Fluorescence-guided resection of primary and recurrent malignant gliomas with 5-aminolevulinic acid. Preliminary results

Wycięcie pierwotnych złośliwych glejaków mózgu oraz ich wznów pod kontrolą fluorescencji z zastosowaniem kwasu 5-aminolewulinowego. Wyniki wstępne

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Abstract

Background and purpose: Extent of resection plays a key role in the treatment of malignant gliomas (MGs). Patients with complete glioma removal, followed by chemoradiation, obtain the longest overall and progression-free survival. Fluorescence-guided resection of MGs enables intraoperative visualization of glioma tissue and increases control of the resection. The authors present preliminary results of 5-aminolevulinic acid (5-ALA) application during the resection of primary and recurrent MGs.

Material and methods: Six patients with either a suspected malignant glioma based on magnetic resonance imaging (MRI) or with recurrent glioblastoma multiforme were enrolled in the study. The extent of resection was calculated according to the postoperative MRI performed within 72 hours. Preoperative and early postoperative neurological status and Karnofsky Performance Scale (KPS) were compared.

Results: Fluorescence of tumour tissue was observed in 5/6 patients (five with the histopathological diagnosis of glioblastoma multiforme and one with neurotoxoplasmosis and AIDS). Complete tumour resection was achieved in 5 patients. Postoperative KPS and neurological status deteriorated in 2 cases. Radiotherapy and chemotherapy did not interfere with the sensitivity of the fluorescence guided tumour visualization.

Streszczenie

Wstęp i cel pracy: Zakres wycięcia guza odgrywa kluczową rolę w leczeniu złośliwych glejaków mózgu. Chorzy, u których wykonano całkowite wycięcie złośliwego glejaka mózgu i których poddano następnie radioterapii i chemioterapii, uzyskują zarówno najdłuższy całkowity czas przeżycia, jak i najdłuższy okres bez progresji choroby. Wycięcie złośliwego glejaka mózgu ukierunkowane fluorescencją umożliwia śródoperacyjne uwidocznienie tkanki glejaka oraz poprawia kontrolę w czasie operacji. Autorzy prezentują wstępne wyniki zastosowania kwasu 5-aminolewulinowego (5-ALA) podczas usuwania pierwotnych złośliwych glejaków mózgu oraz ich wznów.

Materiał i metody: Do badania zostało włączonych 6 chorych, u których na podstawie badania za pomocą rezonansu magnetycznego (RM) podejrzewano złośliwego glejaka mózgu albo odrost glejaka wielopostaciowego. Zakres wycięcia oceniano na podstawie RM wykonanego w ciągu 72 godz. po operacji. Stan neurologiczny chorych oraz ocenę w skali Karnofsky'ego (KPS) porównywano przed operacją i we wczesnym okresie po operacji.

Wyniki: Fluorescencja tkanki guza była widoczna u 5 z 6 pacjentów (u 5 rozpoznano histopatologicznie glejaka wielopostaciowego, u jednego chorego – neurotoksoplazmozę w prze-

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Conclusions: Fluorescence-guided resection of primary and recurrent MGs with 5-ALA improves control of the tumour resection. It enables the cytoreduction to be maximized but experience in neuro-oncological surgery is required to avoid serious, postoperative neurological deficits.

Key words: malignant gliomas, fluorescence, resection.

biegu AIDS). Makroskopowo całkowite wycięcie guza uzyskano u 5 chorych. Pooperacyjnie pogorszenie stanu neurologicznego oraz w skali KPS stwierdzono u 2 chorych. Radioterapia ani chemioterapia nie wpływały na występowanie fluorescencji podczas wycięcia guzów.
Wnioski: Wycięcie pierwotnych złośliwych glejaków mózgu oraz ich wznów ukierunkowane fluorescencją z zastosowaniem 5-ALA poprawia kontrolę śródoperacyjną podczas usuwania guza. Umożliwia osiągnięcie maksymalnej cytoredukcji, jednak aby uniknąć poważnych deficytów neurologicznych w okresie pooperacyjnym, potrzebne jest doświadczenie w chirurgii neuroonkologicznej.

Słowa kluczowe: glejaki złośliwe, fluorescencja, usunięcie guza.

Introduction

Malignant gliomas (MGs) are extremely invasive brain tumours with a high proliferative rate. In spite of significant progress in operative techniques and advances in radiotherapy and chemotherapy, the median survival time is still estimated at less than 2 years after the diagnosis of glioblastoma multiforme [1]. Recent studies advocate cytoreduction as the first line treatment for MGs [2-4]. However, there is still a strong conviction that due to the diffuse tumour nature, cytoreduction is ineffective and tumour biopsy with histopathological diagnosis following oncological treatment should be an initial therapeutic option. Considering the variety of clinical approaches, neurosurgical resection of MGs provides rapid reduction of tumour mass and prolongs progression-free survival (PFS) and overall survival (OS). Therefore, intensive research is being done to optimize the intraoperative visualization and evaluation of real time control of the surgical resection.

The last decades have resulted in the introduction of modern intraoperative techniques: intraoperative magnetic resonance imaging (MRI), neuronavigation, ultrasonography and photodynamic technique. Fluorescence-guided resection is performed with preoperative oral administration of 5-aminolevulinic acid hydrochloride (5-ALA). Five-ALA is a pro-drug that is metabolised intracellularly in enzymatic reactions to protoporphyrin IX (PPIX). The exogenous application of 5-ALA results in its accumulation and transformation mainly to PPIX, but not selectively in malignant glioma tissue. The concentration of PPIX is significantly lower in normal brain tissue than in MGs [5]. A randomized multicenter phase III study, which evaluated fluorescence-guided primary MG resections with 5-ALA, confirmed the prognostic preliminary results [4]. Early postoperative control MRI revealed that total tumour resection, defined as no contrast enhancement, was achieved in 90 (65%) of 139 patients in the fluorescence group compared with 47 (36%) of 131 in the white light group. Six-month PFS was twice as long in the 5-ALA resected group compared with the white light group. Five-ALA was also effectively used for resection of recurrent MGs [6].

The authors present preliminary results of fluorescence-guided resection of primary and recurrent gliomas with 5-ALA. Special attention is paid to intraoperative techniques in MG resections.

Material and methods

Six patients, with either a suspected MG based on MRI scans or with recurrent glioblastoma multiforme with histopathological diagnosis, were enrolled in the study. The following clinical data were determined for each patient: age at the time of operation, gender, tumour location, preoperative and postoperative Karnofsky performance scale (KPS), and neurological status (Table 1). Endpoints used in this study were extent of resection and early postoperative neurological status. Postoperative MRIs were performed within 72 hours after surgery. The extent of resection was calculated using MIPV (Medical Image Processing, Analysis and Visualization) software, version 5.1.1. Images were acquired from a 1.5 T MR scanner using a T1-weighted imaging protocol with a voxel size of 4 mm × 6 mm × 6 mm (0.14 mL). The criterion for the residual tumour was the contrast enhancement volume greater than 0.28 mL (double voxel volume).

Table 1. Preoperative characteristics of patients

Patients	Gender	Age	Tumour localization	Karnofsky performance scale score	Neurological deficits	Radiotherapy/ chemotherapy
Patient 1	male	70	right temporal lobe	70	none	yes
Patient 2	female	33	left frontal lobe	60	none	yes
Patient 3	male	44	left fronto-parietal area	70	none	no
Patient 4	female	60	right parietal lobe	60	left upper limb paresis	yes
Patient 5	male	58	right parietal lobe	70	psychomotor retardation	no
Patient 6	male	42	left frontal lobe	80	none	no

Table 2. Postoperative characteristics of patients

Patients	Karnofsky performance scale score	Neurological deficits	Histopathological diagnosis	Resection	Fluorescence
Patient 1	70	none	recurrent GM	total	positive
Patient 2	60	none	recurrent GM	total	positive
Patient 3	70	none	GM	total	negative
Patient 4	50	left hemiparesis	recurrent GM	total	positive
Patient 5	60	psychomotor retardation	neurotoxoplasmosis/AIDS	total	positive
Patient 6	90	none	GM	partial	positive

GM – glioblastoma multiforme

Pre-treatment with dexamethasone (4 mg three times daily) was obligatory for at least 2 days before surgery and until an early MRI scan had been obtained (within 72 hours after surgery). Patients received freshly prepared 5-ALA solutions (20 mg/kg body weight) orally 3 hours before the induction of anaesthesia.

The study required the tumour resections to be as complete as possible with the priority of avoiding serious neurological complications. In all patients the tumour was resected using an NC 4 OPMI Pentero Neuro FL surgical microscope (Zeiss, Oberkochen, Germany), which enabled switching from conventional standard xenon light to filtered, violet blue excitation light for visualizing fluorescence. Additionally, the BrainLab navigation system was employed for planning the approach and during tumour removal. All patients were evaluated neurologically within 24 hours after the operation.

All participants in the study gave informed, written consent for the surgery with 5-ALA and were informed about possible complications.

Results

Three of 6 patients enrolled in the study had recurrent glioblastoma multiforme and in three other patients MG was suspected due to the MRI findings. Patients from the recurrent glioma group received preoperative radiochemotherapy or radiotherapy alone. Intraoperative fluorescence with blue light was visible in 5 cases. There was no 5-ALA visualization in one case with subsequent histopathological diagnosis of glioblastoma multiforme. There was one case with postoperative diagnosis of cerebral toxoplasmosis and AIDS, in which the intensity of fluorescence was comparable to that observed in MGs. Radiotherapy alone or radiochemotherapy did not reduce the quality of 5-ALA visualization.

Complete tumour resection, defined as no contrast enhancement on postoperative MRI, was achieved in 5/6 patients, including those with neuroinfection and with no intraoperative fluorescence. In a case with partial resection, the marginal portion of the primary glioma could not be removed due to infiltration of the left insula. The neurological status and KPS of two patients deteriorated due to the progression of paresis and psychomotor retardation (Table 2).

Technical note

All the operations were performed with the support of neuronavigation. During preoperative planning, two

objects were created, one corresponding to contrast enhancement on T1-weighted MRI, the second related to hyperintensity on FLAIR MRI. Both objects were injected into the microscope view intraoperatively. Cranial approaches were planned on the basis of FLAIR MRI in three planes. To avoid significant 'brain shift' after dura and arachnoid opening, the authors paid special attention to the proper fixation and positioning of the head. Additionally, to reduce navigation error, the localization of the tumour took place as soon as possible after dura opening. Blue light was initialized after the tumour localization to verify the extent of fluorescence. At later stages of the procedure, blue light was repeatedly applied according to the decision of the neurosurgeon. The resection itself was performed with white light and blue light was switched on for a few seconds only to navigate and verify the border of the tumour. The microscopic view with blue light was not of sufficient quality to safely perform the procedure. Optimal fluorescence was obtained when the operating field was cleaned of haemorrhages. At each stage of the resection, a neurosurgeon should be aware of the location of functional areas, because the territory of fluorescence may be more extensive than was expected before the operation. In addition, the fluorescence may encourage one to expand the resection. Fluorescence-guided resection may require decision-making during the operation related to counterbalancing the range of resection and the risk of neurological complications, so the patient should be informed about this issue before the operation. It is worth remembering that the fluorescence intensity decreases around 30 minutes after the initiation of blue light, but the authors did not observe this effect. The fluorescence-guided technique does not lengthen the time of the operation, since switching on and off the blue light only requires pressing the programmed button on the handle of the microscope.

Discussion

MGs belong to a histologically heterogeneous group of brain tumours. The aims of the therapy are prolongation of PFS and OS and improvement of the quality of life. Cytoreduction with subsequent radiochemotherapy is recommended as the best medical treatment [7]. In 2005, the results of the EORTC-26981 study were published [1]. According to EORTC, patients showed promising outcomes of chemoradiation, which was recommended as a standard treatment of GM. Nevertheless, the most significant conclusion from the EORTC study was that OS after either radiochemotherapy or radiotherapy alone was greatest in patients assessed to have had complete resections, compared with those with incomplete resections or biopsies.

Lacroix *et al.* [2] estimated that the extent of resection greater than 98% causes a significant increase in OS. Stummer *et al.* [4] presented the results of a randomized multicentre phase III trial of surgical treatment of MGs with the use of 5-ALA. The results showed that fluorescence-guided resection allowed for complete tumour removal in 65% of cases. This percentage is almost twice that obtained with standard resection.

In this study the authors present early, postoperative results of MG resections with 5-ALA. In 5/6 patients with primary or recurrent glioma, intraoperative fluorescence enhancement was observed. In one case, where the GM was suspected both on MRI and intraoperatively, histopathological diagnosis confirmed *Toxoplasma* cysts in patient with HIV infection. It is noteworthy that the intensity of fluorescence in infected tissue was comparable to that seen in GM. The explanation of this effect could be the capability of *Toxoplasma gondii* to biosynthesize tetrapyrrole from two 5-ALA molecules using porphobilinogen synthase and finally to produce PPIX [8]. Cerebral HIV infection may lead to neurovasculitis with subsequent damage of the blood-brain barrier (BBB) mainly due to the overexpression of adhesion molecules and increased endothelial permeability [9]. Disrupted BBB enables crossing and accumulation of 5-ALA in the infected brain tissue.

The fluorescence-navigated resection with 5-ALA entails a high risk of postoperative neurological deficits, and therefore the support of neuronavigation and intraoperative MRI is recommended. A particularly high risk of morbidity in the early postoperative period was observed among patients who did not respond to preoperative steroid treatment [10].

Conclusions

1. Fluorescence-guided resection of MGs is an excellent technique for intraoperative detection and differentiation of tumour tissue from normal brain, increasing intraoperative resectional control, decision-making and comfort for the neurosurgeon.
2. Operations with 5-ALA should be performed by experienced neurosurgeons, while fluorescence navigated, expansive tumour removal entails a high risk

of severe postoperative neurological deficits. The authors recommend using a neuronavigation system as an assistant tool. The importance of intraoperative MRI is raised in the literature [11], but the authors have no experience on this field.

3. Preoperative planning of the neurosurgical approach should consider a larger volume of glioma when visualized with fluorescence than the contrast enhancement of the tumour mass observed on MRI.
4. MG resection with 5-ALA increases the percentage of cases with complete glioma resection, which is the predictive value for prolongation of PFS and OS.

Disclosure

Authors report no conflict of interest.

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