic effect of IFN-β.1) IFN-β is known to have a differentiating effect on malignant tumors.13,21) Neurophysiological mapping and monitoring are essential for brain stem surgery. Facial nerve mapping and brain stem auditory-evoked potential monitoring are commonly used in approaches through the floor of the fourth ventricle.17) In the present case, the enhanced lesion was located in the cerebral peduncle, so MEPs were monitored following transcranial high-voltage stimulation together with direct peduncular stimulation.12,26) Transcranial MEP seems to be the obvious candidate because stimulation evokes large and multiple descending motor volleys.16) In our experience, high-voltage (600 V) stimulation can reach a deep site including the brain stem, whereas relatively low voltage (300–400 V) stimulation after craniotomy can be localized near the motor cortex. Transcranial MEP seemed to be useful for monitoring the pyramidal tract during brain stem surgery in which the motor area does not need to be exposed.

MEP monitoring using direct stimulation of a motor area is widely used for brain tumor surgery.3,10) The pyramidal tract, such as the corona radiata and posterior limb of the internal capsule, may also be stimulated through the wall of the tumor cavity.1) In contrast, little information is available on direct stimulation of the corticospinal tract in brain stem surgery.17) Intraoperative direct brain stem stimulation after temporal lobectomy for epilepsy found that monophasic cathodal stimulus at 2 to 10 mA was effective.4) This first successful recording of MEPs by direct brain stem stimulation was not used for mapping or monitoring for pyramidal tract preservation. Percutaneous electrical stimulation of corticospinal pathways at the level of the pyramidal decussation had also been performed in humans.24) The present case illustrates our method for intraoperative direct stimulation of the pyramidal tract in the brain stem for intraoperative monitoring or mapping. The stimulation was a train of five bipolar 25 mA pulses, and was intended to map the pyramidal tract to select the entry point for tumor biopsy, rather than monitoring, since the patient had shown relatively serious hemiparesis. We failed to record the contralateral target muscle response, but obtained information about the pyramidal tract by recording the ipsilateral muscle response. We performed partial resection of the tumor at a site at which no MEP was recorded. We think that the mapping was successful because the pyramidal tract was not injured during the operation despite the tumor involvement.
Compound MEPs were recorded only from the left limbs on stimulation of the bilateral cerebral peduncles. The response in the ipsilateral limbs to stimulation of the left pyramidal tract may have resulted from co-stimulation of the contralateral tract by the relatively intense stimulation (25 mA) or the presence of uncrossed fibers in the corticospinal tract.\(^2,17\) Since bipolar stimulation was performed along the longitudinal axis using a bipolar stimulator, stimulation of the contralateral side may have been difficult. The existence of a pyramidal tract fiber connected to the ipsilateral anterior corticospinal tract which does not pass through the pyramidal decussation is well known.\(^2\) An ipsilateral corticospinal pathway to a forearm muscle may exist in humans.\(^2\) It is not clear why these lesser fibers were not involved.

We have applied IAT based on the expression of MGMTmRNA since 1997.\(^1,9\) Recently, real-time RT-PCR has been used to quantify MGMTmRNA.\(^20\) MGMT expression is closely related to resistance to ACNU.\(^1,4\) In our retrospective study, no patients with MGMT RQV of more than 1 responded to adjuvant therapy using ACNU. In our recent unpublished experience, IAT treatment has had an effective rate, defined as more than 50% regression of the tumor volume, of greater than 50%, and the effective rate, defined as more than 50% regression.

\(^\)In the present patient, the RQV of MGMT was very high and platinum-based adjuvant therapy was effective, although the tumor has shown very slow regression. Regression is often slow, especially with the co-administration of IFN-\(\beta\), possibly due to the immunological effect of IFN-\(\beta\). The therapy must be evaluated after at least 2 months, and the drug should not be changed too soon as long as progression of the tumor is not observed.

References

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