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Fluorescence in neurosurgery: Its diagnostic and therapeutic use. Review of the literature

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ABSTRACT

Fluorescent agents, e.g. 5-aminolevulinic acid (5-ALA), fluorescein and indocyanine green (ICG) are in common use in neurosurgery for tumor resection and neurovascular surgery. Protoporphyrine IX (PPIX) as major metabolite of 5-ALA is a strong fluorescent substance accumulated within malignant glioma tissue and a very sensitive and specific tool for visualizing high grade glioma tissue during surgery. Furthermore, 5-ALA or rather PPIX also offers an intratumoral therapeutic option stimulated by laser light in specific wavelength. Fluorescein was demonstrated to show similar fluorescent reactions in neurosurgery, but is controversial in its use, especially in high grade tumor surgery. Intraoperative angiography during resection of arterio-venous malformations, extracranial–intracranial-bypass or aneurysm surgery is supported by ICG fluorescence. Generally ICG will provide beneficial information for both, exposure of the pathology and illustration of healthy structures. This manuscript shows an overview of the literature focussing fluorescence in neurosurgery.

1. Introduction

Fluorescent agents are in common use in neurosurgery for fluorescence guided tumor resection, e.g. by 5-aminolevulinic acid (5-ALA) or fluorescein, fluorescence based photodynamic therapy (PDT) as off-label treatment in recurrent gliomas, or for intraoperative angiography during resection of arterio-venous malformations, extracranial–intracranial-bypass or aneurysm surgery. One of the most used fluorescent agents is 5-ALA, which is a natural biochemical precursor of haemoglobin that elicits synthesis and accumulation of fluorescent porphyrins (PPIX) within malignant glioma tissues [101,102,105]. Intraoperative tumor fluorescence derived from 5-ALA has found to be a sensitive and specific tool for visualizing residual contrast-enhancing tumor during surgery for high grade gliomas [104,105], while cytoreductive surgery of these malignant gliomas is generally accepted to be of benefit for patients [65,87,103]. Further, if exposed at 635 nm, PPIX acts as a potent photosensitizer for photodynamic therapy of malignant gliomas and various cancers [80,46,41]. Because of its intratumoral synthesis, 5-ALA differs from other fluorescent agents that have been investigated for tumor discrimination such as fluorescein. But, there are only a few numbers of published experiences with fluorescein for tumor resection. While 5-ALA's main field of application is tumor surgery, indocyanine green (ICG) is of value in cerebrovascular procedures [55,88]. Similar to other neurosurgical purposes the main goal of intraoperative angiography by ICG is to understand and safely resect the pathology, and simultaneously to preserve cerebral perfusion [49]. ICG is widely used in ophthalmology [100,28] and hepatic surgery [116,61] due to similar reasons.

2. Role of 5-aminolevulinic acid in glioma surgery

The challenge in glioma surgery is to manage complete and safe removal of contrast enhancing tumor tissue which might help patients by reducing tumor volume and intracranial pressure. Malignant brain tumor tissue is usually difficult to distinguish from normal brain tissue and going too far might create neurological deficits after surgery. Beside other tools for optimizing resection like intraoperative MRI, neuro-navigation or ultrasound, 5-ALA is a natural biochemical precursor of haemoglobin that elicits synthesis and accumulation of strongly fluorescent PPIX within malignant glioma tissues. In a multicentre, randomized Phase III study,

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Stummer et al. could demonstrate a significant increase in rate of complete resection and progression free survival (PFS) controlled by postoperative MRI [104]. Their multivariate analysis showed that especially less or none residual tumor volume has a beneficial effect on overall survival ($P = 0.0006*$) more than Karnofsky Performance Score (KPS) ($P = 0.0055*$) and age ($P = 0.0132*$). However, intra-tumoral kinetic and accumulation of PPIX depends on different enzymes in the heme synthesis. There is also a serum-dependent export of PPIX by ATP-binding cassette transporter G2 and ferrochelatase (FECH) inhibition by nitrite oxide donor (NOC18) or deferoxamine, which increased cellular PPIX [79,110]. Further, Blake et al. showed in an in vitro comparison of the iron-chelating agents CP94 and dexrazoxane a significant effect on PPIX accumulation for photodynamic therapy and fluorescence guided resection [15]. Beside FECH, there may also be other mechanisms directly or indirectly responsible for 5-ALA uptake. Suzuki et al. could estimate an increased expression of Cadherin 13 in non-fluorescent tumor tissue [108], which influenced 5-ALA uptake into the cell by peptide transporter (Pept 1) [78] and 5-ALA efflux of the cell by ATP-transporter ABCG2 [106]. According to literature, ABCG2 is described as marker for tumor initiating cells (TICs) [16]. In contrast to ABCG2 as negative factor for intracellular PPIX fluorescence, another ATP-transporter ABCB6 is supposed to have a positive influence on tumor fluorescence [124].

A study about fluorescent and non-fluorescent glioma tissue, in which different TICs could be analyzed, underline our hypothesis that histologically, same tumor areas with different 5-ALA-induced fluorescence are also different regarding their molecular characterization [86]. There are only few studies, which correlate positive or negative fluorescent areas in astrocytomas to histological markers. Low grade fibrillary astrocytomas with slight proliferation rate mostly showed no fluorescence after 5-ALA incubation [119]. The same authors could even estimate that WHO Grade III tumors, like anaplastic astrocytomas, revealed no contrast enhancement in cerebral MRI, but fluorescence of intracellular PPIX in anaplastic foci with an increased cell amount and proliferation rate [118]. The value of Gadolinium-enhanced MRI, O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) PET and intraoperative, 5-ALA derived tissue fluorescence for anaplastic foci in diffuse gliomas is controversely discussed. Diffuse gliomas sometimes harbor anaplastic foci which determine final histopathological grading, are an indicator of prognosis and dictate adjuvant therapies such as radio- or chemotherapy. Undergrading as a consequence of sampling non-representative tumor may result in necessary therapies being deferred. Gadolinium-enhanced MRI is not always sensitive for detecting anaplastic foci. In an own study, we could show that in low grade gliomas 5-ALA fluorescence is the exception and FET PET is more sensitive. High grade areas in diffuse gliomas with anaplastic foci usually fluoresce, if they are FET PET positive. In consequence, FET PET appears valuable for pre-operative identification of anaplastic foci and hot spots are strongly predictive for 5-ALA-derived fluorescence, which highlight anaplastic foci during resection [36] (see Fig. 1).

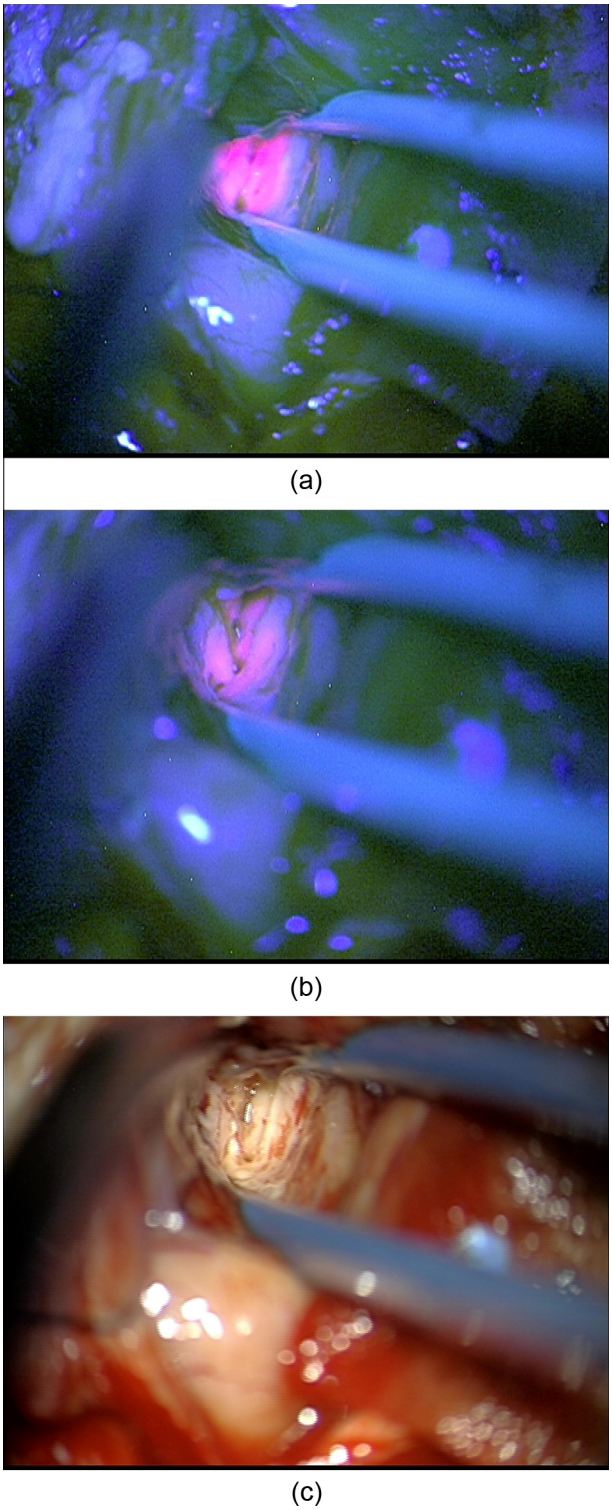

Fig. 1. 5-ALA-mediated fluorescence guided resection. Salmon like fluorescence inside the resection cavity shows malignant glioma tissue (A/B). There is a difference in fluorescence grading: strong fluorescence (A) for highly specific malignant tissue with necrosis and high tumor cell density, mild fluorescence (B) for the infiltration zone between malignant and normal brain tissue. Intraoperative microscope view in (C) with white light and (A/B) with fluorescent light. One part of fluorescending specimen is always directly checked by neuropathologists concerning their tumor entity.

3. Role of 5-aminolevulinic acid in photodynamic therapy

Photodynamic therapy (PDT) in combination with the photosensitizer 5-ALA is an emerging treatment strategy for glioma as well as for other cancers including medulloblastoma, melanoma, lung, and breast cancer [17,21,112]. There are some pathobiologic factors with noteworthy impact on the clinical application of PDT: Even if a tumor consists of progeny developed from a single neoplastic cell, there will be heterogeneity of tumor cells in terms of their morphologies and differentiation status. Kushibiki et al. found differential effects and sensitivity of PDT on morphologically distinct tumor cells derived from a single precursor cell [64] by separating two subclones from a tumor cell line after